# Childhood-Onset Bipolar Disorder: Evidence for Increased Familial Loading of Psychiatric Illness

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**ABSTRACT**

**Objective:** To determine whether childhood-onset bipolar disorder (BP) is associated with an increased psychiatric family history compared with adolescent-onset BP. **Method:** Semistructured psychiatric interviews were conducted for 438 youth with BP spectrum disorders. To evaluate the effects of age at onset and psychiatric family history, the sample was divided into childhood-onset BP (age and BP onset <12 years; $n$ = 192), adolescents with early-onset BP (age ≥12 years and BP onset <12 years; $n$ = 136), and adolescents with late-onset BP (age and BP onset ≥12 years; $n$ = 110). Lifetime family history of psychiatric illness was ascertained for first- and second-degree relatives through both direct interview of caretakers and the Family History Screen. **Results:** After significant demographic and clinical factors were controlled for, children and adolescents with childhood-onset BP showed higher percentages of positive first-degree family history for depression, anxiety, attention-deficit/hyperactivity, conduct, and substance dependence disorders and suicidal behaviors compared with adolescents with late onset. Subjects with childhood-onset BP also showed elevated familial loading for depression and attention-deficit/hyperactive disorder in second-degree relatives. **Conclusions:** These data support a model that postulates a higher density of familial risk for a broad range of psychopathology in childhood-onset BP. *J. Am. Acad. Child Adolesc. Psychiatry,* 2007;46(2):197–204. **Key Words:** bipolar disorder, age at onset, childhood, family history.

Age at onset of bipolar disorder (BP) is associated with a number of clinical characteristics (Leboyer et al., 2005). Studies of adult populations that obtained retrospective accounts of age at onset have revealed that onset before adulthood (Bromet et al., 2005), particularly before adolescence (Mick et al., 2003), is associated with a more pernicious disease presentation, including a longer duration of illness, a more chronic course, and increased comorbidity with other psychiatric disorders. Prospective studies of pediatric BP have reported that childhood onset is linked to lower rates of recovery, more time in mixed/rapid cycling episodes, and more symptom and polarity changes than those whose illness started during puberty and adulthood (Birmaher et al., 2006; Carlson et al., 2002; Craney and Geller, 2005; Geller et al., 2004; Geller and Tillman, 2005; Perlis et al., 2004).

There have been suggestions that childhood-onset BP may reflect a particularly strong familial loading for BP (Faraone et al., 2003; Leboyer et al., 2005; Strober, 1992). Prior studies have reported elevated rates of BP in relatives based on early versus later onset, with especially high rates associated with onset in childhood (Neuman et al., 1997; Pauls et al., 1992; Rice et al., 1987; Strober

et al., 1988). There is also evidence of specificity in that there is an increased familial loading for BP in pediatric BP cases compared with attention-deficit/hyperactivity disorder (ADHD) cases (Geller and Tillman, 2005). These studies support the notion that childhood onset may index a well-defined or narrow familial subtype of BP.

One consideration in evaluating the familial subtype model of childhood-onset BP is the substantial comorbidity observed for pediatric BP across a number of studies, especially for childhood-onset cases (Leboyer et al., 2005; Pavuluri et al., 2005). Thus, two additional possibilities have been considered with respect to familial loading for psychiatric disorder. One possibility is that there may be comorbid subtypes of childhood-onset BP that reflect familial loading for the particular comorbid disorders. Most notable have been suggestions that the high levels of comorbidity between childhood-onset BP and ADHD reflect a common familial disposition to both disorders (Faraone et al., 2003). An alternate model postulates that childhood-onset BP may be associated with an increased familial loading for a number of psychiatric disorders rather than a specific disorder comorbid with BP (Faraone et al., 2003; Strober, 1992). If this were the case, it would suggest that childhood-onset BP may reflect a more diffuse familial liability to a range of psychiatric disorders rather than a higher familial density of just BP or a comorbid subtype of BP.

Here, we address these issues by examining family loading for a range of psychiatric disorders in first- and second-degree relatives of bipolar children and adolescents participating in the multisite (University of Pittsburgh, Brown University, University of California at Los Angeles) collaborative National Institute of Mental Health–funded Course and Outcome of Bipolar Illness in Youth (COBY; Axelson et al., 2006; Birmaher et al., 2006). As described in detail below, lifetime history of psychiatric disorder in caretakers was assessed through direct interviews, and the family history method was used to collect information on psychiatric disorders in first- and second-degree relatives. Early-onset (childhood; <12 years old) and late-onset BP cases were established through detailed interviews with parents and youth, and percentages of subjects with a positive family history for psychiatric disorders were compared on the basis of onset.

## METHOD

### Participants

Axelson et al., 2006 give a complete description of the sample. Briefly, children and adolescents ages 7 to 17 years, 11 months (mean = 12.8 years; SD = 3.2 years) whose primary diagnoses were *DSM-IV* BP-I (*n* = 255), BP-II (*n* = 30), or BP-not otherwise specified (NOS; *n* = 153) and their parents were enrolled in the three-site COBY study (Axelson et al., 2006; Birmaher et al., 2006). Subjects were recruited from consecutive admissions to outpatient (64.6%) and inpatient (16.3%) services, advertisement (11.4%), and referrals from other physicians (7.6%), and they were enrolled independently of current state of bipolar illness or treatment status. Subjects with current or lifetime diagnoses of schizophrenia, mental retardation, autism, and mood disorders secondary to substance abuse, a medical condition, or use of medications were excluded. Other comorbid disorders were allowed in the study.

### Procedures

This study was approved by the institutional review boards at participating sites. Parallel procedures were carried out across sites. After referral to the study, a telephone screen was conducted by research staff to determine study eligibility, and an intake appointment was scheduled for all positive telephone screens. Both parental consent and adolescent assent were obtained. Intake assessments included diagnostic interviews, an interview to assess family psychiatric history, and self-report measures completed by youth and parents. Both parent and youth were compensated for their participation. In addition, a summary of assessment results was provided to the parent and/or youth's treatment provider on request of the parent. Referrals to treatment providers in the community also were made as requested.

All of the interviews were administered by bachelor's-, master's-, and doctoral-degree–level clinicians. All of the interviewers and doctoral-level supervisors underwent training and certification in the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS; see below) at each site. Interviews were audiotaped for purposes of reliability coding. In addition, all of the cases were staffed during weekly clinical consensus team meetings at each site to confirm diagnoses. This clinical consensus team comprised doctoral-degree–level child psychiatrists and/or psychologists and the interviewers. During this meeting, the K-SADS symptoms and medical records were reviewed. A best-estimate clinical consensus procedure was used to confirm child psychiatric diagnoses.

### Measures

*K-SADS-Present and Lifetime Version.* The K-SADS-Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997) is a widely used semistructured diagnostic interview that provides a reliable and valid measurement of *DSM-IV* (American Psychiatric Association, 1994) psychopathology in children and adolescents. Probes and objective criteria are provided to rate individual symptoms. The K-SADS-PL is administered first to the parent and then to the child, and both parties may be reinterviewed to resolve informant discrepancies. Interrater agreement for scoring screens and diagnoses is high (range, 93%–100%). Test-retest reliability and κ coefficients are in the excellent range for present and/or lifetime

diagnoses of major depressive, any bipolar, generalized anxiety, conduct, and oppositional defiant disorders (0.77–1.00) and in the good range for other diagnoses (0.63–0.67) (Kaufman et al., 1997). The Kiddie Mania Rating Scale (Axelson et al., 2003) and the depression section of the K-SADS Present Version (Chambers et al., 1985) also were administered to aid in mood disorder diagnoses. The overall κ coefficients for the psychiatric disorders assessed in this study were >0.80.

Because the *DSM-IV* criteria for BP-NOS are vague, the COBY investigators set the inclusion threshold for the BP-NOS group as subjects who did not meet the *DSM-IV* criteria for BP-I or BP-II but had a distinct period of abnormally elevated, expansive, or irritable mood, plus (1) two *DSM-IV* manic symptoms (three if the mood is irritable only) that were clearly associated with the onset of abnormal mood; (2) clear change in functioning; (3) mood and symptom duration of a minimum of 4 hours within a 24-hour period for a day to be considered meeting diagnostic threshold; and (4) a minimum of 4 days (not necessarily consecutive) meeting the mood, symptom, duration and functional change criteria over the subject's lifetime, which could be two 2-day episodes, four 1-day episodes, and so forth. Most subjects with BP-NOS were not diagnosed with BP-I primarily because they did not meet the *DSM-IV* duration criteria for a manic or mixed episode (Axelson et al., 2006).

*Age/Age at Onset.* Because age and age at onset of BP symptoms were highly correlated ($\frac{2}{5}$ = 0.70, $p < .001$), a composite variable, age/age at BP onset, was created with three levels: childhood-onset BP (<12 years; $n$ = 176), adolescents with early-onset BP (age ≥12 years and BP onset <12 years; $n$ = 132), and adolescents with late-onset BP (age ≥12 years and BP onset ≥12 years; $n$ = 97). Information on age at onset was derived from the K-SADS-PL.

*Family History of Psychiatric Disorder.* A biological parent primary caretaker of the subject was interviewed at intake about his or her personal lifetime psychiatric history using the Schedule for Clinical Interview of *DSM-IV* (SCID; First et al., 1995). In addition, the primary caretaker was interviewed about the psychiatric status of the subject's first- and second-degree relatives with the Family History Screen (FHS; Weissman et al., 2000). For each disorder, the interviewer indicates which family members were reported as having experienced the disorder, separately for first- and second-degree relatives, using a 3-point scale (1 = not present, 2 = possible, and 3 = definite). The disorders examined in the current analyses were major depression, mania, anxiety disorders, ADHD, conduct disorder, schizophrenia, substance abuse, substance dependence, suicidal behavior, and suicidal attempts/completions. The FHS yields acceptable test-retest reliability and validity as determined by comparing informant family history diagnosis to best-estimate diagnoses based on direct interview (Weissman et al., 2000). Here, we created a summary dichotomous variable indicating whether any first-degree relative had a definite history of each disorder to improve power (based on SCID interview of caretaker plus FHS interview for other first-degree relatives). We also created a summary dichotomous variable indicating whether any second-degree relatives had a definite history of each disorder (based on FHS interview).

## Statistics

Standard nonparametric tests were performed to test differences between BP subjects based on age/age at onset. Logistic regression models were used to determine the significance of adjusted odds ratios after controlling for relevant potential confounds. All probability values are based on two-tailed tests, with α = .05.

## RESULTS

### Demographic and Clinical Correlates of Age at Onset

We first examined whether age/age at onset of BP was associated with demographic variables, subtype of BP (BP-I versus BP-II and BP-NOS), and comorbid psychiatric disorders in subjects to determine possible confounds in the association between age/age at onset and family loading for psychiatric disorders. As presented in Table 1, childhood-onset subjects were more likely to be male, younger, and prepubertal and to have lower socioeconomic status compared with adolescents with either early or late onset. Childhood-onset subjects also had lower rates of BP-I and higher rates of BP-NOS compared with adolescents with late onset. Both children and adolescents with early onset less frequently lived with both natural parents compared with adolescents with late onset.

As shown in Table 2, both children and adolescents with early onset had higher rates of ADHD compared with adolescents with late onset. Adolescents with early onset had higher rates of any anxiety disorder compared with adolescents with late onset. In addition, adolescents with early onset had higher rates of suicidal ideation compared with both childhood-onset subjects and adolescents with late onset. Childhood-onset subjects had lower rates of conduct disorder, substance abuse/dependence, suicidal attempts, panic disorder, and physical/sexual abuse compared with both adolescent groups.

Variables that distinguished either of the early-onset groups from the adolescent late-onset group were retained as covariates for the logistic regression models described below.

### Association Between Age at Onset and Family History of Psychiatric Disorders

Percentages of subjects with a positive first- and second-degree family history for each psychiatric disorder based on the three categories of age/age at onset are presented in Table 3. Both childhood-onset subjects and adolescents with early onset had a higher positive first-degree family history for ADHD, conduct disorder, anxiety disorders, substance dependence, suicidal behavior, and suicide attempt/completion compared with adolescents with late onset. Compared with adolescents with late onset, adolescents with early onset had a higher percentage of cases with a positive

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**TABLE 1**
Demographic and Clinical Characteristics Based on Age at Onset

|  | Childhood-Onset BP (<12 y) ($n$ = 192) | Adolescents With Early-Onset BP (<12 y) ($n$ = 136) | Adolescents With Late Onset BP (>12 y) ($n$ = 110) | Statistics | $p$ |
|---|---|---|---|---|---|
| Demographics |  |  |  |  |  |
| Age (mean ± SD), y | $9.5 ± 1.5^a$ | $14.5 ± 1.6^b$ | $16.0 ± 1.3^c$ | $\chi^2_{KW}$ = 339.9 | <.001* |
| Sex, % male | $64.6^a$ | $49.3^b$ | $38.2^b$ | $\chi^2$ = 20.8 | <.001* |
| Race, % white | 84.4 | 80.9 | 78.2 | $\chi^2$ = 1.9 | NS |
| Living situation, % both natural | $39.1^a$ | $34.6^a$ | $54.5^b$ | $\chi^2$ = 10.9 | .004 |
| Pubertal status, % |  |  |  |  |  |
| I | $69.3^a$ | $3.5^b$ | $0.0^b$ | $\chi^2_4$ = 253.1 | <.001* |
| II/III | 28.2 | 33.3 | 14.9 |  |  |
| IV/V | $2.5^a$ | $63.2^b$ | $85.1^b$ |  |  |
| BP subtype, % |  |  |  |  |  |
| I | $53.1^a$ | $59.6^{a,b}$ | $65.5^b$ | $\chi^2_4$ = 19.3 | .001* |
| II | 3.1 | 8.1 | 11.8 |  |  |
| NOS | $43.8^a$ | $32.3^{a,b}$ | $22.7^b$ |  |  |
| SES (mean ± SD) | $3.2 ± 1.2^a$ | $3.5 ± 1.2^{a,b}$ | $3.8 ± 1.1^b$ | $F$ = 6.9 | .001* |

*Note:* BP = bipolar disorder; NOS = not otherwise specified; SES = socioeconomic status. Different superscripts indicate pairwise $p ≤ .05$.
* Significant after Bonferroni correction.

first-degree family history of depression and substance abuse. No differences based on age/age at onset were found for mania and schizophrenia. As shown in Table 3, childhood-onset subjects and adolescents with early-onset BP had a higher percentage of cases with a positive second-degree family history for depression, ADHD, and substance dependence compared with adolescents with late onset. In addition, childhood-onset subjects had a higher percentage of second-degree relatives with suicide attempts/completion compared with both adolescents with early onset and adolescents with late onset.

### Logistic Regression Models With Covariates

Logistic regression models were run to assess the significance of the elevated percentages of cases with positive family history of psychiatric disorder after accounting for possible clinical (ADHD, conduct disorder, panic disorder, substance abuse/dependence, BP subtype) and demographic (sex, socioeconomic status, living situation) confounds that were shown to vary by age at onset (Table 1). Pubertal status and age were not entered as covariates given the high collinearity with age/age at onset. Adjusted odds ratios and corresponding 95% confidence intervals and significance levels are presented in Table 4. Early onset of BP (childhood-onset subjects and adolescents with early

onset versus adolescents with late onset) remained significantly associated with positive first-degree family history for depression, ADHD, conduct disorder, anxiety disorders, substance dependence, and suicidal behavior after adjustment for the covariates. Early onset of BP (both childhood-onset subjects and adolescents with early onset versus adolescents with late onset) remained significantly associated, with a higher percentage of cases with a positive second-degree family history for depression and ADHD after controlling for covariates. In the logistic regression models, we also included a term representing the interaction between the onset variable and BP subtype. This interaction term did not reach significance in any of the models reported above, suggesting that the association between onset and family history did not differ significantly across subtype of BP.

### DISCUSSION

This report used a bottom-up design (Rende and Weissman, 1999) to compare family history of psychiatric illness in pediatric BP subjects with onset in childhood (early onset) versus onset in adolescence (late onset). After potential clinical and demographic confounds were controlled for, children and adolescents with early onset had higher percentages of positive first-degree family history for depression, anxiety disorders,

ADHD, conduct disorder, substance dependence, and suicide behaviors compared with late-onset subjects. The data on second-degree relatives highlighted elevated familial loading for depression and ADHD in children and adolescents with early onset after controlling for covariates. Overall, these findings are consistent with a model that postulates a diffuse family history for psychiatric illness associated with childhood onset of BP because there was little suggestion of specific aggregation of comorbid disorders and family history. It is also worth noting that the data on second-degree relatives are consistent with models that emphasize genetic transmission of depression and ADHD, respectively (Rende and Waldman, 2006).

It is important to consider that the early- and late-onset groups did not differ in family history of mania. It may be that onset before adulthood is associated with increased familial loading for mania but that family history for other psychiatric disorders better distinguishes childhood from adolescent onset of BP. We do note, however, that prior psychometric work on the FHS (Weissman et al., 2000) did not evaluate the reliability and validity of obtaining family history for mania and that early onset of BP was associated with family history for depression, suggesting elevated familial risk for affective disorders. Further evaluation of this issue is warranted.

An interesting methodological comparison that is possible with the COBY data is to consider the distinction between age at onset and chronological age of assessment. There were few differences in family history between the children and adolescents with early onset, and most significant findings were based on differences between both of these early-onset groups versus adolescents with late onset. We interpret these results to indicate that the assignment of age at onset in adolescent cases was valid and that there were no selection biases in the preadolescent cases that influenced the association with family history of psychiatric disorder.

Another important issue is the association between early onset and BP subtype. Childhood-onset subjects were less frequently diagnosed with BP-I and more frequently diagnosed with BP-NOS than were adolescents with late onset. However, the children and adolescents with early onset did not differ in BP subtype; associations between early onset and family history of psychiatric disorder remained significant after controlling for BP subtype, and there was no significant interaction between BP subtype and age at onset in predicting family history of psychiatric disorder. Axelson et al., 2006 found that 86% of the BP-NOS subjects in COBY had all of the mania/hypomania symptoms, but they were not diagnosed as

**TABLE 2**
Clinical Lifetime Comorbidity Based on Age at Onset

| | Childhood-Onset BP (<12 y) (n = 192) | Adolescents With Early-Onset BP (<12 y) (n = 136) | Adolescents With Late-Onset BP (>12 y) (n = 110) | $\chi^2$ | p |
|---|---|---|---|---|---|
| Any anxiety (SAD, social phobia, GAD, OCD, PTSD, panic disorder) | $38.0^{a,b}$ | $46.3^a$ | $31.8^b$ | 5.5 | NS (.06) |
| ADHD | $73.4^a$ | $67.6^a$ | $26.4^b$ | 69.5 | <.001* |
| Conduct disorder | $6.8^a$ | $19.1^b$ | $15.5^b$ | 11.8 | .003 |
| ODD | 43.8 | 38.2 | 33.6 | 3.1 | NS |
| Psychosis (MRS and K-SADS) | 27.1 | 30.9 | 24.5 | 1.3 | NS |
| Substance abuse/dependence | $0^a$ | $11.0^b$ | $22.7^c$ | 44.4 | <.001* |
| Suicidal ideation | $71.2^a$ | $85.3^b$ | $73.6^a$ | 9.2 | .01 |
| Suicidal attempt | $19.9^a$ | $40.4^b$ | $37.3^b$ | 18.8 | <.001* |
| Self-injurious behavior | 35.6 | 44.0 | 33.9 | 3.3 | NS |
| Panic disorder | $0.5^a$ | $11.0^b$ | $7.3^b$ | 17.9 | <.001* |
| Mixed | 20.8 | 30.1 | 30.0 | 4.8 | NS (.09) |
| Physical/sexual abuse | $17.7^a$ | $29.4^b$ | $21.8^{a,b}$ | 6.3 | .04 |

*Note:* BP = bipolar disorder; SAD = social anxiety disorder; GAD = general anxiety disorder; OCD = obsessive-compulsive disorder; PTSD = posttraumatic stress disorder; ADHD = attention-deficit/hyperactive disorder; MRS = Mania Rating Scale; K-SADS = Kiddie Schedule for Affective Disorders and Schizophrenia. Different superscripts indicate pairwise $p \le 0.05$.
* Significant after Bonferroni correction.

**TABLE 3**
Family History* of Psychiatric Disorders Based on Age at Onset

| | Childhood-Onset BP (<12 y) (n = 192) | Adolescents With Early-Onset BP (<12 y) (n = 136) | Adolescents With Late-Onset BP (≥12 y) (n = 110) | Statistics | p |
|---|---|---|---|---|---|
| First-degree depression | $72.9^a$ | $84.6^b$ | $63.1^a$ | $\chi^2 = 13.6$ | .001† |
| First-degree mania | 37.5 | 38.2 | 26.9 | $\chi^2 = 4.0$ | NS |
| First-degree ADHD | $32.9^a$ | $37.6^a$ | $17.2^b$ | $\chi^2 = 10.9$ | .004† |
| First-degree conduct disorder | $22.4^a$ | $30.9^a$ | $10.9^b$ | $\chi^2 = 11.7$ | .003† |
| First-degree schizophrenia | 0.6 | 3.7 | 0.0 | FET = 4.7 | NS |
| First-degree anxiety disorder | $61.0^a$ | $56.5^a$ | $34.0^b$ | $\chi^2 = 20.0$ | <.001† |
| First-degree substance abuse | $26.1^a$ | $41.9^b$ | $26.5^a$ | $\chi^2 = 9.8$ | .007† |
| First-degree substance dependence | $35.4^a$ | $38.7^a$ | $17.5^b$ | $\chi^2 = 13.5$ | .001† |
| First-degree suicidal behavior | $35.1^a$ | $39.8^a$ | $18.6^b$ | $\chi^2 = 12.5$ | .002† |
| First-degree suicide attempt/ completion | $27.0^a$ | $26.6^a$ | $12.7^b$ | $\chi^2 = 8.5$ | .02 |
| Second-degree depression | $76.4^a$ | $72.6^a$ | $59.4^b$ | $\chi^2 = 9.2$ | .01 |
| Second-degree mania | 41.3 | 33.9 | 30.7 | $\chi^2 = 3.5$ | NS |
| Second-degree ADHD | $32.7^a$ | $29.1^a$ | $14.9^b$ | $\chi^2 = 9.4$ | .009† |
| Second-degree conduct disorder | 26.5 | 28.8 | 19.3 | $\chi^2 = 2.5$ | NS |
| Second-degree schizophrenia | 4.8 | 7.3 | 5.5 | $\chi^2 = 0.8$ | NS |
| Second-degree anxiety disorder | 53.5 | 42.7 | 42.6 | $\chi^2 = 4.6$ | NS |
| Second-degree substance abuse | 41.5 | 50.4 | 49.5 | $\chi^2 = 2.9$ | NS |
| Second-degree substance dependence | $50.9^a$ | $49.2^a$ | $33.7^b$ | $\chi^2 = 8.4$ | .02 |
| Second-degree suicidal behavior | 36.8 | 31.5 | 26.7 | $\chi^2 = 3.0$ | NS |
| Second-degree suicide attempt/completion | $39.7^a$ | $29.0^b$ | $24.8^b$ | $\chi^2 = 7.5$ | .02 |

*Note:* Different superscripts indicate pairwise $p \leq .05$. FET = Fisher exact test.

\* At least one family member with disorder (yes/no).

† Significant after Bonferroni correction.

BP-I or BP-II because they did not meet the *DSM-IV* duration requirements to make these diagnoses. Thus, it is not surprising that there were no differences in family loadings by BP subtype. One consideration is that some of the non–BP-I cases are converting as they age (Birmaher et al., 2006), so it may be somewhat premature to fully evaluate this issue. Future longitudinal assessment of this sample will provide a stronger opportunity to examine the associations among age at onset, BP subtype, and family history of psychiatric disorder (see Althoff et al., 2005).

Family studies represent an important first step in genetic research strategies for childhood disorders (Rende and Waldman, 2006). Overall, the findings reported here support a rather complex model of familial liability to pediatric BP, with early onset reflecting an especially high density of familial risk for a range of psychiatric illness. Because family studies of

**TABLE 4**
Adjusted Odds Ratios for Family History Based on Age at Onset[a]

| | OR | CI | *p* |
|---|---|---|---|
| First-degree depression | 2.00 | 1.13–3.54 | <.02 |
| First-degree mania | 1.58 | 0.80–3.10 | NS |
| First-degree ADHD | 2.16 | 1.14–4.10 | <.02 |
| First-degree conduct disorder | 2.42 | 1.09–5.34 | .03 |
| First-degree schizophrenia | —[b] | — | — |
| First-degree anxiety disorder | 2.52 | 1.47–4.31 | .001 |
| First-degree substance abuse | 1.39 | 0.73–2.66 | NS |
| First-degree substance dependence | 2.02 | 1.05–3.88 | <.04 |
| First-degree suicidal behavior | 2.16 | 1.16–4.04 | <.02 |
| First-degree suicide attempt/completion | 1.68 | 0.74–3.78 | NS |
| Second-degree depression | 2.05 | 1.19–3.54 | <.01 |
| Second-degree mania | 1.16 | 0.51–2.20 | NS |
| Second-degree ADHD | 2.14 | 1.06–4.31 | <.04 |
| Second-degree conduct disorder | 1.71 | 0.81–3.65 | NS |
| Second-degree schizophrenia | —[b] | — | — |
| Second-degree anxiety disorder | 1.04 | 0.62–1.72 | NS |
| Second-degree substance abuse | 0.63 | 0.38–1.09 | NS |
| Second-degree substance dependence | 1.60 | 0.94–2.71 | NS (.08) |
| Second-degree suicidal behavior | 1.40 | 0.83–2.35 | NS |
| Second-degree suicide attempt/completion | 1.14 | 0.60–2.17 | NS |

[a] Early-onset children and adolescents versus late-onset adolescents.
[b] Not computed because of the low base rate.

age at onset of BP often have been used to inform genetic models (Lin et al., 2006), one implication from the present study is that genetic studies of early-onset BP may need to consider transmission of both disease-specific and nonspecific genes that contribute to risk for BP and comorbid disorders. Similarly, the risk environments that surround the onset of BP in childhood may be influenced by high levels of psychopathology in family members. Future studies that incorporate candidate gene markers, indicators of environmental risk, and careful diagnostic assessment are necessary to determine whether the underlying etiologic factors differ for early- or late-onset pediatric BP, which would imply that they represent, in part, different nosological entities.

## Limitations

It is important to consider three limitations to our findings, especially because there are a number of caveats to the family history method and the bottom-up design (Rende and Weissman, 1999). First, lifetime history of psychiatric disorder was assessed using an informant for relatives other than primary caretakers. The family history method typically provides less

specificity of diagnosis than direct interviewing, and this may be especially true for second-degree relatives. Second, potential biases arise when pediatric subjects are referred for treatment because a parent typically is involved in the process, raising the possibility that offspring with disorders may be referred more frequently because of parental illness. These caveats are critical considerations for designs that provide comparisons between clinical and nonclinical control groups but are of less concern for within-group comparisons such as those presented here (in which both groups derive from similar recruitment procedures). Third, the findings from COBY should not be used to generalize beyond clinical settings and primarily white populations.

## Clinical Implications

The results from this study have important clinical implications. Prior research has indicated that age at onset may be an important predictor of course of illness, and this study suggests that ascertainment of age at onset also may index substantial psychopathology in family members. Thus, clinical management may be served by considering the family climate and

the role of history of psychopathology in parents (and other family members), particularly for early-onset pediatric BP cases.

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