

# Controlled, Blindly Rated, Direct-Interview Family Study of a Prepubertal and Early-Adolescent Bipolar I Disorder Phenotype

## Morbid Risk, Age at Onset, and Comorbidity

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**Context:** A key question is whether a prepubertal and early-adolescent bipolar I disorder phenotype (PEA-BP-I) is the same illness as adult BP-I. This question arises because of the greater severity, longer current episode duration, preponderance of mania, and high rates of ultradian rapid cycling and comorbid attention-deficit/hyperactivity disorder (ADHD) in PEA-BP-I.

**Objectives:** To examine morbid risk (MR) of BP-I in first-degree relatives of PEA-BP-I, ADHD, and healthy control probands, as well as imprinting, sibling recurrence risk, and anticipation.

**Design:** Controlled, blind direct interview. There were no family psychopathology exclusions for any proband group.

**Setting:** University medical school research unit.

**Participants:** First-degree relatives 6 years and older ( $n=690$ ) of 219 probands (95 with PEA-BP-I, 47 with ADHD, and 77 healthy controls). The PEA-BP-I and ADHD probands were obtained by consecutive new case ascertainment, and healthy controls were from a ran-

dom survey; proband diagnoses were validated via 4-year prospective follow-up. The PEA-BP-I probands had a mean  $\pm$  SD age of  $10.8 \pm 2.6$  years.

**Main Outcome Measure:** Morbid risk.

**Results:** The MR of BP-I was higher in relatives of PEA-BP-I probands compared with ADHD or healthy controls ( $P < .001$  for both); the MR in relatives of ADHD and healthy controls was similar. The MR of BP-I in relatives with ADHD was higher ( $P < .001$ ) and age at onset of BP-I was younger in parents with ADHD than in those without ( $P < .001$ ). The MR of BP-I in relatives with oppositional, conduct, or antisocial disorders was higher than in those without ( $P < .001$ ). Anticipation was evidenced by a younger age at onset of BP-I in probands than in their parents ( $P < .001$ ). No imprinting was found.

**Conclusions:** Findings support that PEA-BP-I and adult BP-I are the same diathesis, 7 to 8 $\times$  greater familiarity in child vs adult BP-I, and family study validation of PEA-BP-I, including its differentiation from ADHD.

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**A** KEY QUESTION IS WHETHER children with a prepubertal and early-adolescent bipolar I disorder phenotype (PEA-BP-I) have the same illness as their adult counterparts.<sup>1,2</sup> This question arises because of the greater severity, longer current episode, preponderance of mania, and high rates of ultradian rapid cycling and comorbid attention-deficit/hyperactivity disorder (ADHD) in child mania in prospective and retrospective studies.<sup>2-14</sup> In most<sup>2,13,14</sup> but not all<sup>15</sup> studies, children with BP-I resemble the most severely ill adults with BP-I, of whom approximately 20% also have long episodes and rapid cycling, fueling interest in whether they are the same disorder.<sup>12,16</sup> Speculations include that they

are the same disorder with developmental phenotypic differences so that age at onset would be earlier for genetic and environmental reasons.<sup>1</sup> Another postulation is that early- and later-onset adult BP-I may be different diatheses.<sup>17</sup>

Another prominent difference between PEA-BP-I and adult BP-I is the profile of comorbidities.<sup>6,13,18,19</sup> Attention-deficit/hyperactivity disorder is present in most pediatric subjects, whereas these subjects have lower prevalences of panic and substance use diagnoses, perhaps owing to their young age.<sup>6,13,18-20</sup> It is not yet known what the clinical phenotype of BP-I with comorbid ADHD means.<sup>21,22</sup> Speculations have included that comorbid ADHD in child BP is developmental; that is, the normal motoric activity of chil-

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**Table 1. Controlled, Blindly Rated, Direct-Interview Family Studies of BP-I in First-Degree Relatives of BP-I Probands**

Source	BP-I Probands, No.	Proband Age, Mean (SD), y	Relative Age, y	Adult Relative Instrument	Child Relative Instrument	Blind, %	Relative Direct Interview, %	BP-I, %	Morbid Risk of BP-I
Gershon et al, <sup>23</sup> 1982*	96	44.4 (1.0)	NA	SADS-L	NA	75.0	78.0	NA	4.5
Andreasen et al, <sup>25</sup> 1987*	151	38.0 (14.4)	≥17	SADS-L	NA	NA	NA†	3.9	NA
Strober et al, <sup>28</sup> 1988*	50	NA‡	≥18	SADS-L	NA	NA	88.7	13.9	NA
Present study§	95	10.8 (2.6)	≥6	SADS-LB	WASH-U-KSADS¶	99.7	84.8	28.2	34.0

Abbreviations: BP-I, bipolar I disorder; NA, not available; SADS-L, Schedule for Affective Disorders and Schizophrenia–Lifetime Version; SADS-LB, Schedule for Affective Disorders and Schizophrenia–Lifetime Bipolar Version; WASH-U-KSADS, Washington University in St Louis Kiddie Schedule for Affective Disorders and Schizophrenia.

\*Used *Research Diagnostic Criteria for a Selected Group of Functional Disorders*.

†Analyses were conducted only on directly interviewed relatives (39.4% were directly interviewed).

‡The mean (SD) value was not given; the age range was 13 to 17 years.

§Used the *DSM-IV*.

||Adult relatives were assessed using the SADS-LB, modified for *DSM-IV*, along with the WASH-U-KSADS mania and attention-deficit/hyperactivity disorder items about their own childhood.

¶Child relatives were assessed using the complete WASH-U-KSADS, given separately to parents about their children and to children about themselves.

dren added to BP-I produces the clinical picture of ADHD.<sup>6,22</sup> Another speculation is that BP-I with ADHD is a specific diathesis and thus may differ in etiopathogenesis from non-BP ADHD.<sup>21,22</sup> In any case, this phenotypic presentation strongly indicates that a control group with ADHD without a mood disorder is the most relevant for PEA–BP-I. This is dissimilar to the use of controls with schizophrenia in the study by Gershon et al<sup>23</sup> of BP-I in adults. However, the rarity of schizophrenia in children<sup>24</sup> would make using a schizophrenia control group problematic for the pediatric group. Also, no subject in the PEA–BP-I proband group became schizophrenic during 4-year prospective follow-up, and only 1.4% of the relatives of PEA–BP-I probands had a schizoaffective diagnosis and none had schizophrenia. These data support that schizophrenia is a less compelling differential diagnosis for relatives of PEA–BP-I probands than for relatives of adult BP-I probands.<sup>1,2</sup> Andreasen et al<sup>25</sup> used a unipolar depression control group. However, children with prepubertal major depressive disorder (MDD) and a mean ± SD age of 10.3 ± 1.5 years had a 10-year prospective switch rate to BP-I of 33.3% by mean ± SD age 20.7 ± 2.0 years,<sup>26</sup> so unipolar depression would not be an appropriate control group for PEA–BP-I. In contrast, the switch rate in adults is substantially lower because most switching occurs earlier in life.<sup>27</sup> To our knowledge, this is the first controlled, blindly rated, direct-interview family study of probands with PEA–BP-I using the Schedule for Affective Disorders and Schizophrenia (SADS) series diagnostic instruments (**Table 1**).

## METHODS

Methods were used that fit the Merikangas et al<sup>29</sup> consensus guidelines on family study methods for genetic linkage and other studies. These methods included consecutive new case ascertainment of PEA–BP-I and ADHD probands to avoid biases from obtaining participants via media advertisements or other non-systematic avenues.<sup>4</sup> Longitudinal stability of the PEA–BP-I phenotype was established by 4-year prospective follow-up.<sup>1,2,30–32</sup> Raters were blind to any information about the proband. Families were instructed not to mention the proband during the in-

terview, and the blinding was 99.7% (Table 1). Only 2 relatives broke the blind study design by inadvertently referring to the proband's baseline group. There were no family psychopathology exclusions in any proband group to avoid biases.<sup>33</sup> For specificity, a control group with another psychiatric disorder was used: the ADHD group.

## DEFINITION OF PEA–BP-I

To address ambiguities in the field of pediatric BP, including how to differentiate prepubertal mania from ADHD, subjects needed to fit *DSM-IV* criteria for mania with at least 1 of the cardinal mania criteria (ie, elated mood and/or grandiosity). This schema followed the *DSM-IV* pattern of needing a cardinal symptom of depression (ie, sad mood or anhedonia) to fit the diagnosis of MDD.<sup>34</sup> The cardinal symptom approach obviated the problem of diagnosing pediatric BP using criteria that overlapped with those for ADHD (eg, hyperactivity and distractibility).<sup>4,5,35</sup>

Another issue is that some researchers had stressed that child mania was characterized by irritable rather than elated mood or concurrent elated and irritable moods.<sup>36</sup> Irritability in BP-I across the age span has been reported in numerous studies.<sup>4,13,14,16,20,35,37</sup> For example, 87.1% of subjects with PEA–BP-I had both elated mood and irritability.<sup>3,4</sup> Irritability, however, although very sensitive, is highly nonspecific because it occurs in multiple other child diagnoses.<sup>37–39</sup> Kim-Cohen et al<sup>37</sup> investigated whether young adults with multiple psychiatric diagnoses had a childhood diagnosis and found that 20% to 60% of adults with a psychiatric diagnosis had a childhood disorder characterized by irritability and aggression (eg, conduct disorder [CD]).

## ASCERTAINMENT OF PROBANDS

Probands were subjects enrolled in the National Institute of Mental Health–funded “Phenomenology and Course of Pediatric Bipolar Disorders” study<sup>4</sup> that entered participants between 1995 and 1998.

Subjects with current PEA–BP-I and ADHD were recruited from designated outpatient child psychiatric and pediatric sites by means of consecutive new case ascertainment.<sup>4</sup> In the consecutive new case ascertainment schema, all new patients at the designated facilities were assessed for exclusions. For example, a child who visited a pediatric site with a sore throat was given the same assessment for exclusions as a child who visited a psychiatric site with hyperactivity. Outpatient sites were used instead of inpa-

tient sites because the planned inpatient venues in St Louis closed before participant ascertainment. At the time of subject enrollment, there were no pediatric or psychiatric facilities available that served families of lower socioeconomic status. Pediatricians from private practices who saw patients from lower socioeconomic backgrounds did not agree to participate in the study because of the increased workload (eg, sending letters to all new patients about the study). Healthy control subjects were obtained from a random survey and were matched to the PEA-BP-I group by age, sex, socioeconomic status, ethnicity, and ZIP code.

## STUDY INCLUSION AND EXCLUSION CRITERIA FOR PROBANDS

The study inclusion and exclusion criteria have been reported in detail previously.<sup>4</sup> In brief, inclusion criteria for the PEA-BP-I probands were age 7 to 16 years, males and females, good physical health, and current *DSM-IV* BP-I (mania or mixed phase) for at least 2 weeks (actual mean  $\pm$  SD prospective current episode length was 79.2  $\pm$  66.7 weeks<sup>2</sup>). In addition, subjects with PEA-BP-I were required to have at least 1 of the cardinal symptoms of mania (ie, elation and/or grandiosity). A Children's Global Assessment Scale (CGAS) score of 60 or less was needed to establish significant clinical impairment.<sup>40,41</sup>

Exclusion criteria were an IQ less than 70, adopted status, pervasive developmental disorders, schizophrenia, epilepsy or another major medical or neurologic disorder, baseline substance dependency or pregnancy, and manic symptoms only while taking antidepressant, stimulant, or other mania-inducing medications. There were no family history exclusions.

The rationales for these PEA-BP-I inclusion and exclusion criteria included the following. Because this was a phenomenology study, participants were required to be experiencing a current episode. The rationale for the cardinal symptom approach is discussed previously herein. A lower age of 7 years was chosen for credibility of interview assessments in 1995, and an upper age of 16 years was selected so that participants would still be teenagers at 2-year follow-up.<sup>32</sup> At baseline, participants could not have substance dependency or pregnancy to avoid confounding the mental status, but those who developed these conditions were retained in the follow-up studies. Adopted participants were excluded because of concurrent family/genetic studies.<sup>42</sup>

Inclusion criteria for the ADHD group were age 7 to 16 years, males and females, good physical health, and *DSM-IV* ADHD (with hyperactivity; ie, combined or hyperactive/impulsive types) with definite clinical impairment (CGAS score  $\leq$  60), onset before age 7 years, and a duration of at least 6 months. Exclusion criteria for the ADHD group were the same as those for the PEA-BP-I group with the addition of no lifetime or current MDD or any BP diagnosis. The rationale for only the combined or hyperactive/impulsive types of ADHD was that the hyperactivity manifestations were the ones that needed to be differentiated from mania.

The healthy controls were aggregatedly matched to the PEA-BP-I probands by age, sex, socioeconomic status, ethnicity, and ZIP code and were in good physical health without clinical impairment (CGAS score  $\geq$  70). Exclusion criteria for the healthy control group were the same as those for the PEA-BP-I group with the addition of any current or past BP diagnoses, MDD, or ADHD.

## ASSESSMENT INSTRUMENTS FOR PROBANDS AND FOR SIBLINGS AGED 6 TO 18 YEARS

Siblings 6 years and older were assessed because, by 1998, the reliability of the Washington University in St Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) and other instruments for children as young as 6 years was established. The WASH-U-KSADS is a lifetime, semistruc-

tured interview with excellent reliability ( $\kappa=0.82-1.00$ ) and 6-month stability of diagnoses and symptoms.<sup>30,43,44</sup> It was administered by experienced research nurses who were blind to probands' diagnostic status (PEA-BP-I, ADHD, or healthy control) and who had established interrater reliability. It was given to parents about their children and separately to children about themselves.<sup>44,45</sup> The WASH-U-KSADS is a lifetime instrument that has extensive sections for prepubertal mania and for ultrarapid and ultradian cycling, multiple levels of severity for each item, onsets and offsets of each symptom and syndrome, and sections for ADHD and other *DSM-IV* diagnoses. A previous study<sup>5</sup> details examples of prepubertal mania manifestations.

Responses from the separate parent and child interviews were combined by using the most severe response from either interview, following the methods described by Bird et al.<sup>46</sup> On the WASH-U-KSADS, item ratings of 4 or greater indicate definite clinical impairment and count toward *DSM-IV* diagnoses. Psychosis was defined as delusions and malignant, pathologic hallucinations that did not occur only hypnagogically or hypnopompically and that caused definite clinical impairment.<sup>2,43</sup>

Symptoms that occurred in overlapping periods were used to establish *DSM-IV* diagnoses based on the fact that every item on the WASH-U-KSADS includes the date of onset and the date of offset. For example, mixed mania was defined as overlapping time periods of *DSM-IV* mania and MDD.<sup>4</sup> Furthermore, if symptoms common to ADHD and mania or other diagnoses occurred during the same time frame, they would count toward both diagnoses providing that the ADHD fit *DSM-IV* criteria (began before age 7 years, occurred in multiple settings, etc). The reasoning is that at present, there is no way of knowing whether the symptom, for example, distractibility, is due to ADHD or mania or both.

Historically, adult rapid cycling was defined as 4 or more episodes per year. Although many adults with BP will have 4 or more episodes per year, this is uncommon in child BP. Instead, children with BP most often have ultradian cycling, which is multiple cycles during a day, every or almost every day, for the length of their long current episodes. For this reason, definitions of episode and cycle that are relevant across the age span were proposed by Tillman and Geller,<sup>7</sup> based on the work of Kramlinger and Post.<sup>47</sup> Episode refers to the entire current illness, and cycles are mood changes occurring within an episode. In this schema, the former adult rapid cycling is 4 or more episodes per year, ultrarapid cycling is mood switches occurring every few days, and ultradian cycling is mood changes occurring on a daily or almost daily basis. For example, an 8-year-old boy had a BP diagnosis with a current episode lasting 2 years. During these 2 years of continuous manic symptoms he cycled twice daily every day. He would be said to have an episode lasting 2 years characterized by ultradian cycling. In a study of PEA-BP-I, 77.4% of subjects had ultradian cycling, 9.7% had ultrarapid cycling, and none had 4 or more separate episodes a year.<sup>3,4</sup>

The CGAS<sup>40,41</sup> is a measure of global severity based on impaired functioning in social, family, school, and work settings. The CGAS scores were derived by the research nurses who administered the WASH-U-KSADS. Socioeconomic status was determined by means of the Hollingshead Four Factor Index of Social Status,<sup>48</sup> and pubertal status was determined by means of the Pubertal Status Questionnaire in participants 10 years and older.<sup>49</sup> No *DSM-IV* hierarchies were used in assigning proband diagnoses.

## ASSESSMENT INSTRUMENTS FOR PARENTS AND FOR SIBLINGS 19 YEARS OR OLDER

The Schedule for Affective Disorders and Schizophrenia-Lifetime Bipolar Version modified for *DSM-IV*<sup>50,51</sup> was administered to relatives 19 years and older by experienced research nurses blind to

any information about the probands and who completed the Global Assessment Scale (GAS).<sup>52</sup> In addition, the mania and ADHD sections of the WASH-U-KSADS were administered to adults about their own childhood, as it has been shown that adults can reliably report on their childhood ADHD symptoms.<sup>53</sup>

## CONSENSUS DIAGNOSES

Only diagnoses that were considered to fit after consensus conferences were counted as present.<sup>54-56</sup> In these meetings, a child psychiatrist (B.G.) and the experienced research nurses who administered the instruments reviewed all the materials, including assessment instruments, school reports, agency records, medical records, pediatrician medical records, psychiatric records, videotapes of WASH-U-KSADS interview sessions with parents, and videotapes of WASH-U-KSADS interview sessions with children.

## FAMILY STUDY SCORING MANUAL

Each *DSM-IV* diagnostic category was scored on a 6-point scale. A score of 1 meant that there was no psychopathology in that diagnostic area. A score of 2 meant that there was doubtful pathology. A score of 3 meant that the relative fit the criteria for the diagnosis but had no clinical impairment (eg, had motor or vocal tics that did not cause any distress, such as being teased at school, low self-esteem, or parental concern leading to pharmacotherapy). Only diagnoses with scores of 4, 5, or 6, which signified definite clinical impairment, were counted for the analyses in this communication. A score of 4 meant that all but 1 symptom of a diagnosis was present and that there was definite clinical impairment. For example, the relative had attempted suicide, had marked sad mood and anhedonia, and took 2 hours to fall asleep. A score of 5 or 6 meant that all the criteria were met with definite clinical impairment. A score of 6 meant that there was definite and very severe impairment (eg, multiple hospitalizations and suicide attempts).

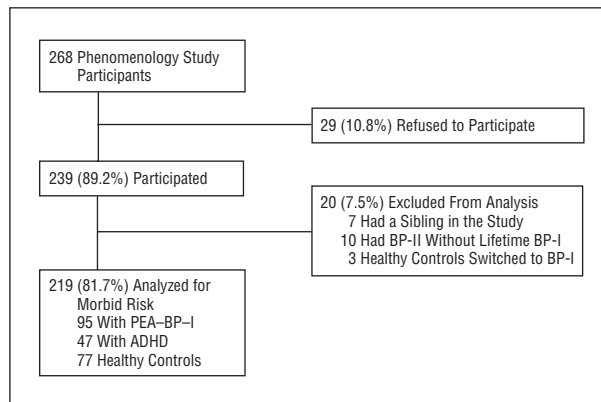
No *DSM-IV* hierarchies were used in assigning relative diagnoses. In relatives, BP-I was diagnosed using the same criteria used for probands. Recurrent MDD was defined as more than 1 lifetime episode or 1 lifetime episode that lasted 2 or more years. In relatives, ADHD included only hyperactive and combined subtypes because these were the subtypes used for the ADHD proband group. Schizoaffective disorder BP-I type was counted as BP-I (2 relatives), and schizoaffective disorder MDD type was counted as MDD (2 relatives), based on the literature.<sup>23</sup>

After complete description of the study, written informed consent was obtained from adults, and parental consent and written assent were obtained from relatives 17 years or younger. This study was reviewed and approved by the Washington University (St Louis) human studies committee.

## STATISTICAL ANALYSES

Demographic characteristics of probands and relatives in the 3 proband groups were analyzed using 2-tailed *t* tests for continuous variables and  $\chi^2$  tests for categorical variables. Lifetime morbid risks (MRs) of BP-I and of recurrent MDD in relatives of each of the 3 proband groups were calculated using the Kaplan-Meier method. Hazard ratios and corresponding 95% confidence intervals were obtained using Cox proportional hazards models with the Wald  $\chi^2$  statistic determining level of significance. Covariates in the Cox proportional hazards models were proband sex, age, and pubertal status, as these differed among proband groups. Relative sex was also controlled for because MR of BP-I and of recurrent MDD differed by this variable.

In addition, lifetime MRs were calculated and hazard ratios



**Figure 1.** Family study flow of probands. ADHD indicates attention-deficit/hyperactivity disorder; BP-I, bipolar I disorder; BP-II, bipolar II disorder; PEA-BP-I, prepubertal and early-adolescent BP-I disorder phenotype.

were compared among relatives with and without ADHD and oppositional defiant disorder (ODD), CD, or antisocial personality disorder (ASP). Age at onset of BP-I in relatives was compared among relatives with and without ADHD and ODD, CD, or ASP using *t* tests.

To test for a parent-of-origin effect, the rate of BP-I among proband offspring of fathers with BP-I was compared with the rate of BP-I among proband offspring of mothers with BP-I using the  $\chi^2$  statistic. For this analysis, any families in which both the mother and father had BP-I were not included.

Sibling recurrence risk was determined in 2 ways. The first method was to calculate the prevalence of BP-I among all siblings of PEA-BP-I probands.<sup>57</sup> The second method included only siblings born after the PEA-BP-I proband, known as the later-sibling method.<sup>58</sup> The rate of BP-I among siblings of probands was calculated for families with no parents with BP-I, 1 parent with BP-I, and 2 parents with BP-I. Wald  $\chi^2$  tests were used to compare these rates, and odds ratios and 95% confidence intervals were computed. The rate of BP-I in siblings instead of the rate in probands was used, since probands were ascertained for the study because they had PEA-BP-I, whereas siblings were not.

Age at BP-I onset in PEA-BP-I probands and their parents with BP-I was compared using a 2-tailed *t* test. Analyses comparing relatives of the 3 proband groups were corrected for multiple comparisons using Bonferroni corrections for the 3 comparisons so that the level of significance was  $P = .02$ . Analyses comparing only 2 groups (eg, MR of BP-I in relatives with vs without ADHD) were not corrected for, so the significance level was  $P = .05$ . All analyses were conducted using a software program (SAS version 8.2; SAS Institute Inc, Cary, NC).

## RESULTS

Family study interviews were conducted between September 13, 1999, and April 20, 2004, and the flow is presented in **Figure 1**. Families of 10 PEA-BP-I (10.8%), 8 ADHD (9.9%), and 11 healthy control (11.7%) probands declined to participate in the family study. There were no significant differences in demographic variables between individuals who participated and those who did not.

The PEA-BP-I probands included those with BP-I at baseline and those with baseline BP-II or ADHD who developed BP-I by age 16 years (upper limit for entry into the Phenomenology and Course of Pediatric Bipolar Disorders study) during prospective follow-up.<sup>2</sup> Three healthy controls switched to BP-I during follow-up. These healthy

**Table 2. Demographic Characteristics of PEA–BP-I, ADHD, and Healthy Control Probands and Their First-Degree Relatives**

	PEA–BP-I	ADHD	Healthy Control	Total
<b>Probands</b>				
Sample size, No.	95	47	77	<b>219</b>
Age, mean (SD), y	10.8 (2.6)	9.5 (1.9)*†	11.1 (2.7)	10.6 (2.6)
Female sex, No. (%)	30 (31.6)	11 (23.4)†‡	32 (41.6)	73 (33.3)
Prepubertal, No. (%)	52 (54.7)	39 (83.0)†§	46 (59.7)	137 (62.6)
SES, mean (SD)	4.0 (0.9)	4.1 (0.8)	4.1 (0.8)	4.1 (0.8)
White race, No. (%)¶	79 (83.2)	42 (89.4)	68 (88.3)	189 (86.3)
Outpatient, No. (%)	95 (100)	47 (100)	77 (100)	219 (100)
<b>First-degree relatives of probands</b>				
Sample size, No.	284	143	263	<b>690</b>
Parents	187	92	154	433
Siblings	97	51	109	257
Age, mean (SD), y	35.0 (15.6)	33.0 (14.3)	32.1 (16.6)#	33.5 (15.7)
Parents	45.0 (6.7)	42.7 (5.6)**	44.9 (7.0)	44.5 (6.6)
Siblings	15.7 (7.4)	15.5 (6.1)	14.1 (5.8)	15.0 (6.5)
Female sex, No. (%)	137 (48.2)	80 (55.9)	128 (48.7)	345 (50.0)
White race, No. (%)¶	256 (90.1)	134 (93.7)	240 (91.3)	630 (91.3)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; PEA–BP-I, prepubertal and early-adolescent bipolar I disorder phenotype; SES, socioeconomic status.

\*Significantly younger than PEA–BP-I ( $t = 3.4$ ;  $P < .001$ ) and healthy control ( $t = 3.7$ ;  $P < .001$ ) probands.

†Proband age, sex, and pubertal status were controlled for in the Cox proportional hazards modeling.

‡Significantly more females than in the healthy control group ( $\chi^2 = 4.2$ ;  $P = .04$ ).

§Significantly more prepubertal participants than in the PEA–BP-I ( $\chi^2 = 10.9$ ;  $P = .001$ ) and healthy control ( $\chi^2 = 7.3$ ;  $P = .007$ ) groups.

||A score of 1 is lowest and 5 is highest.

¶Race was determined by participant self-report, and options were defined by the participant. This variable was assessed for comparability among proband groups.

#Significantly younger than relatives of PEA–BP-I probands ( $t = 2.1$ ;  $P = .04$ ).

\*\*Significantly younger than parents of PEA–BP-I ( $t = 3.0$ ;  $P = .003$ ) and healthy control ( $t = 2.7$ ;  $P = .008$ ) probands.

controls were not included because healthy control probands were obtained through a random survey, which was a different schema than the consecutive new case paradigm used for PEA–BP-I and ADHD probands. There were 7 sibling pairs, but only 1 sibling in each pair was used. All siblings with BP-I were used unless there were 2 siblings with BP-I. Then the one used was randomly selected. Figure 1 shows the family study flow of probands, and **Table 2** gives the demographic characteristics of probands and their first-degree relatives.

#### MR OF BP-I IN RELATIVES

Lifetime MR of BP-I was significantly greater in relatives of PEA–BP-I probands compared with relatives of ADHD and healthy control probands but was similar in relatives of ADHD and healthy control probands (**Table 3**). The MR of BP-I in relatives was significantly greater if relatives had either ADHD or ODD, CD, or ASP (**Figure 2**). The MR of BP-I was significantly higher in male vs female relatives (25.2 vs 13.0; hazard ratio=1.9;  $P = .001$ ).

#### PREVALENCE OF BP-I AND BP-I WITH ADHD IN RELATIVES OF PEA–BP-I VS HEALTHY CONTROL PROBANDS

The prevalences of BP-I (without ADHD) and BP-I with ADHD were significantly greater in relatives of PEA–BP-I vs healthy control probands (BP-I: 11.3% vs 1.9%;  $\chi^2 = 19.0$ ; and BP-I with ADHD: 16.9% vs 1.9%;  $\chi^2 = 35.1$ ;  $P < .001$  for both), demonstrating that comorbid and non-

comorbid BP-I occurred substantially more in relatives of the PEA–BP-I group than of the healthy control group, supporting that both types were more prevalent in PEA–BP-I relatives than in the population.

#### COMPARISON WITH STUDIES USING SIMILAR METHODS

Table 1 gives comparative data for direct-interview, controlled studies that used BP-I probands and SADS series diagnostic instruments. Studies that combined BP-I with schizoaffective probands were not included because relatives of schizoaffective probands are known to be at higher risk for BP-I.<sup>23</sup>

#### MR OF MDD IN RELATIVES

The MR of recurrent MDD was not significantly different between relatives of PEA–BP-I and ADHD probands, although the MRs in both these groups were significantly greater than the risk in relatives of healthy control probands (Table 3). The MR of recurrent MDD was significantly higher in female vs male relatives (25.5 vs 19.5; hazard ratio=1.9;  $P = .002$ ).

#### AGE AT ONSET OF BP-I AND ANTICIPATION

**Figure 3** shows that the age at onset of BP-I in parents was significantly younger if the parent had ADHD. Figure 3 also shows the earlier age at onset of BP-I in PEA–BP-I probands compared with their parents with BP-I.

**Table 3. Morbid Risk of BP-I, Recurrent MDD, and BP-I With Comorbid ADHD in 690 First-Degree Relatives of PEA-BP-I, ADHD, and Healthy Control Probands**

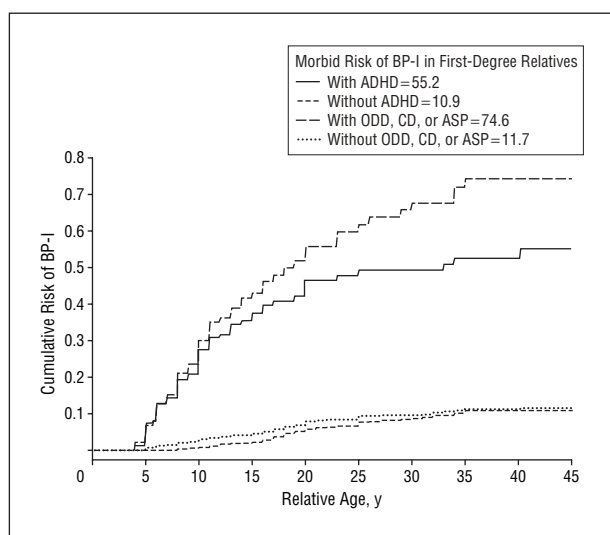
	MR (%)*			HR (95% CI)		
	First-Degree Relatives of			PEA-BP-I vs ADHD	PEA-BP-I vs Healthy Control	ADHD vs Healthy Control
	PEA-BP-I Probands	ADHD Probands	Healthy Control Probands			
<b>BP-I</b>						
Total first-degree relatives	34.0 (28.2)	13.8 (11.2)	4.7 (3.8)	2.7 (1.6-4.8)†	8.4 (4.3-16.4)†	2.4 (1.0-5.7)
Parents	33.4 (33.2)	14.1 (14.1)	4.6 (4.5)	2.7 (1.4-5.0)†	9.2 (4.2-20.2)†	2.4 (0.9-6.4)
Siblings	36.7 (18.6)	7.3 (5.9)	3.0 (2.8)	2.7 (0.7-9.8)	7.2 (2.1-24.8)‡	1.9 (0.3-11.3)
<b>Recurrent MDD (no BP)</b>						
Total first-degree relatives	30.9 (18.3)	26.2 (18.2)	12.0 (7.2)	0.9 (0.6-1.6)	2.4 (1.4-4.1)‡	2.3 (1.2-4.3)‡
Parents	30.9 (24.6)	23.2 (20.7)	10.3 (9.1)	1.1 (0.6-1.9)	2.9 (1.6-5.4)†	2.4 (1.1-5.0)
Siblings	11.8 (6.2)	25.3 (13.7)	12.9 (4.6)	0.5 (0.1-1.6)	1.2 (0.4-3.9)	2.1 (0.6-8.0)
<b>BP-I or recurrent MDD</b>						
Total first-degree relatives	65.5 (46.5)	39.7 (29.4)	16.6 (11.0)	1.8 (1.3-2.6)‡	5.3 (3.5-8.0)†	2.5 (1.5-4.1)†
Parents	65.4 (57.8)	37.2 (34.8)	14.9 (13.6)	2.0 (1.3-3.0)‡	6.2 (3.8-9.9)†	2.6 (1.4-4.7)‡
Siblings	48.8 (24.7)	34.3 (19.6)	15.7 (7.3)	1.2 (0.5-2.6)	3.5 (1.5-7.8)‡	2.2 (0.8-6.4)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BP-I, bipolar disorder; CI, confidence interval; HR, hazard ratio; MDD, major depressive disorder; MR, morbid risk; PEA-BP-I, prepubertal and early-adolescent BP-I phenotype.

\*Percentages indicate the proportion of relatives with the specified diagnosis.

† $P < .001$ .

‡ $P < .02$ .

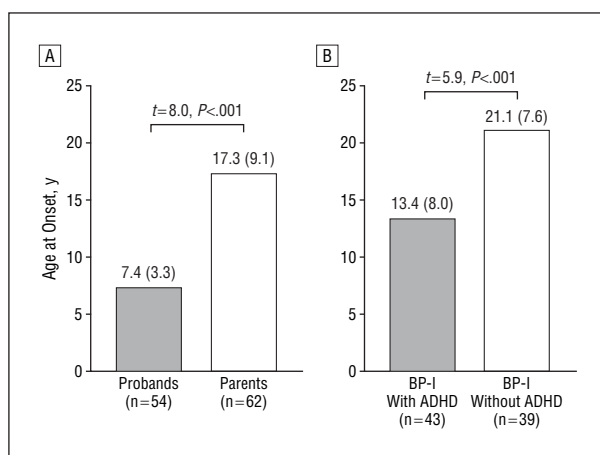


**Figure 2.** Morbid risk of bipolar I disorder (BP-I) in 690 first-degree relatives of prepubertal and early-adolescent BP-I, attention-deficit/hyperactivity disorder (ADHD), and healthy control probands by relative ADHD and by relative oppositional defiant disorder (ODD), conduct disorder (CD), or antisocial personality disorder (ASP) (ADHD: hazard ratio=8.5; 95% confidence interval, 5.7-12.6;  $P < .001$ ; ODD, CD, or ASP: hazard ratio=10.4; 95% confidence interval, 6.9-15.9;  $P < .001$ ).

#### PARENT OF ORIGIN EFFECT AND NUMBER OF PARENTS WITH BP-I

In families with only 1 parent with BP-I, there were 43 fathers with BP-I and 21 mothers with BP-I. The percentage of fathers with BP-I and mothers with BP-I who had BP-I proband offspring was not significantly different (69.8% vs 76.2%;  $\chi^2 = 0.3$ ;  $P = .59$ ).

There also was no significant effect of 2 vs 1 parent with BP-I on BP-I in siblings of probands: 18.9% of siblings of probands with 1 parent with BP-I had BP-I, and 28.6% of



**Figure 3.** Mean (SD) age at onset of bipolar I disorder (BP-I) in prepubertal and early-adolescent BP-I probands with at least 1 parent with BP-I and their parents with BP-I (A) and in parents who had BP-I with and without comorbid attention-deficit/hyperactivity disorder (ADHD) (B). The number of parents with BP-I is greater than the number of PEA-BP-I probands because some probands had 2 parents with BP-I.

siblings of probands with 2 parents with BP-I had BP-I. This difference was not statistically significant ( $\chi^2 = 0.4$ ;  $P = .54$ ).

#### SIBLING RECURRENCE RISK AND AGE AT ONSET IN PEA-BP-I PROBANDS VS THEIR SIBLINGS WITH BP-I

The sibling recurrence risk was 18.6% using all siblings of PEA-BP-I probands and 16.4% using the later-sibling method.

Mean  $\pm$  SD age at onset in PEA-BP-I probands who had at least 1 sibling with BP-I ( $8.2 \pm 3.5$  years) was not significantly different from that in their siblings ( $8.4 \pm 6.3$  years;  $t = 0.2$ ;  $P = .88$ ).

The validity of the interview methods is supported by the similarity of prevalences in the healthy control group to those reported in recent epidemiologic studies that used more extensive items for mania. Grant et al<sup>59</sup> reported a 5.0% lifetime prevalence of BP-I in 12- to 29-year-olds, which is similar to the 2.8% prevalence in siblings of the healthy control probands (Table 3). In the same study,<sup>59</sup> there was a lifetime prevalence of BP-I among 30- to 44-year-olds of 3.7%, similar to the 4.5% prevalence in parents of the healthy control group (Table 3). Furthermore, the rate of MDD in the healthy control sample was similar to the 13% to 16% reported in epidemiologic studies.<sup>59,60</sup>

Findings support that PEA-BP-I and adult BP-I are the same diathesis because BP-I and BP-I with ADHD occurred in the same families. The BP-I with ADHD diagnosis was a proxy for prepubertal age at onset (Figure 3).

Higher MR of BP-I in relatives with ADHD and ODD, CD, or ASP is consistent with the high comorbidity of these conditions in PEA-BP-I,<sup>6,13,18,19</sup> as is the earlier age at onset of BP-I in relatives with ADHD. Reasons for higher MR of BP-I in male relatives and of recurrent MDD in female relatives are not known. Consistent with the literature on ADHD,<sup>61</sup> the MR of recurrent MDD was not different for relatives of PEA-BP-I vs ADHD probands.

Anticipation, defined as earlier age at onset in more recent generations, was found, consistent with the study by Grigoriou-Serbanescu et al.<sup>62</sup> However, the multitude of caveats in interpreting these anticipation data<sup>63</sup> make this only a suggestive finding. These potential confounding biases include censoring (probands selected because of child age), information (younger age at onset may be from better information with earlier onset), and cohort effect (earlier age at onset in the more recently born).<sup>63</sup>

Greater familial aggregation in child vs adult BP-I, in addition to greater severity and early age at onset in PEA-BP-I,<sup>1,2,4,8-12</sup> is consistent with the Childs and Scriver<sup>64</sup> paradigm for illnesses across the medical spectrum. Reasons for the Childs and Scriver<sup>64</sup> paradigm are not known.

Differences in imprinting have been reported,<sup>65-68</sup> so the lack of imprinting in this sample is consistent with some<sup>65,67</sup> but not all<sup>66,68</sup> of the literature in this area.

The comparison studies in Table 1 used *Research Diagnostic Criteria for a Selected Group of Functional Disorders* (RDC).<sup>69</sup> This is likely comparable with data on relatives from the present study, as the category of probable in the Family Study Scoring Manual (see previously herein) is similar to that of the RDC.

Family study validation, using the criteria of Robins and Guze,<sup>70</sup> was supported because there was greater familial aggregation of BP-I in relatives of the PEA-BP-I probands compared with the ADHD and healthy control groups. Also, the ADHD and healthy control groups had similar familial aggregation. These data, added to those previously reported on unique symptoms of PEA-BP-I that do not overlap with those of other syndromes<sup>4</sup> and on longitudinal stability,<sup>2</sup> support the validation of PEA-BP-I and its differentiation from ADHD.<sup>1,4</sup>

The lack of an effect of 2 parents vs 1 parent with BP-I on the percentage of siblings with BP-I may be a type II

error due to the small number of families with 2 parents with BP-I (n=9). This contrasts with data<sup>23</sup> from an adult sample in which having 2 parents with BP-I, BP-II, unipolar depression, or schizoaffective disorder was associated with increased risk of BP-I in offspring.

The high sibling recurrence risk using 2 methods (16.4%-18.6%) supports that PEA-BP-I would be an informative sample for genetic studies. This risk was higher than that for another childhood-onset illness, autism (sibling risk, 0.0%-8.6%).<sup>57,71-78</sup>

The prevalence of schizophrenia among all relatives was zero, and the prevalence of schizoaffective disorder among relatives of PEA-BP-I probands was 1.4%, which is similar to rates in epidemiologic studies<sup>79</sup> and supports that schizophrenia is less of a differential diagnostic problem for child mania.

Sibling age at onset was not significantly different from that of the probands, consistent with findings from Bellivier et al.<sup>9</sup> However, some siblings are not yet through the age of risk, so this may not hold over time. Because, to our knowledge, there is no controlled, blindly rated, systematic study of BP-II in childhood, the relationship between MR of BP-I and child BP-II cannot yet be investigated.

## LIMITATIONS

As detailed previously herein, the sample is largely white and middle or upper class. Therefore, these findings may not generalize to populations with other demographic features. Also, for reasons discussed previously herein, the probands were outpatients, which differs from some adult studies.<sup>80,81</sup> In contrast to adults with BP-I, however, even very psychotic PEA-BP-I children are often outpatients, as evidenced by the high prevalence of psychosis (76.3%) in PEA-BP-I probands (n=257) from the National Institute of Mental Health-funded Phenomenology and Course of Pediatric Bipolar Disorders and Treatment of Early Age Mania (TEAM) outpatient studies.<sup>82</sup>

The family study findings from the PEA-BP-I probands may not generalize to other child BP phenotypes, such as the essentially adult type with short episodes and without ultradian cycling.<sup>15</sup> Longer current episodes seem to be the most common in child BP (eg, retrospective and prospective median, 52 weeks<sup>83</sup>; prospective mean  $\pm$  SD, 79.2  $\pm$  66.7 weeks<sup>2</sup>). It is not clear what the relationship of PEA-BP-I is to the Hudziak et al<sup>84</sup> Child Behavior Checklist BP phenotype. Most<sup>85-90</sup> but not all<sup>91</sup> studies using the Child Behavior Checklist have not found it to be a good diagnostic tool or screen for child BP. Differences in methods can also make comparisons with other child BP samples problematic.<sup>45</sup>

Underestimation of BP-I in relatives potentially occurred because of the need for either elation or grandiosity as 1 criterion and for a CGAS or GAS score in the definite impairment range because these criteria were not used by other investigators (Table 1). The relationship of these findings to epidemiologic samples is unknown.

## FUTURE STUDIES

Future studies will examine the relationship of relatives' diagnoses to longitudinal outcome in the ongoing

natural history study of PEA–BP-I, ADHD, and healthy control probands and to earlier reported predictors of outcome.<sup>2,30-32</sup> In addition, characteristics of adult relatives with BP-I will be compared with those in PEA–BP-I probands, especially regarding cycling and episode length. Finally, MRs for other *DSM-IV* diagnoses will be analyzed. Probands are being followed until adult age, when it will be possible to examine the familiarity of panic, substance use disorders, and BP-II.

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