

Lifetime Psychiatric Disorders in School-aged Offspring of Parents With Bipolar Disorder

The Pittsburgh Bipolar Offspring Study

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Context: Whether offspring of parents with bipolar disorder (BP) are at specifically high risk to develop BP and other psychiatric disorders has not been adequately studied.

Objective: To evaluate lifetime prevalence and specificity of psychiatric disorders in offspring of parents with BP-I and BP-II.

Design: Offspring aged 6 to 18 years who have parents with BP and community control subjects were interviewed with standardized instruments. All research staff except the statistician were blind to parental diagnoses.

Setting: Parents with BP were recruited primarily through advertisement and outpatient clinics. Control parents were ascertained by random-digit dialing and were group matched for age, sex, and neighborhood to parents with BP.

Participants: Three hundred eighty-eight offspring of 233 parents with BP and 251 offspring of 143 demographically matched control parents.

Main Outcome Measures: *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) Axis I disorders.

Results: Adjusting for demographic factors, living with 1 vs both biological parents, both biological parents' non-BP psychopathology, and within-family correlations, offspring of parents with BP showed high risk for BP spectrum disorders (odds ratio [OR] = 13.4; 95% confidence interval [CI], 2.9-61.6) and any mood (OR = 5.2; 95% CI, 2.3-11.4), anxiety (OR = 2.3; 95% CI, 1.3-4.0), and Axis I (OR = 2.2; 95% CI, 1.5-3.3) disorders. Offspring of parents with BP with high socioeconomic status showed more disruptive behavior disorders and any Axis I disorders than offspring of control parents with high socioeconomic status. Families in which both parents had BP had more offspring with BP than families with only 1 parent with BP (OR = 3.6; 95% CI, 1.1-12.2). More than 75.0% of offspring who developed BP had their first mood episode before age 12 years, with most of these episodes meeting criteria for BP not otherwise specified and, to a lesser degree, major depression.

Conclusions: Offspring of parents with BP are at high risk for psychiatric disorders and specifically for early-onset BP spectrum disorders. These findings further support the familiarity and validity of BP in youth and indicate a need for early identification and treatment.

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UP TO 60% OF ADULTS WITH bipolar disorder (BP) experience their first mood symptoms before age 21 years.¹⁻³ Because better outcome may be associated with earlier treatment, it is important for clinicians to identify and treat BP early in life to hopefully be able to prevent the high psychosocial and medical morbidity and mortality associated with this disorder.¹ The single best predictive factor associated with the risk of developing BP is high family loading for the disorder.^{1,3,4} Therefore, carefully evaluating and prospectively following the psychopathology of offspring of

parents with BP and comparing them with offspring of parents with and without non-BP psychopathology, are critical for identifying the early clinical presentation of BP.

A meta-analysis and more recent studies have reported rates of BP between 4% and 15% in the offspring of parents with BP and between 0% and 2% in the offspring of healthy parents.⁵ Bipolar disorder may first manifest in the form of depression,^{1,3,6,7} and the symptoms of BP overlap and may be confused with symptoms of other common child psychiatric disorders such as attention-deficit/hyperactivity disorder (ADHD) or disruptive behavior disorders

(DBDs).^{3,6-9} Therefore, in addition to BP, it is important to evaluate the rates of non-BP disorders in offspring of parents with BP. In the meta-analysis cited earlier,³ rates of any mood disorders were 26.5% in offspring of parents with BP vs 8.3% in offspring of healthy control parents and the rates of any psychiatric disorder were 52% vs 29%, respectively. More recent studies¹⁰⁻¹⁶ also reported high risk for both mood and nonmood disorders in offspring of parents with BP when compared with offspring of parents with and without non-BP psychopathology. However, there is substantial variability in the results.

Discrepancies among the existing studies are likely owing to methodological limitations, including small samples, use of convenience samples, ascertainment bias (eg, recruiting clinically referred children whose parents also have BP), lack of direct interviews with children, differences in the instruments and conceptualization of BP, lack of specification of the BP subtypes studied, method of counting the overlapping symptoms of BP and other disorders, and evaluations by interviewers who were not blinded to parental diagnoses.^{5,13,15,16} Furthermore, with the exception of a few studies,^{11,14} most studies included only offspring of healthy parents as a comparison group. Finally, most studies did not take into account the effects of other factors that could have influenced the prevalence of the child's psychopathology such as parents' non-BP psychopathology, demographic characteristics, and family environment.

The main goal of this article is to evaluate the prevalence of lifetime psychiatric disorders in offspring of parents with BP and a random sample of community control parents ascertained through the Bipolar Offspring Study (BIOS). Subsequent reports will focus on other important cross-sectional and longitudinal data collected through BIOS such as rates of potential clinical phenotypes for BP (eg, irritability, sleep patterns), the cosegregation and temporal relation of non-BP and BP disorders, the effects of negative events on the child's outcome, and rates of categorical and dimensional psychopathology in toddlers of parents with BP. Based on the extant literature, it was hypothesized that offspring of parents with BP have higher rates of BP, major depressive disorder (MDD), anxiety disorders, DBDs, and ADHD when compared with offspring of control parents.

METHODS

SUBJECTS

Parents with BP were recruited through advertisement (53.0%), adult BP studies (31.0%), and outpatient clinics (16.0%). There were no differences in BP subtype, age at BP onset, or rates of non-BP disorders on the basis of recruitment source. Parents were required to fulfill *DSM-IV*¹⁷ criteria for BP-I or BP-II. Exclusion criteria included current or lifetime diagnoses of schizophrenia, mental retardation, mood disorders secondary to substance abuse, medical conditions, or medication use, and living more than 200 miles away from Pittsburgh, Pennsylvania.

Control parents consisted of healthy parents or parents with non-BP psychiatric disorders from the community and were group matched by age, sex, and neighborhood using the area code and the first 3 digits of the telephone number and the zip code of the parents with BP. The exclusion criteria for the control par-

ents were the same as those for the parents with BP, with the additional requirements that neither of the biological parents could have BP and they could not have a first-degree relative with BP. Control parents were recruited by the University Center for Social and Urban Research, University of Pittsburgh in an approximate ratio of 1 control parent for every 2 parents with BP.

With the exception of children who were unable to participate (eg, those diagnosed with mental retardation), all offspring aged 6 to 18 years from each family were included in the study.

PROCEDURES

After institutional review board approval and obtaining consent from parents and assent from children, parents were assessed for psychiatric disorders, family psychiatric history, and other variables such as dimensional psychopathology, family environment, and exposure to negative life events. Only instruments directly related to this article will be discussed.

For probands and biological coparents who participated in direct interviews (30.0%), *DSM-IV* psychiatric disorders were ascertained through the Structured Clinical Interview for *DSM-IV*¹⁸ plus the ADHD, DBD, and separation anxiety disorder sections from the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL).¹⁹

The family history—research diagnostic criteria method²⁰ plus ADHD and DBD items from the K-SADS-PL were used to ascertain the psychiatric history of second-degree relatives, biological coparents not seen for direct interview, and siblings of offspring who were too old (aged >18 years) to participate at intake.

Parents were interviewed about their children and the children were directly interviewed for the presence of lifetime non-mood psychiatric disorders using the K-SADS-PL. To evaluate the severity of each mood symptom, the K-SADS-PL Mania Rating Scale^{21,22} and the depression section of the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present Version were used (for these instruments, see <http://www.wpic.pitt.edu/research> under “Assessment Instruments”).

As per the instructions for the K-SADS-PL, mood symptoms that were also in common with other psychiatric disorders (eg, hyperactivity) were not rated as present in the mood sections unless they intensified with the onset of abnormal mood. Comorbid diagnoses were not assigned if they occurred exclusively during a mood episode.

All of the diagnoses were made using the *DSM-IV* criteria. However, to avoid diagnosing youth with “soft” BP symptoms, an operationalized and more strict *DSM-IV* BP not-otherwise-specified (NOS) diagnosis was used (see the articles by Axelson et al⁷, Birmaher et al²³, and Leibenluft and Rich²⁴ for further details). Youth with this more strict BP-NOS diagnosis have similar but less severe clinical pictures, comorbid disorders, family history, and longitudinal outcomes than the subjects with BP-I.^{7,23} Moreover, about 25.0% of these youth diagnosed with BP-NOS had their diagnoses converted to BP-I or BP-II.²³ With the exception of BP-NOS in children and biological coparents, other NOS and adjustment disorders for children or adults were not included in this study.

Onset of a mood episode was defined as the first episode of MDD or BP. Onset of BP was defined as the first episode of mania, hypomania, mixed, or operationalized criteria for BP-NOS. Given the controversies of diagnosing BP in very young children, the minimum age at onset for BP spectrum disorders was arbitrarily set at age 4 years.

Bachelors- or masters-level interviewers completed all of the assessments after intensive training for all of the instruments and after 80% agreement or better with a certified rater. The overall Structured Clinical Interview for *DSM-IV* and K-SADS-PL κ statistics for psychiatric disorders were 0.8 or greater.

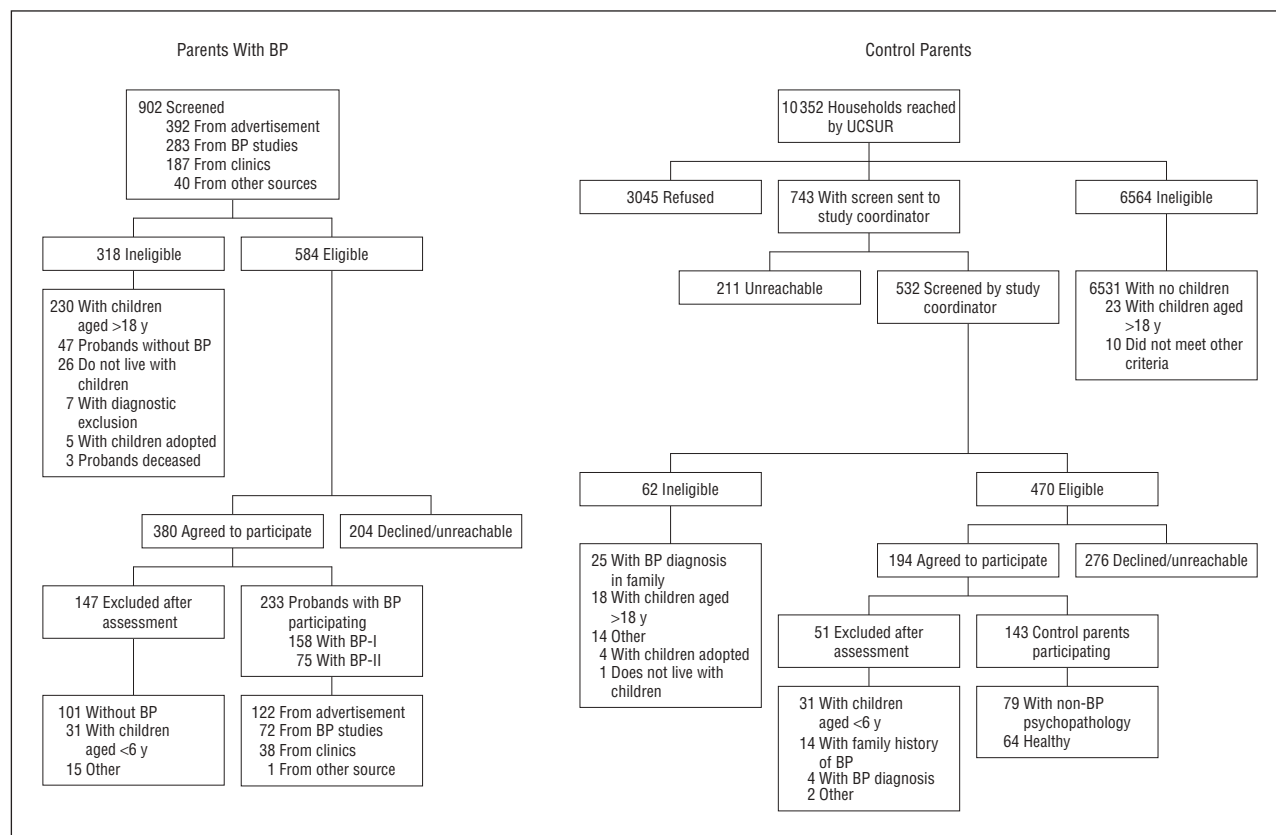


Figure 1. Recruitment of parents with bipolar disorder (BP) and community control parents (probands). UCSUR indicates University Center for Social and Urban Research.

About 90.0% of assessments were carried out in the subjects' homes. To ensure blindness to parental diagnoses, the interviewers who met with the parents to assess parental psychopathology were different from the interviewers who assessed their children's psychopathology. All of the data (from the adult, child, and family) were presented to a child psychiatrist for diagnostic confirmation. The child psychiatrists were also blinded to the psychiatric status of the parents. When necessary, subjects' medical and psychiatric records were obtained and reviewed by their respective interviewers. All diagnoses in the parents, children, and relatives were made according to the best-estimate procedure.²⁵

The Petersen Pubertal Developmental Scale²⁶ and respective Tanner stages^{27,28} were used to evaluate pubertal development. Socioeconomic status (SES) was ascertained using the Hollingshead scale.²⁹

STATISTICAL ANALYSES

The demographic and clinical characteristics between the groups were evaluated using t , χ^2 , and Fisher exact tests as appropriate. Analyses of the effects of any between-group demographic differences and non-BP psychiatric disorders of both biological parents from the BP and control groups were performed using a series of hierarchical logistic regressions. To account for the presence of within-family correlations, mixed-effects nominal logistic regressions were used.³⁰

The cumulative rates of mood episodes by age at onset between the offspring of parents with BP and control parents were analyzed using the Kaplan-Meier procedure. Because age and pubertal status were highly correlated ($p=0.88$; $P<.001$), only age effects are included in this article. Effect sizes for continuous and categorical variables (d and h , respectively) were calculated as described by Cohen.³¹

All of the P values are based on 2-tailed tests with $\alpha=.05$.

RESULTS

PARENTS

Parents With BP

Of the 902 subjects screened by telephone, 584 were qualified for a face-to-face interview with the Structured Clinical Interview for DSM-IV to verify that they had BP (**Figure 1**). Of these, 204 declined further participation (for reasons of geographic distance, lack of time, custody issues, or not wanting their children to know that they have BP) or were unreachable. Because screening was done over the telephone and prior to obtaining subjects' consent, the institutional review board did not permit the recording of demographic information. Thus, comparisons between subjects who declined and those who agreed to further participation are not available. Of the 380 subjects who agreed to be interviewed, 147 were excluded mainly because they did not fulfill criteria for BP or they only had children younger than 6 years, for a final sample of 233 parents with BP (158 with BP-I and 75 with BP-II). Of the 233 parents with BP, 187 (80.3%) were female. Ten families had 2 parents with BP spectrum disorders (1 family with both parents having BP-I, 1 family with both parents having BP-II, 4 families with 1 parent having BP-I and 1 parent having BP-II, 3 families with 1 parent having BP-I and 1 parent

Table 1. Demographic Characteristics and Lifetime Axis I Psychiatric Disorders of Parents With Bipolar Disorder vs Community Control Parents

Characteristic	Parents With Bipolar Disorder (n=233)	Community Control Parents (n=143)	Statistic	P Value (Effect Size)
Demographic				
Age, mean (SD), y	39.5 (7.6)	40.9 (7.4)	$t=1.82$.07 (0.19)
Female, %	80.3	77.6	$\chi^2=0.37$.50 (0.05)
White, %	88.4	75.5	$\chi^2=10.69$.001 (0.32)
SES, mean (SD) ^a	2.9 (1.2)	3.2 (1.1)	$t=2.10$.04 (0.26)
Married at intake, %	48.5	65.7	$\chi^2=10.64$.001 (0.37)
No. of offspring included, mean (SD)	1.7 (0.8)	1.8 (0.8)	$t=1.03$.30 (0.13)
Lifetime Axis I psychiatric disorders, %				
Any Axis I disorders	100.0	54.5	$\chi^2=128.04$	<.001 (1.50)
BP-I	67.8	0.0	NA	NA
BP-II	32.2	0.0	NA	NA
Unipolar MDD	NA	25.2	NA	NA
Dysthymic disorder	2.6	5.6	$\chi^2=2.25$.10 (0.15)
Any anxiety disorders	72.5	20.3	$\chi^2=97.05$	<.001 (1.10)
Panic disorder	39.9	4.9	$\chi^2=55.66$	<.001 (0.92)
DBDs ^b	36.9	8.4	$\chi^2=37.40$	<.001 (0.73)
ADHD	27.5	2.8	$\chi^2=36.41$	<.001 (0.77)
Any substance abuse ^c	63.9	28.0	$\chi^2=45.88$	<.001 (0.72)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BP, bipolar disorder; DBDs, disruptive behavior disorders; MDD, major depressive disorder; NA, not applicable; SES, socioeconomic status.

^aA value of 3 is equivalent to an SES of III, middle class, on the Hollingshead scale.

^bIncludes oppositional defiant disorder and conduct disorder.

^cIncludes alcohol, marijuana, and cocaine.

having BP-NOS, and 1 family with 1 parent having BP-II and 1 parent having BP-NOS). About 64.0% of the parents with BP reported that their mood disorder started when they were younger than 20 years, 48.0% when they were younger than 17 years, and 18.0% when they were younger than 13 years.

Control Parents

Of the 743 community parents referred by the University Center for Social and Urban Research, 532 were reachable and screened by one of the coordinators from BIOS by telephone (Figure 1). Of these, 470 were eligible for face-to-face interviews with the Structured Clinical Interview for DSM-IV; 276 declined participation or were not able to schedule or attend an intake assessment. Owing to institutional review board reasons previously mentioned, demographic information was not available from subjects who declined participation or were unreachable. Fifty-one of the remaining 194 subjects were excluded primarily because of a diagnosis or family history of BP, resulting in a final number of 143 community control parents (79 with non-BP psychiatric disorders and 64 without any psychopathology). Of these cases, none reported BP in their known second-degree relatives.

Demographic Comparisons

Parents with BP were more likely to be white, were less likely to be married at intake, and had slightly lower SES than control parents (**Table 1**). Compared with the control parents with non-BP psychopathology, parents with BP showed similar demographic characteristics. On average, both groups of parents included 2 children in the study.

Axis I Disorders

With the exception of dysthymic disorder, all of the psychiatric disorders were present in higher rates in the parents with BP than in the control parents (all $P \leq .001$; effect size [ES], 0.72-1.50) (Table 1). Within the parents with BP, there were no significant differences in the rates of psychopathology between those recruited through advertisement and those recruited through other means.

Psychopathology in the Biological Coparent

There was no difference in the proportion of direct assessments used to obtain the nonproband biological parent's psychiatric disorders between parents with BP and control parents (26.3% vs 27.8%, respectively). The biological coparents of the offspring of parents with BP as compared with the biological coparents of the offspring of control parents showed higher rates of any Axis I psychiatric disorders (48.2% vs 29.1%, respectively), BP (3.9% [3 subjects with BP-I, 3 subjects with BP-II, and 3 subjects with BP-NOS] vs 0%, respectively), substance abuse (30.2% vs 16.6%, respectively), and DBDs (5.9% vs 1.3%, respectively) (all $P \leq .03$). No other differences were found.

OFFSPRING

Demographic Comparisons

Three hundred eighty-eight offspring of parents with BP and 251 offspring of control parents (161 from parents with ≥ 1 parent with non-BP psychopathology and 90 from healthy parents) were recruited (**Table 2**). No fami-

Table 2. Demographic Characteristics and Axis I Lifetime Psychiatric Disorders of Offspring of Parents With Bipolar Disorder vs Offspring of Community Control Parents

Characteristic	Offspring of Parents With BP (n=388)	Offspring of Community Control Parents (n=251)	Statistic	P Value (Effect Size)
Demographic				
Age, mean (SD), y	11.9 (3.6)	11.8 (3.5)	$t=0.54$.60 (0.03)
Female, %	48.5	54.6	$\chi^2=2.29$.10 (0.14)
White, %	81.4	74.1	$\chi^2=4.88$.03 (0.17)
Tanner stage, % ^a				
I, II, or III	65.6	66.4	$\chi^2=0.04$.80 (0.00)
IV or V	34.4	33.6		
Living with both biological parents, %	42.5	60.2	$\chi^2=18.96$	<.001 (0.36)
Lifetime Axis I psychiatric disorders, %				
Any Axis I disorders	52.1	29.1	$\chi^2=32.82$	<.001 (0.47)
Any mood disorder	21.1	4.4	$\chi^2=34.39$	<.001 (0.55)
BP spectrum disorders	10.6	0.8	$\chi^2=23.18$	<.001 (0.48)
BP-I	2.1	0.0	FET	.03 (0.28)
BP-II	1.3	0.4	FET	.40 (0.10)
BP-NOS	7.2	0.4	$\chi^2=16.35$	<.001 (0.44)
Any depression	10.6	3.6	$\chi^2=10.30$.001 (0.27)
Dysthymic disorder	1.5	0.4	FET	.26 (0.15)
MDD	9.1	3.2	$\chi^2=8.26$.004 (0.26)
Any anxiety disorders	25.8	10.8	$\chi^2=21.58$	<.001 (0.39)
SAD, GAD, and/or SP	22.2	7.6	$\chi^2=23.64$	<.001 (0.40)
Panic disorder	1.0	1.6	FET	.70 (0.08)
OCD	2.6	0.4	FET	.06 (0.25)
PTSD	4.6	3.6	$\chi^2=0.42$.50 (0.05)
DBDs	19.1	8.0	$\chi^2=14.98$	<.001 (0.33)
ODD	17.0	6.4	$\chi^2=15.41$	<.001 (0.36)
CD	3.6	2.4	$\chi^2=0.74$.40 (0.12)
ADHD	24.5	16.7	$\chi^2=5.44$.02 (0.17)
Any substance abuse	3.9	2.8	$\chi^2=0.53$.50 (0.06)
Alcohol	1.8	1.6	FET	>.99 (0.00)
Drugs	3.6	1.6	$\chi^2=2.26$.10 (0.12)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BP, bipolar disorder; CD, conduct disorder; DBDs, disruptive behavior disorders; FET, Fisher exact test; GAD, generalized anxiety disorder; MDD, major depressive disorder; NOS, not otherwise specified; OCD, obsessive-compulsive disorder; ODD, oppositional defiant disorder; PTSD, posttraumatic stress disorder; SAD, separation anxiety disorder; SP, social phobia.

^aA Tanner stage of I indicates prepubertal; II to III, midpubertal; and IV to V, postpubertal.

lies were rejected if 1 of the children refused to participate. Only 7 children of parents with BP and 4 children of control parents were not eligible or refused to participate. The diagnoses of these children were captured in the family history.

Offspring of parents with BP were more likely to be white and less likely to be living with both biological parents than offspring of control parents. There were no other between-group demographic differences.

Axis I Disorders

With the exceptions of BP-II and dysthymic, panic, obsessive-compulsive, posttraumatic stress, conduct, and substance use disorders, all psychiatric disorders were present in higher rates in the offspring of parents with BP than in the offspring of control parents (all $P \leq .02$; ES, 0.17-0.55) (Table 2).

Specifically for BP spectrum disorders, offspring of parents with BP showed significantly more BP spectrum disorders (41 of 388 children [10.6%]; 8 with BP-I, 5 with BP-II, and 28 with BP-NOS) than offspring of control parents (2 of 251 children [0.8%]) ($P < .001$; ES, 0.48). This increased rate of BP was accounted for by significantly higher rates of BP-I ($P = .03$; ES, 0.28) and BP-NOS

($P < .001$; ES, 0.44). Nearly all of the BP-NOS cases were not given the diagnosis of BP-I or BP-II because they did not meet the DSM-IV duration criteria. In addition to elation and/or irritability, all of the children with BP-NOS had an average of 4 clinically significant DSM-IV BP symptoms (range, 3-9 symptoms), whereas children with BP-I or BP-II had an average of 5 symptoms (range, 2-9 symptoms). Within the 41 children with BP spectrum disorders who have parents with BP, 31 (75.6%) had onset of their BP prior to age 12 years and 10 (24.4%) had onset at or after age 12 years, with most of these first episodes being NOS (19 vs 4 subjects, respectively), followed by MDD (8 vs 4 subjects, respectively), mania (3 subjects vs 1 subject, respectively), and hypomania (1 subject each) (all $P > .05$). Of the 41 subjects, 35 (85.4%) had a comorbid disorder (51.0% had any anxiety disorder, 53.0% had DBD, and 39.0% had ADHD).

Offspring of families with 2 parents with BP spectrum disorders had BP significantly more often when compared with families with 1 parent with BP (4 of 14 subjects [28.6%] vs 37 of 374 subjects [9.9%], respectively; Fisher exact test, $P = .05$; odds ratio [OR] = 3.6; 95% confidence interval [CI], 1.1-12.2). There were no other differences in child psychopathology between offspring of families with 1 or 2 parents with BP.

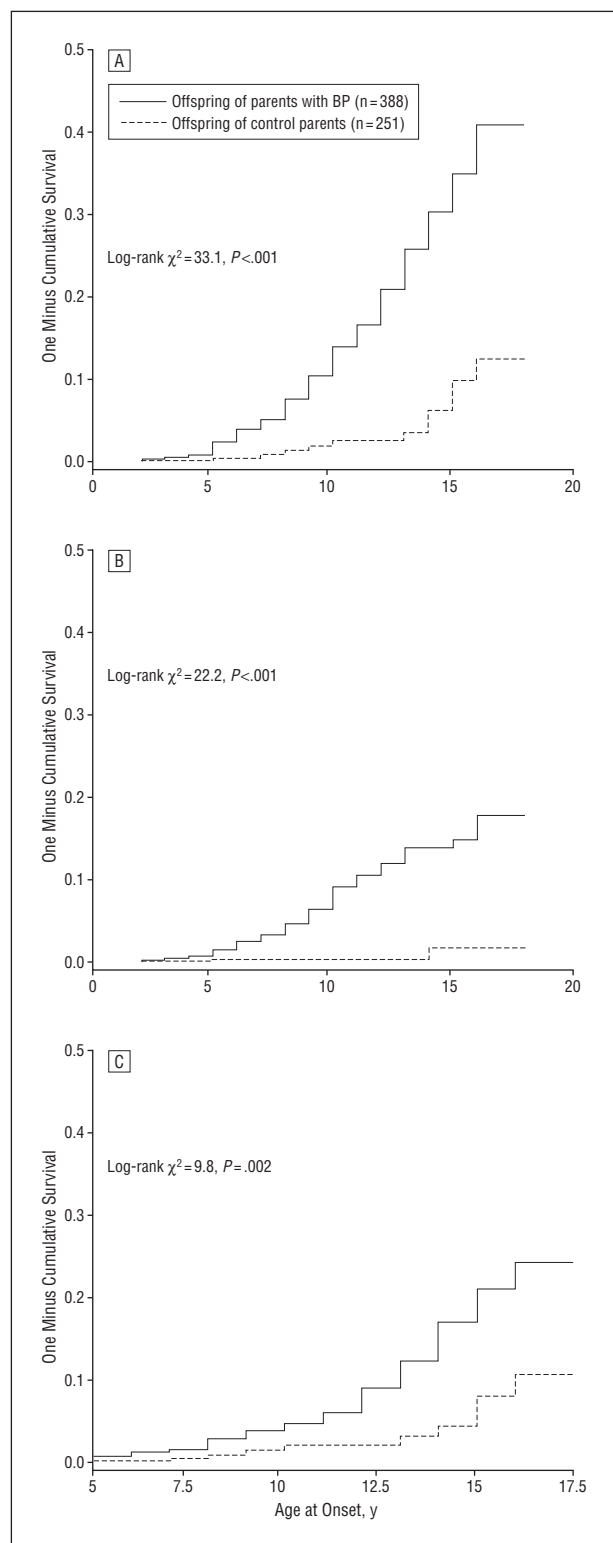


Figure 2. Cumulative rates by age at onset of any mood episodes (A), bipolar disorder (BP) episodes (mania, hypomania, mixed, or operationalized BP not-otherwise-specified episodes) (B), and depressive episodes (major depressive episodes excluding youth with BP) (C).

As shown in **Figure 2A**, offspring of parents with BP had higher morbid risk of any mood episodes with a cumulative risk of approximately 20.9% by age 12 years and 40.8% by age 18 years (hazard ratio=5.1; 95% CI, 2.7-

9.6). Offspring of parents with BP also had a significantly higher risk of BP and depressive episodes. For BP (**Figure 2B**), the cumulative risk was 12.0% by age 12 years and 17.8% by age 18 years (hazard ratio=3.0; 95% CI, 1.4-6.1). For MDD (**Figure 2C**), the cumulative risk was 9.1% by age 12 years and 24.3% by age 18 years (hazard ratio=13.5%; 95% CI, 3.3-55.8). For all of the earlier-noted comparisons, there were no age \times group interactions.

Mixed-Effects Logistic Regression

After adjusting for offspring's age, race, SES, living with both biological parents, both biological parents having non-BP disorders, and within-family correlations, when compared with the offspring of control parents, the offspring of parents with BP showed significantly higher risk for any Axis I disorders (OR=2.2; 95% CI, 1.5-3.3), any mood disorder (OR=5.2; 95% CI, 2.3-11.4), BP spectrum disorders (OR=13.4; 95% CI, 2.9-61.6), and any anxiety disorders (OR=2.3; 95% CI, 1.3-4.0) (OR=3.0 for separation anxiety disorder, generalized anxiety disorder, and/or social phobia) (**Table 3**).

Offspring of parents with BP and SES higher than the median (34, which corresponds to class III) showed significantly more DBDs and any Axis I disorders than offspring of control parents with higher SES (DBDs: 15.2% vs 2.1%, respectively; $\chi^2=15.9$; OR=5.6; 95% CI, 1.6-19.0; Axis I disorders: 49.1% vs 17.5%, respectively; $\chi^2=34.4$; OR=3.6; 95% CI, 2.1-6.3). In contrast, in parents with SES of 34 or lower, there were no between-group differences in the rates of DBDs and Axis I disorders between offspring of parents with BP and control parents (DBDs: 22.1% vs 15.7%, respectively; Axis I disorders: 54.4% vs 44.4%, respectively). There were no effects of race or sex. Similar results were observed when oppositional defiant disorder and conduct disorder were analyzed separately, after excluding offspring with DBDs from the analyses of any Axis I disorders, or after adjusting for multiple comparisons.

For comparison with the existing literature, in addition to showing the adjusted ORs for all of the offspring of the control parents, **Table 3** shows the adjusted ORs for the offspring of the control parents stratified by the presence of parental non-BP psychopathology.

COMMENT

As compared with offspring of control parents, offspring of parents with BP showed a 14-fold increase in the rates of BP spectrum disorders and approximately a 2- to 3-fold increase in any mood and anxiety disorders after adjusting for both biological parents' non-BP psychiatric disorders, significant between-group demographic variables, and within-family correlations. Also, the offspring of parents with BP and higher SES showed 4- and 6-fold increases in the rates of any Axis I disorders and DBDs, respectively. Families in which both parents had BP had more offspring with BP spectrum disorders than families in which only 1 parent had BP. Most of the offspring's BP episodes started during childhood, with most first episodes being of the NOS type and, to a lesser degree, depression episodes. As expected, about

Table 3. Adjusted Odds Ratios for Bipolar and Other Psychiatric Disorders in Offspring of Parents With Bipolar Disorder

Disorders	OR (95% CI)		
	Offspring of Parents With BP vs Offspring of All Control Parents ^a	Offspring of Parents With BP vs Offspring of Control Parents With Non-BP Psychopathology ^b	Offspring of Parents With BP vs Offspring of Healthy Control Parents ^b
Any Axis I disorders	2.2 (1.5-3.3) ^c	2.0 (1.3-3.1) ^c	4.0 (1.3-12.1) ^c
Any mood disorder	5.2 (2.3-11.4) ^c	4.3 (1.9-9.7) ^c	18.3 (1.7-200.0) ^c
BP spectrum disorders	13.4 (2.9-61.6) ^c	9.1 (2.0-41.7) ^c	15.1 (2.7-∞) ^{c,d}
Depressive disorders ^e	2.1 (0.9-4.9)	1.9 (0.8-4.6)	4.8 (0.3-68.6)
Any anxiety disorders	2.3 (1.3-4.0) ^c	2.2 (1.2-3.9) ^c	3.8 (0.5-27.5)
SAD, GAD, and/or SP	3.0 (1.5-5.9) ^c	2.9 (1.5-5.9) ^c	4.1 (0.4-46.5)
DBDs	2.1 (0.9-4.4)	2.1 (0.9-4.6)	1.9 (0.2-22.6)
ODD	1.9 (0.9-4.0)	2.0 (0.9-4.3)	1.3 (0.1-19.3)
CD	1.3 (0.2-8.2)	1.2 (0.2-8.9)	2.8 (0.1-220.7)
ADHD	1.4 (0.9-2.3)	1.2 (0.7-2.1)	3.5 (1.1-11.4) ^c
Substance abuse	0.7 (0.1-6.1)	0.7 (0.3-2.3)	2.1 (0.2-17.5)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BP, bipolar disorder; CD, conduct disorder; CI, confidence interval; DBDs, disruptive behavior disorders; GAD, generalized anxiety disorder; ODD, oppositional defiant disorder; OR, odds ratio; SAD, separation anxiety disorder; SP, social phobia.

^aAdjusting for offspring's age, race, socioeconomic status, living with both biological parents, and within-family correlations.

^bAdjusting for offspring's age, race, socioeconomic status, living with both biological parents, both biological parents' non-BP psychopathology, and within-family correlations.

^cResults are significant, with $P \leq .04$.

^dThe upper 95% confidence limit to ∞ is owing to no BP in offspring of healthy control parents.

^eIncludes major depressive disorder and dysthymic disorder.

85.0% of children with BP had other comorbid disorders, mainly anxiety disorders, DBDs, and ADHD.

Before discussing each of the earlier-noted findings, the limitations of the study deserve comment. First, because most children have not reached the age of highest risk to develop BP, the rate of BP in these children is likely to continue to increase with further follow-up. Second, as in any pediatric study, the probands for both the BP and control groups were much more likely to be the mothers rather than the fathers. In addition, the psychopathology in the biological coparents was mainly ascertained by interviewing the probands. However, there were no between-group differences in rates of mothers serving as the probands and no differences in the proportion of direct and indirect interviews of the co-biological parents with BP and control parents. Third, because the diagnosis of BP-II in adults appears to be low even with direct interviews,³² it is possible that in using indirect interviews we could have missed some of these diagnoses in relatives of both groups. Nevertheless, the rates of BP-II found in the study are similar to those reported in epidemiological studies.^{33,34} Fourth, although there are contradictory results in the literature and the effects seem to be small,³⁵⁻³⁸ parents with psychopathology could have been more interested in having their children evaluated through the study and may have had greater knowledge of the disorder, possibly inflating the rate of disorders in their offspring. However, at least for the control parents (of whom 50% had psychopathology), the rates of lifetime psychiatric disorders in their offspring were similar to those described in other community studies.³⁹⁻⁴¹ Finally, although the literature is controversial,^{42,43} parents who participated in BIOS could have had more psychopathology than those who did not participate. However, the rates of psychiatric disorders in parents with BP and their age at BP onset were similar to those reported in the adult BP literature.^{1,33,34,44,45} Moreover, parents with BP and control parents with non-BP psy-

chopathology were comparable in demographic characteristics and recruitment origin. Finally, taking into consideration the age and sex of the control parents recruited in BIOS, the lifetime prevalence of psychiatric disorders found in these parents is similar to that reported in a recent large epidemiological study in the United States.⁴⁶

Both biological parents of the offspring of parents with BP showed considerably higher rates of Axis I psychiatric disorders than the control parents. Thus, it is not surprising that their offspring showed more psychopathology than the offspring of control parents. However, together with prior "top-down"^{5,10-16} and "bottom-up" BP family studies,^{1,3,47-51} BIOS provides further evidence that offspring of parents with BP are at specifically high risk to develop early-onset BP. Noticeably and similar to BIOS, in a review of the adult BP literature, the average age-adjusted lifetime prevalence for BP spectrum disorders in first-degree relatives was 10.7%, compared with 1.0% for the relatives of healthy control subjects.¹

In BIOS, most of the children diagnosed with BP fulfilled the operationalized criteria for BP-NOS^{7,24} and 56.0% of the first episodes were of the NOS type. As in another investigation,⁷ most of these youth did not meet criteria for BP-I or BP-II because they lacked the current *DSM-IV* episode duration requirements for the diagnosis of these disorders. Thus, it appears that early-onset BP with genetic loading may often present with subthreshold manic symptoms before reaching full *DSM-IV* criteria for BP-I or BP-II. Because youth with the stricter definition of BP-NOS are at high risk for diagnoses converting to BP-I or BP-II,²³ follow-up of the subjects with BP-NOS in BIOS will provide an additional test of the validity of the BP-NOS phenotype in a nonreferred high-risk sample.

Consistent with the literature,^{2,45,52-54} most parents with BP recollected that their illness started before age 20 years and about 20.0% had illness that started before age 13 years. In contrast, most of their children developed their first BP

episode before age 12 years, suggesting the possibility that parents were more perceptive of their children's symptoms early in life or perhaps that BP has more penetrance and manifests earlier in new generations.^{45,52,55}

Offspring of families in which both parents had BP were 3.6 times more likely to have BP, without being at higher risk for any other psychiatric disorders as compared with families with only 1 parent with BP. One child study and other adult family studies reported similar findings,^{1,56} giving further evidence to the specificity of the family transmission of BP. Future articles will examine the earlier-noted results in greater depth and analyze other important issues such as the parent-of-origin effect and the effects of second-degree family psychopathology.

Similar to a meta-analysis of studies of pediatric high risk for BP⁵ and other recent studies,¹⁴ after adjusting for confounding factors, there were no between-group differences in the rates of MDD in the offspring. Bottom-up family studies have also shown that the first-degree relatives of youth with BP have significantly more depression when compared with first-degree relatives of healthy children⁴⁸⁻⁵⁰ but not when compared with the first-degree relatives of children with non-BP disorders.^{49,50,57} As expected,^{11,12,14,58,59} rates of depression increased during adolescence. Because BP may manifest its first symptoms with depression (30.0% in BIOS),^{3,60-63} particularly if there is family history of BP,^{61,64-66} it is likely that a significant proportion of the depressed children of parents with BP included in this study will eventually develop BP.

After adjusting for confounding factors, the offspring of parents with BP showed significantly higher rates of anxiety disorders, particularly generalized anxiety disorder, social phobia, and/or separation anxiety disorder, when compared with the offspring of control parents. There were no differences in the rates of other anxiety disorders, but the base rate of these disorders was low. Other studies of high risk for BP and studies of adults and youth with BP have also reported high rates of anxiety disorders.^{7,9,67-73} Also, high rates of anxiety disorders have been consistently observed in adults with early-onset BP when compared with adults with late-onset BP,^{1,70,71} and anxiety disorders appear to be associated with increased risk of developing BP during adulthood.^{44,74,75} Ongoing prospective follow-up of children recruited into BIOS will help to address this question.

High rates of DBDs and ADHD have been reported in offspring of parents with BP when compared with offspring of healthy parents^{5,9,16} and parents with non-BP disorders.¹¹ Because some of the symptoms of these disorders overlap with the symptoms of BP⁶⁹ and because mood disorders in youth are often manifested by severe irritability, ADHD-like symptoms, and oppositional behaviors, the earlier-noted findings have suggested that these symptoms may be one of the ways BP is manifested early in life or may be prodromal symptoms of BP.^{14,76-78} In BIOS, initial analyses also showed significant differences in the rates of DBDs, oppositional defiant disorder, and ADHD between the offspring of parents with BP and control parents. However, after adjusting for confounding variables, there were differences only in the rate of DBDs between offspring of parents with BP and healthy parents but not between offspring of parents with BP and control parents

with non-BP psychopathology (Table 3). Thus, the presence of DBDs in the offspring of parents with BP seems to be related to general parental psychopathology or other related factors.

Of note, offspring of parents with BP with high SES showed more DBDs and any Axis I disorders than offspring of control parents with high SES. Because low SES has been associated with higher risk for childhood psychopathology, particularly behavior disorders,⁷⁹ it is possible that higher SES is not protective in offspring of parents with BP. Alternatively, low SES may be such a strong predictor of DBDs that having a parent with BP confers no further risk of DBDs among subjects with low SES. Follow-up of the BIOS sample will further clarify whether early symptoms of ADHD and DBDs in offspring of parents with BP are early indicators for BP, particularly if these symptoms are severe.⁸⁰

The rates of substance abuse for all of the offspring groups were relatively low, but most of the youth had not yet reached the age of highest risk for substance abuse. Youth with BP appear to be at higher risk for developing substance abuse than youth with other psychopathology.^{81,82} Moreover, substance use may lower the threshold for BP.⁸³ Thus, early detection and treatment of these children are warranted before they develop substance use or abuse.

Taken together, our findings from BIOS have several potential clinical implications. Clinicians who treat adults with BP should question those who are parents about their children's psychopathology to offer prompt identification and early interventions for any psychiatric problems that may be affecting the children's functioning, particularly early-onset BP. Some of the psychopathology presenting in offspring of parents with BP, particularly depression and anxiety, could be associated with the development of BP. However, it is not clear what the optimal treatment would be, given the possible risk of antidepressants inducing the onset of BP in these high-risk children. Also, clinicians who treat offspring of parents with BP should be alerted to parental psychopathology because as shown in this and other studies,¹ their parents may have other comorbid disorders besides BP that could convey negative implications for the children's longitudinal outcomes. Effective treatment of these parents may diminish and perhaps prevent psychopathology in their children.^{84,85}

Because nearly half of the offspring of parents with BP have not yet manifested any diagnosable psychiatric illness, there is a great need and opportunity for primary prevention in this high-risk population. Thus, it is critical to have prospective longitudinal studies of the offspring of parents with BP that include comparisons with offspring of parents with and without non-BP disorders to evaluate clinical and biological phenotypes and genetic polymorphisms that can help determine who is at risk to develop BP.

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