

**Correction notice:** This article is the 2/12/2014 corrected version of the original article. An incorrect number of relatives and coding error led the authors to reanalyze the data, but the interpretation of findings and conclusions did not change. An explanation and detailed description of the corrections have been published.

# Further Evidence for Robust Familiality of Pediatric Bipolar I Disorder: Results From a Very Large Controlled Family Study of Pediatric Bipolar I Disorder and a Meta-Analysis

Janet Wozniak, MD; Stephen V. Faraone, PhD; MaryKate Martelon, MPH; Hannah N. McKillop, BA; and Joseph Biederman, MD

## ABSTRACT

**Objective:** To determine the risk for bipolar I disorder in first-degree relatives of children with *DSM-IV* bipolar I disorder via meta-analysis and expanded controlled study.

**Data Sources and Extraction:** Meta-Analysis. We searched the PubMed database for scientific articles published in the world literature in the English language through 2011. The keywords searched were *bipolar disorder*, *first-degree relatives*, *family study*, *control*. All online abstracts were reviewed and relevant full manuscripts were collected and reviewed. Citations were also examined for other potential relevant articles. We included only controlled family studies that examined rates of bipolar I disorder in all first-degree relatives (parents and siblings) of pediatric bipolar I probands and included only studies that had age- and sex-matched controls. Family history studies were excluded. Also excluded were studies that were not in English, did not report the rates of all first-degree relatives, and reported only bipolar spectrum rates. We also excluded family studies that included only adult probands. We conducted a meta-analysis of the 5 controlled family studies of pediatric bipolar I probands that met our search criteria using the random effects model of DerSimonian and Laird.

**Method:** Family Study. We greatly expanded our previous sample of *DSM-IV* bipolar I probands using structured diagnostic interviews. Our new study included 239 children satisfying full *DSM-IV* diagnostic criteria for bipolar I disorder ( $n=687$  first-degree relatives), 162 ADHD (without bipolar I disorder) probands ( $n=511$  first-degree relatives), and 136 healthy control (without ADHD or bipolar I disorder) probands ( $n=411$  first-degree relatives). We used the Kaplan-Meier cumulative failure function to calculate survival curves and cumulative, lifetime risk in relatives. Cox proportional hazard models were used to calculate the risk of bipolar I disorder in relatives.

**Results:** The pooled odds ratio for bipolar I disorder in relatives was estimated to be 6.96 (95% confidence interval [CI], 4.8 to 10.1). We also found first-degree relatives of bipolar I probands to be significantly more likely than first-degree relatives of both ADHD (hazards ratio [HR]=2.73; 95% CI, 1.66 to 4.50;  $P<.001$ ) and control probands (HR=2.71; 1.57 to 4.66;  $P<.001$ ) to have bipolar I disorder.

**Conclusions:** Our results document an increased familial risk for bipolar I disorder in relatives of pediatric probands with *DSM-IV* bipolar I disorder.

*J Clin Psychiatry* 2012;73(10):1328–1334  
© Copyright 2012 Physicians Postgraduate Press, Inc.

Submitted: March 8, 2012; accepted August 1, 2012; corrected February 12, 2014 (doi:10.4088/JCP.12m07770).

Corresponding author: Janet Wozniak, MD, Massachusetts General Hospital, 55 Fruit St, Yawkey 6A, Boston, MA 02114 (jwozniak@partners.org).

An emerging pediatric literature documents that pediatric bipolar disorder is prevalent and estimated to afflict more than 1% of children. Lewinsohn et al<sup>1</sup> reported a 1% prevalence of bipolar I disorder in a community sample of adolescents in Oregon. More recently, Merikangas et al<sup>2</sup> reported a 2.9% prevalence of bipolar disorder in a large epidemiologic sample of over 10,000 adolescents. A meta-analysis of international epidemiologic studies estimated the prevalence of pediatric bipolar disorder to be 1.8% and found no significant difference in prevalence between the United States and other countries<sup>3</sup>; that study also found no evidence of an increase in prevalence between 1985 and 2007. While these studies support the notion that a sizable minority of youth suffer from bipolar disorder, controversies remain as to the whether the pediatric form of bipolar disorder is a valid clinical entity.

Family studies are a cornerstone for the external validation of any psychiatric disorder<sup>4</sup> and can be useful in supporting the validity of pediatric bipolar disorder. Indeed, many twin studies of adults show that bipolar disorder is a highly heritable condition,<sup>5</sup> which suggests that if pediatric bipolar disorder is a valid entity, it too should be heritable. Although an emerging pediatric literature has begun to document the familiality of pediatric bipolar disorder, uncertainties remain as to the magnitude of this effect.<sup>6,7</sup>

The main aims of the present study were 2-fold. First, we sought to examine the magnitude of the familiality of pediatric bipolar disorder as documented in the extant literature. To this end, we conducted a meta-analysis by aggregating data from all published controlled family studies of pediatric bipolar disorder. Second, we aimed to extend our previous work examining the familiality of pediatric onset bipolar disorder by substantially expanding our original sample of youth with bipolar I disorder and their first-degree relatives. We used as comparators probands and relatives of an age and sex matched group of youth with attention-deficit/hyperactivity disorder (ADHD) and similarly matched healthy control (controls) youth without bipolar I disorder or ADHD, assessed with similar research methodology. We hypothesized that relatives of youth with bipolar I disorder would have higher rates of bipolar I than relatives of ADHD youth and control youth. To the best of our knowledge, this is the largest family study of pediatric bipolar to date in the research literature.

- By providing information that is one step removed from a diagnosis in an affected child, family studies remain the cornerstone for the validation of complex psychiatric disorders such as pediatric bipolar disorder.
- By documenting the high familiarity of pediatric bipolar disorder, our study provides strong support for the validity of pediatric bipolar disorder.
- By providing evidence for the validity of pediatric bipolar disorder, this work will support efforts in the community for the identification and treatment of children manifesting a clinical picture consistent with the diagnosis of bipolar disorder.

## METHOD

### Meta Analysis

We searched the PubMed database for scientific articles published in the world literature in the English language. The keywords searched were *bipolar disorder, first-degree relatives, family study, control*. All online abstracts were reviewed and relevant full manuscripts were collected and reviewed. Citations were also examined for other potential relevant articles. We included only controlled family studies that examined rates of bipolar I disorder in all first-degree relatives (parents and siblings) of pediatric bipolar I probands and included only studies that had age- and sex-matched controls. Family history studies were excluded. Also excluded were studies that were not in English, did not report the rates of all first-degree relatives, and reported only bipolar spectrum rates. We also excluded family studies that included only adult probands.

### Family Study

**Subjects.** This study represents a large expansion of our previous sample of 157 families of pediatric probands with bipolar I disorder diagnosis ascertained through NIMH grants.<sup>8</sup> The expanded sample was possible through the support of a philanthropic grant to increase the sample size using the same methodology (all of these funding sources are noted in the acknowledgments section).

As previously described, families were recruited and assessed at the Clinical and Research Program in Pediatric Psychopharmacology and Adult ADHD at Massachusetts General Hospital based on the presence of a diagnosis of bipolar I disorder in proband youth 6–17 years of age of both sexes.<sup>8</sup> Comparators were youth with ADHD and controls without ADHD or bipolar disorder of similar age and sex along with their first-degree relatives.<sup>9–12</sup> All studies used the same assessment methodology regardless of the disorder used to classify probands as cases. All study procedures were reviewed and approved by the subcommittee for human subjects of our institution. All subjects' parents or guardians signed written informed consent forms and children older than 7 years of age signed age-appropriate written assent forms.

For this study, we recruited an additional 82 probands and their 200 first-degree relatives for a total of 239 bipolar I probands and their 687 first-degree relatives. From 522 families participating in our case-control ADHD family studies, we randomly selected 162 nonbipolar ADHD (511 first-degree relatives) and 136 nonbipolar, non-ADHD control probands (411 first-degree relatives) so that the age and gender distribution was similar to that of the bipolar I probands. ADHD probands with comorbid bipolar disorder were not included in the present analyses.

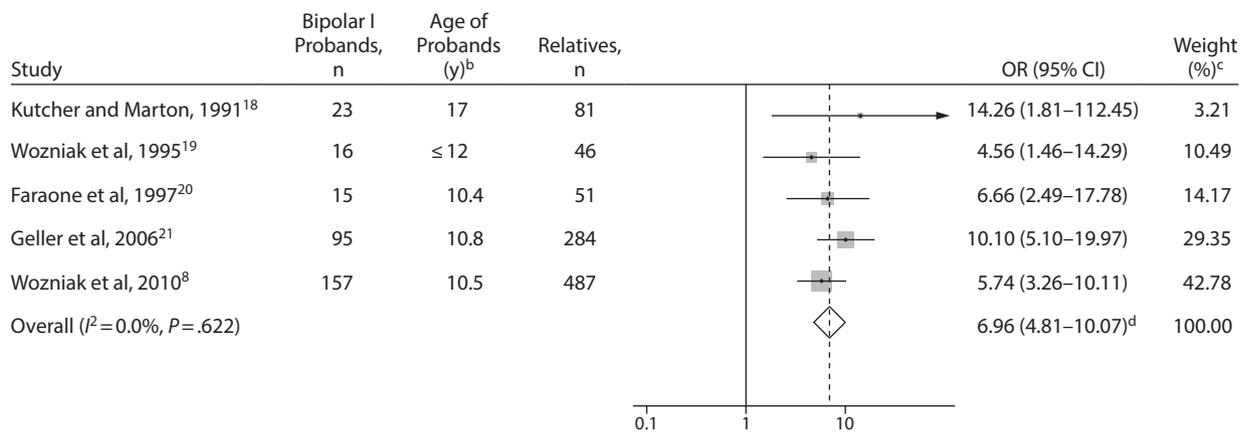
**Ascertainment method.** Potential bipolar I probands were ascertained from our clinical service, referrals from local clinicians, or self-referral in response to advertisements. To avoid biasing our sample toward familial cases of bipolar disorder, all probands were ascertained blind to the diagnostic status of their relatives. Subjects were administered a phone screen, reviewing symptoms of *DSM-IV* bipolar I disorder and, if criteria were met, were scheduled for a face-to-face structured diagnostic interview. In addition to the structured diagnostic interview, the principal investigator (J.W.) met with each proband and his or her parents for a clinical interview in order to confirm the diagnosis of bipolar disorder using the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) mania module. We have published data on the convergence of these clinical interviews with our structured interview diagnosis on the first 69 cases. We report 97% agreement between the structured interview and clinical diagnosis in this analysis of 69 children.<sup>13</sup>

As previously reported,<sup>8–10</sup> ADHD cases were identified from either a major academic medical center, where we selected ADHD subjects from referrals to a pediatric psychopharmacology program, or from a health maintenance organization, in which ADHD subjects were selected from pediatric clinic outpatients. Controls were ascertained from outpatients referred for routine physical examinations to pediatric medical clinics at each setting, identified from their computerized records as not having ADHD. Screening procedures were similar to those described for the recruitment of the bipolar probands with the exception that we queried about ADHD (and not bipolar disorder) in the initial telephone screening and each proband was not assessed clinically. No co-occurring disorders in probands or relatives were excluded.

**Diagnostic procedures.** Psychiatric assessments of subjects younger than 18 years were made with the K-SADS-E (epidemiologic version),<sup>14</sup> and assessments of adult family members were made with the Structured Clinical Interview for *DSM-IV* (SCID),<sup>15</sup> supplemented with modules from the K-SADS-E to cover childhood disorders. Diagnoses were based on independent interviews with mothers and direct interviews with children older than 12 years of age. Data were combined such that endorsement of a diagnosis by either report resulted in a positive diagnosis.

Interviews with both the K-SADS-E and SCID were conducted by extensively trained and supervised psychometricians with undergraduate degrees in psychology. This training involved several weeks of classroom instruction

**Figure 1. Meta-Analysis of Previous Family Studies<sup>a</sup>**



<sup>a</sup>Small dot indicates estimated odds ratio (OR), the size of the square surrounding the dot is proportional to the sample size, and the horizontal line indicates the 95% confidence interval (CI). Odds ratios greater than 1 indicate greater transmission of bipolar I disorder from relatives of bipolar I probands compared with control probands.

<sup>b</sup>Expressed as mean values except for Wozniak et al.<sup>19</sup>

<sup>c</sup>Weights are from random-effects analysis.

<sup>d</sup> $P < .001$ .

of interview mechanics, diagnostic criteria, and coding algorithms. They also observed interviews by experienced raters and clinicians and were observed while conducting interviews during the final training period. In addition, all diagnoses were reviewed by a sign-off committee of experienced board-certified child and adolescent psychiatrists or clinical psychologists. The committee members were blind to the subjects' ascertainment status, ascertainment site, and data collected from other family members. We computed  $\kappa$  coefficients of agreement by having experienced clinicians diagnose subjects from audiotaped interviews made by the assessment staff. Based on 500 interviews, the median  $\kappa$  coefficient between raters and clinicians was 0.99. For individual diagnoses, the  $\kappa$  values were ADHD (0.88), conduct disorder (1.0), major depression (1.0), mania (0.95), separation anxiety (1.0), agoraphobia (1.0), panic (0.95), substance use disorder (1.0), and tics/Tourette's (0.89). The median agreement between individual clinicians and the clinical review committee was 0.87 and for individual diagnoses was ADHD (1.0), conduct disorder (1.0), major depression (1.0), bipolar (0.78), separation anxiety (0.89), agoraphobia (0.80), panic (0.77), substance use disorder (1.0), and tics/Tourette's (0.68).

Children and adolescents were diagnosed with bipolar I disorder according to *DSM-IV* criteria. The *DSM-IV* requires subjects to meet criterion A for a distinct period of extreme and persistently elevated, expansive or irritable mood lasting at least 1 week, plus criterion B, manifested by 3 (4 if the mood is irritable only) of 7 symptoms during the period of mood disturbance. To ensure that the B criterion symptoms were concurrent with A criterion mood disturbance, subjects were directed to focus on the worst or most impairing episode of mood disturbance while being assessed for the presence of the confirmatory B criterion symptoms. That is, the subject was asked to consider the time during which the screen was at its worst for the

purpose of determining whether the remaining symptoms were also evident at the same time as the screening item. Also recorded was the onset of first episode, the number of episodes, offset of last episode, and total duration of illness. Any subject meeting criteria for bipolar II disorder or bipolar disorder not otherwise specified was not included in this study. To gauge a distinct episode, our interviewers asked for "a distinct period (of at least 1 week) of extreme and persistently elevated, expansive or irritable mood" and further required that the irritability endorsed in this module is "super" and "extreme."

**Statistical analysis.** Our meta-analysis used the random effects model of DerSimonian and Laird<sup>16</sup> as implemented in Stata 12.0. We used the  $I^2$  index to assess the heterogeneity of effect sizes.<sup>17</sup> Its value lies between 0 and 100 and estimates the percentage of variation among effect sizes that can be attributed to heterogeneity. A significant  $I^2$  suggests that the effect sizes analyzed are not estimating the same population effect size.

For our family study, differences in demographics and clinical characteristics were assessed using ANOVA for continuous outcomes, Pearson  $\chi^2$  for binary outcomes, and Kruskal-Wallis for socioeconomic status (SES). The Kaplan-Meier cumulative failure function was used to calculate survival curves and cumulative lifetime risk in relatives. The cumulative failure function was calculated based on the ages at onset for the individual disorders for affected subjects and the age at the time of interview for unaffected subjects. The individual disorders were assessed during the structured diagnostic interview. Cox proportional hazard models were used to calculate the risk of bipolar disorder as well as other psychiatric disorders in relatives. All diagnoses reported represent lifetime rates. Data are expressed as mean  $\pm$  SD unless otherwise specified. All tests were 2-tailed, and our  $\alpha$  level was set at .05 for all analyses, unless otherwise noted. We calculated all statistics using STATA, version 12.0.

**Table 1. Clinical and Demographic Characteristics (N = 2,146)<sup>a</sup>**

	Bipolar I Families	ADHD Families	Control Families	Statistic
<b>Probands</b>	<b>n = 239</b>	<b>n = 162</b>	<b>n = 136</b>	
Age, y	10.7 ± 3.3	10.6 ± 3.0	10.7 ± 3.0	$F_{2,534} = 0.03, P = .97$
Gender, n (%) male	174 (73)	121 (75)	99 (73)	$\chi^2_2 = 0.21, P = .9$
Past GAF score	40.7 ± 5.8	50.7 ± 7.3	70.5 ± 8.5	$F_{2,532} = 778.53, P < .001$
Current GAF score	46.6 ± 5.9	57.4 ± 8.2	73.3 ± 7.3	$F_{2,532} = 628.35, P < .001$
<b>Parents</b>	<b>n = 444</b>	<b>n = 323</b>	<b>n = 269</b>	
Age, y	42.8 ± 6.3	41.3 ± 6.4	41.6 ± 5.8	$F_{2,1032} = 6.16, P = .0022$
Gender, n (%) male	212 (48)	161 (50)	133 (49)	$\chi^2_2 = 0.38, P = .83$
Past GAF score	51.8 ± 9.8	57.0 ± 12.6	63.5 ± 12.4	$F_{2,1031} = 88.61, P < .001$
Current GAF score	63.4 ± 7.7	68.5 ± 9.5	73.0 ± 7.9	$F_{2,983} = 110.25, P < .001$
<b>Siblings</b>	<b>n = 243</b>	<b>n = 188</b>	<b>n = 142</b>	
Age, y	12.3 ± 4.6	13.8 ± 5.9	12.9 ± 5.1	$F_{2,570} = 4.14, P = .016$
Gender, n (%) male	112 (46)	103 (55)	74 (52)	$\chi^2_2 = 3.42, P = .18$
Past GAF score	57.5 ± 9.6	61.8 ± 12.0	66.0 ± 10.7	$F_{2,570} = 28.27, P < .001$
Current GAF score	62.9 ± 7.7	67.9 ± 10.8	71.1 ± 8.4	$F_{2,569} = 41.01, P < .001$
<b>Total</b>	<b>n = 926</b>	<b>n = 673</b>	<b>n = 547</b>	
Socioeconomic status <sup>b</sup>	1.8 ± 0.9	1.8 ± 1.0	1.5 ± 0.7	$\chi^2_2 = 9.33, P = .009$
Race/ethnicity, n (%)				
White	877 (95)	667 (99)	536 (98)	$\chi^2_6 = 41.19, P < .001$
African-American	32 (3)	6 (1)	7 (1)	
More than 1	15 (2)	0 (0)	0 (0)	
Unknown	2 (<1)	0 (0)	4 (1)	

<sup>a</sup>Values expressed as mean ± SD unless otherwise noted.

<sup>b</sup>For socioeconomic status, 1 = most advantaged, 5 = most disadvantaged.

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, GAF = Global Assessment of Functioning.

## RESULTS

### Meta Analysis Results

Our literature search identified 5 manuscripts that met our inclusion and exclusion criteria.<sup>8,18-21</sup> The meta-analysis of these studies is presented in Figure 1. In the figure, the small dot gives the estimated odds ratio, the size of the square surrounding the dot is proportional to the sample size, and the horizontal line gives the 95% confidence interval. Odds ratios greater than 1 indicate greater transmission of bipolar I disorder from relatives of bipolar I probands compared with control probands. As Figure 1 shows, all studies reported significant differences in the rates of bipolar I disorder in the first-degree relatives of pediatric bipolar I probands when compared with rates in relatives of controls. The pooled odds ratio of risk for bipolar I disorder to relatives of pediatric bipolar I probands was estimated to be 6.96 (95% CI, 4.8 to 10.1). There was no statistically significant heterogeneity among studies ( $I^2 = 0\%$ ,  $P = .62$ ) suggesting that each study was estimating a common odds ratio.

### Expanded Sample Family Study Results

Clinical and demographic characteristics are presented in Table 1. We found statistically significant differences in the ethnic and sociodemographic composition between groups. The control families had the highest SES and the bipolar I families had the most ethnic diversity. As a result, all subsequent analyses were adjusted for SES and ethnicity. Siblings of bipolar I probands were significantly younger compared to the siblings of ADHD and control probands. While bipolar I probands had a significantly lower GAF

score than the ADHD and control probands, there were no statistically significant differences between the age and sex distributions of the proband groups. Relatives of the bipolar I probands had significantly lower GAF scores compared to relatives of ADHD and control probands and were significantly older than the relatives of ADHD and control probands. We found no other significant differences in demographic characteristics of relatives.

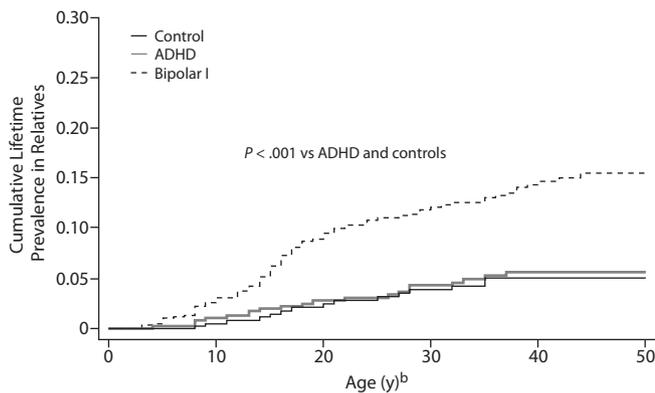
### Risk for Bipolar I Disorder in First-Degree Relatives

The age-dependent cumulative, lifetime prevalence risk of bipolar I disorder in relatives is illustrated in Figure 2. First-degree relatives of bipolar I probands were significantly more likely than first-degree relatives of both ADHD (hazard ratio [HR] = 2.73; 95% confidence interval [CI], 1.66 to 4.50;  $P < .001$ ) and control probands (HR = 2.71; 95% CI, 1.57 to 4.66;  $P < .001$ ) to have bipolar I disorder (Figure 2). In contrast, relatives of ADHD probands were not at an increased risk for bipolar I disorder compared to relatives of control probands (HR = 0.99; 95% CI, 0.51 to 1.92;  $P = .98$ ). These findings remained significant after controlling for psychiatric comorbidity in probands (disruptive behavior disorders/antisocial personality disorder, major depression, multiple ( $\geq 2$ ) anxiety disorders, and substance [drug or alcohol] use disorders).

## DISCUSSION

To the best of our knowledge, this study represents the largest controlled, blinded, direct interview family study of pediatric bipolar disorder to date. This new expanded sample increased by over 50% (N = 239) our previous report of 157

**Figure 2. Familial Risk of Bipolar I Disorder in First-Degree Relatives of Pediatric Bipolar I Probands, ADHD Probands, and Control Probands<sup>a</sup>**



<sup>a</sup>Bipolar I, n = 687 relatives in 239 families; ADHD, n = 511 relatives in 162 families; controls, n = 411 relatives in 136 families.

<sup>b</sup>Ages at onset for individual disorders were assessed during the structured diagnostic interview.

Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

bipolar I probands. In this much expanded sample of pediatric bipolar I probands, we replicated our initial findings documenting that rates of bipolar I disorder were significantly greater in the first-degree relatives of pediatric probands with bipolar I disorder than in the first-degree relatives of ADHD and control probands. These results, coupled with those of the meta-analysis of the extant literature, provide strong support for the familiarity of bipolar I disorder, which provides further support for the validity of pediatric bipolar I disorder as a diagnostic entity.

As shown in the meta-analysis, our findings documenting high level of familiarity of pediatric bipolar I disorder are consistent with the prior pediatric literature on the subject. They are also consistent with family studies of adult bipolar I probands that document high levels of heritability of bipolar disorder in adults that range from 59%–87%.<sup>22</sup>

In our meta-analysis, the studies that met our criteria (direct interview, controlled, all first-degree relatives included) reported odd ratios indicating that the risk for bipolar I disorder to relatives of bipolar I probands is 4 to 14 times greater than the risk to relatives of nonbipolar probands. In addition to finding significant familial transmission in all prior studies, we found no evidence of heterogeneity in the magnitude of familial transmission. This finding can be seen in Figure 1, which shows that the confidence intervals for the odds ratios overlap among the different studies. This lack of differences between studies suggests that the familial transmission of bipolar disorder cannot be accounted for by the diagnostic traditions of a single group of investigators. While all research groups employ standardized structured diagnostic techniques, they differ in the interviews they employ, which may lead to differences in sample characteristics. For example, there are differing approaches to diagnosing bipolar I disorder in the presence of ADHD<sup>23</sup> due to concerns about overlapping symptoms and the use of irritability as a mood criterion for diagnosing bipolar I disorder in youth.<sup>24</sup>

As in our previous report, the familial transmission of bipolar I disorder in this expanded sample was statistically significant

even when controlling for psychiatric comorbidity in the probands. Aside from the Geller et al<sup>21</sup> study, which controlled for the presence of ADHD, other family studies did not report findings adjusted for psychiatric comorbidity. This finding further supports the hypothesis that bipolar I disorder is not an alternate expression of a different disorder. The lack of difference between the ADHD and control families in the prevalence of bipolar I disorder is consistent with our prior work suggesting that, in the absence of comorbid bipolar disorder, ADHD does not share susceptibility genes with bipolar disorder.<sup>20,25,26</sup>

Our family study results and those of the meta-analysis add to an emerging literature over the last 2 decades that provides compelling support for the validity of pediatric bipolar disorder as a diagnostic entity. Clinical studies have documented the unique diagnostic features associated with this disorder across different clinical and research centers in this country and abroad, reporting high levels of severe and persistent irritability and associated morbidity and disability.<sup>3,27–30</sup> Large-scale follow-up studies have documented persistence of pediatric bipolar disorder into adolescent and young adult years.<sup>30–32</sup> A recent comprehensive review of the extant pharmacologic literature of pediatric bipolar disorder treatments comprises close to 3,000 bipolar youth who had participated in clinical trials. That review documented the safety and efficacy of antimanic treatments for pediatric bipolar disorders.<sup>33</sup> Emerging neuroimaging and genetic studies have also begun to describe neurobiological correlates of pediatric bipolar disorder as well.<sup>7,34–38</sup>

Our findings should be considered in the context of methodological limitations. Although we used lay interviewers with undergraduate degrees in psychology, rather than clinician raters, these raters were extensively trained to high levels of interrater reliability. Although we did not administer structured diagnostic interviews directly to children younger than age 12, the diagnosis of bipolar I disorder in probands was corroborated by clinical assessment by an expert child and adolescent psychiatrist.<sup>13</sup> Although we relied for comparison on existing samples of ADHD and non-ADHD families, these were recruited from the same catchment area and were assessed using the same assessment methods. Because this sample was clinically referred and primarily white, these results may not generalize to nonreferred children or to families of other ethnic groups.

Despite these limitations, results from this large family study and meta-analysis provide compelling evidence for the familiarity of pediatric bipolar I disorder and, thus, robust support for the validity of pediatric onset bipolar I disorder as a diagnostic entity.

**Author affiliations:** Clinical and Research Program in Pediatric Psychopharmacology and Adult ADHD at Massachusetts General Hospital (Drs Wozniak and Biederman and Mss Martelon and McKillop); Department of Psychiatry at Harvard Medical School (Drs Wozniak and Biederman), Boston, Massachusetts; and Departments of Psychiatry and of Neuroscience & Physiology, SUNY Upstate Medical University, Syracuse, New York (Dr Faraone).

**Author contributions:** Dr Wozniak had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr Wozniak substantially contributed to the conception and design, drafting, critical revision of the intellectual content, supervision, administrative/technical/material support, and funding for this manuscript. Dr Faraone substantially contributed to the conception and design, data analysis and interpretation, critical revision of the intellectual content, statistical analysis, and funding for this manuscript. Ms Martelon substantially contributed to the data analysis and interpretation, drafting, and statistical analysis for this manuscript. Ms McKillop substantially contributed to the data analysis and interpretation, drafting, and administrative/technical/material support for this manuscript. Dr Biederman substantially contributed to the conception and design, drafting, critical revision of the intellectual content, administrative/technical/material support, supervision, and funding for this manuscript.

**Potential conflicts of interest:** In 2011, **Dr Wozniak** received research support from McNeil and Shire. In the past, she has received research support, consultation fees or speaker's fees from: Eli Lilly, Janssen, Johnson and Johnson, McNeil, Pfizer, Shire. She is the author of the book *Is Your Child Bipolar*, published May 2009, Bantam Books. In 2011, her spouse John Winkelman MD, PhD received consultation fees from Pfizer, UCB, Zeo, and Sunovion. He received research support from GlaxoSmithKline. In the past, he has received research support, consultation fees or speaker's fees from: Axon Laboratories, Boehringer-Ingelheim, Covance, Cephalon, Eli Lilly, GlaxoSmithKline, Impax, Jazz Pharmaceuticals, King, Luitpold, Novartis, Neurogen, Novadel Pharma, Pfizer, Sanofi-Aventis, Sepracor, Sunovion, Takeda, UCB (Schwarz) Pharma, Wyeth, Zeo. In the past year, **Dr Faraone** received consulting income and research support from Shire and Alcobra and research support from the National Institutes of Health (NIH). In previous years, he received consulting fees or was on Advisory Boards or participated in continuing medical education programs sponsored by: Shire, McNeil, Janssen, Novartis, Pfizer and Eli Lilly. **Dr Faraone** receives royalties from books published by Guilford Press: *Straight Talk About Your Child's Mental Health* and Oxford University Press: *Schizophrenia: The Facts*. **Dr Biederman** is currently receiving research support from the following sources: Elminda, Janssen, McNeil, and Shire. In 2011, **Dr Biederman** gave a single unpaid talk for Juste Pharmaceutical Spain, received honoraria from the MGH Psychiatry Academy for a tuition-funded CME course, and received an honorarium for presenting at an international scientific conference on ADHD. He also received an honorarium from Cambridge University Press for a chapter publication. **Dr Biederman** received departmental royalties from a copyrighted rating scale used for ADHD diagnoses, paid by Eli Lilly, Shire, and AstraZeneca; these royalties are paid to the Department of Psychiatry at MGH. In 2010, **Dr Biederman** received a speaker's fee from a single talk given at Fundación Dr. Manuel Camelo A.C. in Monterrey Mexico. **Dr Biederman** provided single consultations for Shionogi Pharma Inc and Cipher Pharmaceuticals Inc; the honoraria for these consultations were paid to the Department of Psychiatry at the MGH. **Dr Biederman** received honoraria from the MGH Psychiatry Academy for a tuition-funded CME course. In previous years, **Dr Biederman** received research support, consultation fees, or speaker's fees for/from the following additional sources: Abbott, Alza, AstraZeneca, Boston University, Bristol Myers Squibb, Celltech, Cephalon, Eli Lilly, Esai, Fundacion Areces (Spain), Forest, Glaxo, Gliatech, Hastings Center, Janssen, McNeil, Medice Pharmaceuticals (Germany), Merck, MMC Pediatric, NARSAD, NIDA, New River, NICHD, NIMH, Novartis, Noven, Neurosearch, Organon, Otsuka, Pfizer, Pharmacia, Phase V Communications, Physicians Academy, The Prechter Foundation, Quantia Communications, Reed Exhibitions, Shire, the Spanish Child Psychiatry Association, The Stanley Foundation, UCB Pharma Inc., Veritas, and Wyeth. **Mss Martelon** and **McKillop** report no conflict of interest.

**Funding/support:** This work was supported by National Institutes of Health grants K08MH001503 and R01MH066237 to Dr Wozniak and R01MH050657 and R01HD036317 to Dr Biederman. This work was also supported by a grant from the Heinz C. Prechter Bipolar Research Fund, the support of members of the MGH Pediatric Psychopharmacology Council, and the Susan G. Berk Endowed Fund for Juvenile Bipolar Disorder.

**Role of the sponsor:** The study sponsors had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

## REFERENCES

- Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity, and course. *J Am Acad Child Adolesc Psychiatry*. 1995;34(4):454-463.
- Merikangas KR, He JP, Burstein M, et al. Lifetime prevalence of mental disorders in US adolescents: results from the National Comorbidity Survey Replication—Adolescent Supplement (NCS-A). *J Am Acad Child Adolesc Psychiatry*. 2010;49(10):980-989.
- Van Meter AR, Moreira AL, Youngstrom EA. Meta-analysis of epidemiologic studies of pediatric bipolar disorder. *J Clin Psychiatry*. 2011;72(9):1250-1256.
- Robins E, Guze SB. Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. *Am J Psychiatry*. 1970;126(7):983-987.
- Tsuang MT, Faraone SV. Twin studies. In: Tsuang MT, Faraone SV, eds. *The Genetics of Mood Disorders*. Baltimore, MD: The Johns Hopkins University Press; 1990:68-93.
- Althoff RR, Faraone SV, Rettew DC, et al. Family, twin, adoption, and molecular genetic studies of juvenile bipolar disorder. *Bipolar Disord*. 2005;7(6):598-609.
- Faraone SV, Glatt SJ, Tsuang MT. The genetics of pediatric-onset bipolar disorder. *Biol Psychiatry*. 2003;53(11):970-977.
- Wozniak J, Faraone SV, Mick E, et al. A controlled family study of children with DSM-IV bipolar-I disorder and psychiatric co-morbidity. *Psychol Med*. 2010;40(7):1079-1088.
- Biederman J, Faraone SV, Keenan K, et al. Further evidence for family-genetic risk factors in attention deficit hyperactivity disorder: patterns of comorbidity in probands and relatives psychiatrically and pediatrically referred samples. *Arch Gen Psychiatry*. 1992;49(9):728-738.
- Biederman J, Faraone SV, Mick E, et al. Clinical correlates of ADHD in females: findings from a large group of girls ascertained from pediatric and psychiatric referral sources. *J Am Acad Child Adolesc Psychiatry*. 1999;38(8):966-975.
- Biederman J, Monuteaux MC, Mick E, et al. Psychopathology in females with attention-deficit/hyperactivity disorder: a controlled, five-year prospective study. *Biol Psychiatry*. 2006;60(10):1098-1105.
- Biederman J, Monuteaux MC, Mick E, et al. Young adult outcome of attention deficit hyperactivity disorder: a controlled 10-year follow-up study. *Psychol Med*. 2006;36(2):167-179.
- Wozniak J, Monuteaux M, Richards J, et al. Convergence between structured diagnostic interviews and clinical assessment on the diagnosis of pediatric-onset mania. *Biol Psychiatry*. 2003;53(11):938-944.
- Orvaschel H. *Schedule for Affective Disorder and Schizophrenia for School-Age Children Epidemiologic Version*. 5th ed. Ft Lauderdale, FL: Nova Southeastern University, Center for Psychological Studies; 1994.
- First M, Spitzer R, Gibbon M, et al. *Structured Clinical Interview for DSM-IV Axis I Disorders*. Washington, DC: American Psychiatric Press; 1997.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188.
- Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560.
- Kutcher S, Marton P. Affective disorders in first-degree relatives of adolescent onset bipolars, unipolars, and normal controls. *J Am Acad Child Adolesc Psychiatry*. 1991;30(1):75-78.
- Wozniak J, Biederman J, Mundy E, et al. A pilot family study of childhood-onset mania. *J Am Acad Child Adolesc Psychiatry*. 1995;34(12):1577-1583.
- Faraone SV, Biederman J, Mennin D, et al. Attention-deficit hyperactivity disorder with bipolar disorder: a familial subtype? *J Am Acad Child Adolesc Psychiatry*. 1997;36(10):1378-1387, discussion 1387-1390.
- Geller B, Tillman R, Bolhofner K, et al. Controlled, blindly rated, direct-interview family study of a prepubertal and early-adolescent bipolar I disorder phenotype: morbid risk, age at onset, and comorbidity. *Arch Gen Psychiatry*. 2006;63(10):1130-1138.
- Tsuang MT, Faraone SV. *The Genetics of Mood Disorders*. Baltimore, MD: The Johns Hopkins University Press; 1990.
- Youngstrom EA, Arnold LE, Frazier TW. Bipolar and ADHD comorbidity: both artifact and outgrowth of shared mechanisms. *Clin Psychol (New York)*. 2010;17(4):350-359.
- Leibenluft E. Severe mood dysregulation, irritability, and the diagnostic boundaries of bipolar disorder in youths. *Am J Psychiatry*. 2011;168(2):129-142.
- Faraone SV, Biederman J, Mennin D, et al. Bipolar and antisocial disorders among relatives of ADHD children: parsing familial subtypes of illness. *Am J Med Genet*. 1998;81(1):108-116.
- Faraone SV, Biederman J, Monuteaux MC. Attention deficit hyperactivity disorder with bipolar disorder in girls: further evidence for a familial subtype? *J Affect Disord*. 2001;64(1):19-26.

27. Findling RL, Gracious BL, McNamara NK, et al. Rapid, continuous cycling and psychiatric co-morbidity in pediatric bipolar I disorder. *Bipolar Disord*. 2001;3(4):202–210.
28. Biederman J, Faraone SV, Wozniak J, et al. Clinical correlates of bipolar disorder in a large, referred sample of children and adolescents. *J Psychiatr Res*. 2005;39(6):611–622.
29. Birmaher B, Axelson D, Strober M, et al. Clinical course of children and adolescents with bipolar spectrum disorders. *Arch Gen Psychiatry*. 2006;63(2):175–183.
30. Geller B, Tillman R, Bolhofner K, et al. Child bipolar I disorder: prospective continuity with adult bipolar I disorder; characteristics of second and third episodes; predictors of 8-year outcome. *Arch Gen Psychiatry*. 2008;65(10):1125–1133.
31. Wozniak J, Petty CR, Schreck M, et al. High level of persistence of pediatric bipolar-I disorder from childhood onto adolescent years: a four year prospective longitudinal follow-up study. *J Psychiatr Res*. 2011;45(10):1273–1282.
32. Birmaher B, Axelson D, Goldstein B, et al. Four-year longitudinal course of children and adolescents with bipolar spectrum disorders: the Course and Outcome of Bipolar Youth (COBY) study. *Am J Psychiatry*. 2009;166(7):795–804.
33. Liu HY, Potter MP, Woodworth KY, et al. Pharmacologic treatments for pediatric bipolar disorder: a review and meta-analysis. *J Am Acad Child Adolesc Psychiatry*. 2011;50(8):749–762. e39.
34. Mick E, Wozniak J, Wilens TE, et al. Family-based association study of the BDNF, COMT and serotonin transporter genes and DSM-IV bipolar-I disorder in children. *BMC Psychiatry*. 2009;9(1):2.
35. Doyle AE, Biederman J, Ferreira MA, et al. Suggestive linkage of the child behavior checklist juvenile bipolar disorder phenotype to 1p21, 6p21, and 8q21. *J Am Acad Child Adolesc Psychiatry*. 2010;49(4):378–387.
36. Pavuluri MN, Passarotti AM, Harral EM, et al. An fMRI study of the neural correlates of incidental versus directed emotion processing in pediatric bipolar disorder. *J Am Acad Child Adolesc Psychiatry*. 2009;48(3):308–319.
37. Moore CM, Biederman J, Wozniak J, et al. Mania, glutamate/glutamine and risperidone in pediatric bipolar disorder: a proton magnetic resonance spectroscopy study of the anterior cingulate cortex. *J Affect Disord*. 2007;99(1–3):19–25.
38. Moore CM, Frazier JA, Glod CA, et al. Glutamine and glutamate levels in children and adolescents with bipolar disorder: a 4.0-T proton magnetic resonance spectroscopy study of the anterior cingulate cortex. *J Am Acad Child Adolesc Psychiatry*. 2007;46(4):524–534.

*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.