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Arch Gen Psychiatry. 2011 October ; 68(10): 1012–1020. doi:10.1001/archgenpsychiatry.2011.126.**A High-Risk Study of Bipolar Disorder:****Childhood Clinical Phenotypes as Precursors of Major Mood Disorders**

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Abstract

Context—The childhood precursors of adult bipolar disorder (BP) are still a matter of controversy.

Objective—To report the lifetime prevalence and early clinical predictors of psychiatric disorders in offspring from families of probands with *DSM-IV* BP compared with offspring of control subjects.

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Author Contributions: Dr Nurnberger 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.

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Online-Only Materials: The eTables are available at <http://www.archgenpsychiatry.com>.

Additional Contributions: Kimberly Quaid DeCordon, PhD, and Boris Birmaher, MD, provided consultation on the development of the assessment battery.

Design—A longitudinal, prospective study of individuals at risk for BP and related disorders. We report initial (cross-sectional and retrospective) diagnostic and clinical characteristics following best-estimate procedures.

Setting—Assessment was performed at 4 university medical centers in the United States between June 1, 2006, and September 30, 2009.

Participants—Offspring aged 12 to 21 years in families with a proband with BP (n=141, designated as cases) and similarly aged offspring of control parents (n=91).

Main Outcome Measure—Lifetime *DSM-IV* diagnosis of a major affective disorder (BP type I; schizoaffective disorder, bipolar type; BP type II; or major depression).

Results—At a mean age of 17 years, cases showed a 23.4% lifetime prevalence of major affective disorders compared with 4.4% in controls ($P=.002$, adjusting for age, sex, ethnicity, and correlation between siblings). The prevalence of BP in cases was 8.5% vs 0% in controls (adjusted $P=.007$). No significant difference was seen in the prevalence of other affective, anxiety, disruptive behavior, or substance use disorders. Among case subjects manifesting major affective disorders (n=33), there was an increased risk of anxiety and externalizing disorders compared with cases without mood disorder. In cases but not controls, a childhood diagnosis of an anxiety disorder (relative risk=2.6; 95% CI, 1.1–6.3; $P=.04$) or an externalizing disorder (3.6; 1.4–9.0; $P=.007$) was predictive of later onset of major affective disorders.

Conclusions—Childhood anxiety and externalizing diagnoses predict major affective illness in adolescent offspring in families with probands with BP.

Bipolar Disorder (BP) is a highly heritable disorder with up to 85% of variance in risk determined by genetic factors.^{1,2} Family history remains the strongest predictive factor for development of the disorder. Studies^{3–6} of late adolescent and young adult offspring of parents with BP clearly show an increased onset of major affective disorders, including recurrent major depression, BP type I (BPI), and BPII. Adolescent offspring in families of probands with BP (the initially identified subject in a family/genetic study) are at 8- to 10-fold increased lifetime risk for BP and at 3-fold increased lifetime risk for major affective disorders in general.¹

Studies of offspring of probands with BP have typically found a general increase in psychiatric diagnoses in childhood.^{7–14} It is unclear to what extent this increase in diagnoses is an indicator of risk of later mood disorder and to what extent it reflects the stress of living with an affected parent or other familial factors.

The extant literature points to at least 3 common, clinically significant phenotypes related to BP. Attention deficit and disruptive behavior disorders are more frequently diagnosed in adolescents with bipolar spectrum disorders^{6,11,12,15–18} and are typically diagnosed in advance of BP. In adolescence, there is an increase in the prevalence of substance use disorders in individuals with BP, and such disorders may be associated with early age at onset of mood disorder.^{19–21} There is evidence²¹ that individuals with BP and substance use disorders show an increased prevalence of BP in first-degree relatives compared with other individuals with BP.

There also seems to be an increased rate of anxiety disorders in subjects with BP. A common genetic etiology has been proposed for BP and comorbid anxiety disorders.^{22–24} Severity of major affective illness is related to the presence of comorbid anxiety in adolescents and adults, and children with anxiety disorders are significantly more likely to develop BP^{13,24–26} than are children without anxiety disorders. Anxiety disorders may be increased in offspring of subjects with BP.^{11–13} Finally, mood disorder spectrum conditions are increased in families with a proband with BP, and BP not otherwise specified (BPNOS) may predict BPI or BPII.¹³

We may think of these different syndromes as (1) externalizing (including substance use disorders and disruptive behavior disorders), (2) internalizing, and (3) pure affective. It is unclear whether they should be conceptualized as a latent classification of patients or as vulnerability factors that affect all patients with BP through their life course to varying degrees. These syndromes may affect the onset and course of BP and related conditions and may offer different opportunities for preventive intervention. In the present study, we attempted to evaluate these 3 psychiatric phenotypes using diagnostic assessment and specific symptom ratings in at-risk subjects.

Studies involving high-risk subgroups have the distinct advantage of engaging study subjects prior to the onset of the disorder; they offer the ability to prospectively detail the emerging psychopathologic condition and provide for comparison between at-risk offspring who become affected and those who do not become affected.^{19,24} Longitudinal studies that ascertain at-risk participants and monitor them prospectively are the most effective approach for identifying specific etiologic factors.^{8,9,26–28} The present study uses best-estimate diagnoses for childhood disorders as well as adolescent/young adult mood disorder; we also investigated the time course of disorder onset.

We identified at-risk offspring from cohorts specifically selected for genetic study. Cases and controls were compared for lifetime diagnoses; we then characterized subtypes of case offspring at increased risk for major affective disorders. We hypothesized that early internalizing disorders and externalizing disorders (or both) would predict the onset of major affective disorders in families affected by bipolar illness. The advantage of the study design is that it identifies subphenotypes and allows incorporation of cohort-specific genetic risk markers as the study progresses.

METHODS

SUBJECTS

All the clinical procedures were approved by institutional review boards at the 4 subject collection sites: Indiana University School of Medicine, Indianapolis (coordinating site); University of Michigan, Ann Arbor; The Johns Hopkins University School of Medicine, Baltimore, Maryland; and Washington University at St Louis, St Louis, Missouri. Informed consent (or assent with parental consent for subjects <18 years old) was obtained after a thorough explanation of the study. “Case” offspring (the term as used herein does not connote illness but rather “at-risk” status) were ascertained through probands with BP, available from the National Institute of Mental Health Genetics Initiative bipolar sample

(<http://zork.wustl.edu>)²⁹ or similar genetic studies. To our knowledge, all the probands were in treatment at the time of ascertainment (approximately 95% in outpatient treatment and 5% in inpatient treatment).

Probands were characterized using the Diagnostic Interview for Genetic Studies²⁹ and the Family Instrument for Genetic Studies³⁰ and had a lifetime *DSM-IV* diagnosis of BPI (n=126 offspring of 78 probands), BPII with recurrent major depression (n=10 offspring of 6 probands), or schizoaffective disorder, bipolar type (n=5 offspring of 4 probands). For 114 offspring, the proband was a parent, for 13 an older sibling, for 13 an uncle or aunt, and for 1 grandparent. Second-degree relatives were included only when the family was multiplex (at least a proband with BPI and a first-degree relative of the proband with BPI/schizoaffective disorder, bipolar type); multiplex families are associated with a generally higher risk of illness in relatives.³¹ The high-risk sample comprised 91 families, 55 with a single offspring, 26 with 2 offspring, 8 with 3 offspring, and 1 each with 4 and 6 offspring. Of the 141 adolescent cases, 85 were from multiplex BP families (41 confirmed by family study and 44 by the Family Instrument for Genetic Studies), 51 were from simplex families (proband with BP, no first-degree relative with BP), and 5 were from BP families with an unknown extended family history.

Control parents were recruited through general medicine clinics, motor vehicle records, and campus advertising. Exclusion criteria for control parents included BPI, BPII, recurrent major depression, schizoaffective disorder, or schizophrenia in either parent; we also excluded parents with a first-degree relative with a psychiatric hospitalization. The 91 controls are from 58 families: 33 with 1 adolescent offspring, 18 with 2, 6 with 3, and 1 with 4. Forty-eight percent of cases were male compared with 53% of controls ($P=.59$). Eighty-nine percent of cases were European American vs 66% of controls ($P<.001$). Ethnicity was assessed by self-report using the 7 US census categories. The mean (SD) age of cases was 16.7 (3.3) years and of controls was 16.0 (3.1) years ($P=.11$). Subsequent analyses adjusted for these variables. The occupation of the head of the household was used as a proxy for socioeconomic status (no significant difference between groups). These data are summarized in Table 1.

Data were collected between June 1, 2006, and September 30, 2009. In families of cases and controls, all offspring aged 12 to 21 years were invited to participate by being interviewed (using the Kiddie Schedule for Affective Disorders [K-SADS]) and providing a blood specimen for DNA analysis. At least 1 parent had to be living and available for interview; parents were interviewed about themselves (using the Diagnostic Interview for Genetic Studies), about their spouse and other relatives (using the Family Instrument for Genetic Studies), and about all their offspring (using the K-SADS, Parent Version [K-SADS-P]).³² Fifteen offspring in the age range in the case families did not participate in the study; family history information indicates that 1 of the nonparticipants had autism. Four offspring in the age range in the control families did not participate; family history information indicates that 1 had cerebral palsy. Probands with substantial cognitive impairment were not included. In offspring, IQ was not formally tested, but each subject was required to be able to complete the interview and the individual questionnaires as part of the study protocol. One control

participant was diagnosed as having a learning disability and possible intellectual disability during the best-estimate process.

PROCEDURE

The initial task was to establish an assessment procedure for Axis I disorders in children and adolescents. The versions of the K-SADS we reviewed had 2 major limitations: (1) they did not define specific episodes in time and duration before assessing symptoms and (2) they did not include questions targeting each *DSM-IV* criterion item for affective disorders. We adapted questions and interviewer instructions from the Diagnostic Interview for Genetic Studies to address these issues. Additional questions from the Washington University version of the K-SADS³³ were incorporated to provide phenomenologic detail. We developed anchor points for each symptom. We also incorporated screening for organic affective syndromes and psychosis. We then piloted the resulting interview in adolescent subjects (K-SADS) and their parents (K-SADS-P) at each of the collaborative sites. The interview was prepared in computer-scorable form, which can also be used for data entry. The K-SADS-BP is now available at <http://www.bipolargenes.org/hrdownloads.html> and is fully computerized. Diagnoses are not algorithmic but are generated by clinical consensus, as noted later herein. Interviewers were extensively trained by the principal investigators and coordinators at each site after a weeklong common training at the Indiana University coordinating site. At each site, the interviewers or clinical coordinators had an extensive clinical background. Interviews were performed either in person (35.2%) or by telephone (64.8%). The reliability of telephone interview for such purposes has been documented.³⁴ Interviewers were not blind to subject status, in keeping with previous family study practices.³⁵ Interviewers were blind to the specific hypotheses of the study.

Diagnoses and age at onset determinations were made on the basis of consensus between 2 clinicians (ie, psychiatrists with child specialty training, clinical psychologists, or clinical social workers), including information from direct interview (retrospective data), medical records (cross-sectional data), and parent interview (retrospective data). Best-estimate clinicians were blinded to the case-control status of the participant. Lifetime diagnoses were assigned according to *DSM-IV* criteria, including BPNOS, which was generally diagnosed only if the participant approached the criteria for BPII but had 1 fewer symptom in the hypomanic and depressive categories. Diagnoses of mania were made by consensus, with strict adherence to *DSM-IV* criteria. The κ value for interrater reliability for a major affective disorder diagnosis was 0.82 and for other disorder categories ranged from 0.70 to 0.85. A subgroup of 30 subjects with an interview diagnosis of major affective disorder was examined as an assessment of internal validity: 25 of these subjects also had major affective disorders on best estimate (83%); 21 of 30 (70%) showed agreement on disorder subtype. The best-estimate process also included consensus ratings of lifetime symptom severity (a combination of frequency and intensity of symptoms) in the categories of mood, anxiety, and behavior using a 7-point scale. Weighted κ values were 0.77 for ratings of lifetime mood symptom severity, 0.70 for behavioral symptoms, and 0.67 for anxiety symptoms.

STATISTICAL ANALYSES

Demographic and clinical characteristics were compared between cases (n=141) and controls (n=91) using the Fisher exact test, the 2-sided *t* test for quantitative data, or the Wilcoxon test for ordinal data. A logistic regression model, using generalized estimating equations to account for correlation between siblings, was used to compare cases and controls on dichotomous diagnoses while adjusting for age, sex, and ethnicity. Exact logistic regression was used when dichotomous diagnoses had a 0 cell count. Linear mixed models were used to compare cases and controls on symptom ratings. The SAS GENMOD and MIXED procedures were used for generalized estimating equations and linear mixed-model estimation, respectively.

Using age-at-onset data, we constructed Kaplan-Meier survival curves for major affective disorders (BPI; schizoaffective disorder, bipolar type; BPII; and major depression, recurrent or single episode), minor affective disorders (BPNOS, adjustment disorder with depressed mood, depression NOS, and dysthymia), anxiety disorders (obsessive-compulsive disorder, panic disorder with or without agoraphobia, simple phobia, specific phobia, separation anxiety disorder, generalized anxiety disorder/overanxious disorder, adjustment disorder with anxious mood, posttraumatic stress disorder, and other anxiety disorder), and externalizing disorders (attention-deficit/hyperactivity disorder, any alcohol use disorder, any drug use disorder, conduct disorder, oppositional defiant disorder, and other behavioral disorder). We report a *P* value for the log-rank test for the survival function. The Cox proportional hazards regression model, estimated using an R package routine (R Foundation for Statistical Computing, Vienna, Austria), was used to estimate hazard ratios for the survival analysis while adjusting for the effects of covariates and the familial correlation. The hazard ratio may be interpreted as a relative risk (RR), and we use this term in the analyses reported herein.

Additional analyses were performed on subgroups of cases with major affective disorders (n=33), minor affective disorders (n=21), and no affective disorder (n=87). Subjects with major affective disorders had a higher average age (18.2 years) than did those with minor affective disorders (16.5 years) or no affective disorder (16.2 years); no significant differences were noted in sex and ethnicity. We included all these characteristics (and sibling correlation) in the statistical models for consistency between the main analyses and the subgroup analyses.

RESULTS

CASE-CONTROL COMPARISONS

Table 2 provides the distribution of diagnoses in the sample: 23.4% of cases (n=33) were diagnosed as having major affective disorders vs 4.4% of controls (n=4) (adjusted *P*=.002). No difference in minor affective disorders (as a category or individually) was seen between the groups. No differences were seen in anxiety disorders, substance use disorders, attention-deficit/hyperactivity disorder/disruptive behavior disorders, or any specific disorder in these diagnostic categories. No chronic psychotic disorder was seen in subjects in either group. If we combine subgroups of BP, 8.5% of case offspring (n=12) had BPI, BPII, or BPNOS

compared with 0% of control offspring (adjusted $P=.007$). Figure 1 shows a significant difference between cases and controls in the onset of major affective disorders (log-rank test $P<.001$). The adjusted RR was 5.33 (95% confidence interval [CI], 1.8–15.7; $P=.002$). By age 16 years, a mean (SE) of 25.4% (4%) of cases had a diagnosis compared with 5.7% (3%) of controls. No significant difference in the onset of other affective disorders, anxiety disorders, or behavior disorders was seen between cases and controls after adjustment (Table 2). Sixty percent of cases had 1 or more diagnoses compared with 40% of controls ($P=.09$).

Best-estimate clinicians' impressions of lifetime severity of symptoms in 3 domains are provided in eTable 1 (<http://www.archgenpsychiatry.com>). Ratings for mood symptoms were increased before, but not after, correction for covariates ($P=.10$); behavioral ratings were not higher in cases than controls ($P=.70$). Symptom ratings were intercorrelated (Pearson r for anxiety and mood ratings= 0.60 ; anxiety and behavior ratings $r=0.41$; mood and behavior ratings $r=0.53$; all $P<.001$).

Table 3 compares the features of illness in cases ($n=54$) and controls ($n=17$) with major or minor affective disorders. Cases were more likely to have major affective diagnoses (61.1% vs 23.5%, $P=.01$), multiple mood episodes (37.0% vs 5.9%, $P=.02$), and impairment at home, at school, or with peers (44.0% vs 11.8%, $P=.02$). Symptom ratings for cases and controls with major or minor affective disorders followed the same pattern as noted previously herein: mood ratings were elevated in cases ($P=.007$) compared with controls, and anxiety and behavior ratings were not different in the 2 groups.

DIFFERENTIATING AFFECTED AND UNAFFECTED CASES

Within the case sample, some offspring have manifested major affective disorder and some have not. We divided the cases into 3 subgroups: those with major affective disorder ($n=33$), those with minor affective disorders ($n=21$), and those with no affective disorder ($n=87$). We used this division to check certain ascertainment variables: no difference was found in the distribution of cases in the 3 groups depending on whether the proband was a parent or not ($\chi^2 P=.64$); it also did not make a difference whether the case was interviewed by telephone or in person ($\chi^2 P=.51$). There is no difference in the distribution of multiplex and simplex families in the 3 groups ($\chi^2 P=.74$). There is also no difference when we compare offspring in families with a BPI proband to offspring in families with a BPII proband (Fisher exact test $P=.90$). There is also no difference when we compare offspring in families in which the interviewed parent was affected compared with those in which the interviewed parent was unaffected (Fisher exact test $P=.40$). Symptom ratings for cases divided by mood disorder outcome are presented in eTable 2 and show increased ratings in all domains for affected subjects.

Figure 2A shows a significant difference in the onset of anxiety disorders among the 3 subgroups (log-rank test $P<.001$). Participants with major affective disorders had an adjusted RR of 4.0 (95% CI, 1.9–8.5; $P<.001$) for an anxiety diagnosis in relation to participants with no affective disorder. This was still true when we controlled for the presence of comorbid anxiety disorders in the parent/proband (RR=3.8, $P<.001$). Participants with minor affective disorders did not show an increased risk of anxiety disorder compared with participants with no affective diagnosis.

Figure 2B shows a significant difference in the incidence of externalizing disorders among the 3 subgroups (log-rank test $P<.001$). The adjusted RR for externalizing disorders in participants with major affective disorders was 4.0 (95% CI, 1.8–8.8; $P<.001$) compared with participants with no affective disorder. This was still true when we controlled for comorbid externalizing disorder in the parent/proband (RR=4.2, $P<.001$). The RR for participants with minor affective disorders was 4.0 (95% CI, 1.8–9.3; $P=.001$) compared with participants with no affective disorder. When we considered attention-deficit/hyperactivity disorder/disruptive behavioral disorders separately, the RR for participants with major affective disorders was 4.8 (95% CI, 1.6–14.0; adjusted $P<.005$) and for subjects with minor affective disorders was 5.5 (95% CI, 1.8–16.5; adjusted $P<.002$). When we considered substance use disorders separately, the RR for participants with major affective disorders was 2.1 (95% CI, 0.8–5.3; adjusted $P=.13$) and for participants with minor affective disorders was 2.7 (95% CI, 0.95–7.7; adjusted $P=.06$).

eTable 3 shows a division of affected cases with major affective disorder into those with comorbid anxiety disorders (internalizing), comorbid behavioral disorders (externalizing), both, or purely affective disorder. Those with both anxiety and behavioral comorbid disorders show generally earlier onset of mood disorder diagnosis and more evidence of psychopathology, including significantly greater ratings of mood, anxiety, and behavioral symptoms and an increase in substance use disorders in comparison to other groups.

PREDICTION OF MAJOR AFFECTIVE DISORDERS IN OFFSPRING

We tested the prognostic significance of childhood onset disorders in cases and controls (Figure 3). Two early-onset subgroups were defined to include case subjects who had a lifetime *DSM-IV* diagnosis of an anxiety disorder or an externalizing disorder (generally disruptive behavior disorders) with age at onset of 12 years or younger. Of those with early-onset anxiety disorder, 9 of 25 participants (36.0%) developed a major affective disorder later. The RR (compared with the group without early onset of either type of disorder) after adjusting for comorbid anxiety/behavioral disorders in the parent/proband was 2.6 (95% CI, 1.1–6.3; $P=.04$). Of those with early-onset externalizing disorder, 8 of 19 (42.1%) developed a major affective disorder later. The RR after adjusting for comorbid anxiety/behavioral disorders in the parent/proband was 3.6 (95% CI, 1.4–9.0; $P=.007$). Five participants had early onset of both anxiety and externalizing disorders (data not shown); the adjusted RR in this group was 6.3 (95% CI, 1.4–27.1; $P=.01$).

Two of 25 controls (8%) with any early-onset psychiatric disorder developed a major affective disorder compared with 2 of 66 controls (3%) without an early-onset disorder ($P=.25$).

COMMENT

Nearly one-quarter of adolescent offspring in families with probands with BP demonstrated major affective disorders at an average assessment age of 17 years compared with 4% of controls. More than 8% of cases were diagnosed as having BPI, BPII, or BPNOS, whereas no control offspring received such a diagnosis. No difference was seen in any other disorder or group of disorders. Survival analysis showed a similar pattern, with the 2 groups

diverging on rate of mood disorders in childhood (at age 12 years, the risk of major affective disorders is 10% in cases vs 1% in controls) but not in the onset of other disorders. Most of the excess risk in cases is for nonbipolar major depressive disorders (either recurrent or single episode). The onset of minor affective disorders is not elevated in cases, although case subjects with minor affective disorders show an excess of comorbid externalizing disorders compared with other cases and deserve careful follow-up.

It is important to underscore the fact that most offspring in families with probands with BP will not develop BP themselves. Bipolar disorder is present in 1% to 2% of the population and perhaps up to 4% if BPNOS is included.³⁶ Many of these disorders will have onset in adolescence (in the National Institute of Mental Health Genetics Initiative BPI sample of probands with BPI and affected relatives, 45% had their first onset of major mood disorder between ages 12 and 21 years; see the study by Dick et al³⁷ for ascertainment and assessment methods), but few of these subjects with BPI had prepubertal onset of major mood disorder (approximately 5%–10%). See also the study by Merikangas et al³⁸ for comparable results using epidemiologic methods. Most prepubertal mood episodes will be depressions, not manias. The median age at onset of depression for 858 subjects in the National Institute of Mental Health Genetics Initiative sample was 18.9 years, and the median age at onset of mania was 22.0 years (n=576). Approximately 12% of first episodes of major depression in this group were seen at 12 years or younger; approximately 5% of first episodes of mania were seen in that age range. On the basis of these data, we predict a population prevalence of 0.05% for prepubertal mania. In a report from the Systematic Treatment Enhancement Program for Bipolar Disorder,³⁹ 72 of 983 patients with BP had onset of mania at 13 years or younger, leading to an estimated population prevalence of 0.05% to 0.1%. We suggest that substantially higher estimates may be targeting a different disorder (such as the syndrome of severe mood dysregulation described by Leibenluft et al^{40,41}). In the present study, 3 of 141 case subjects (2.1%) and 0 of 91 controls reported mania during childhood years. Affectively ill case subjects in this study tended to be episodically rather than chronically ill.

We did not find an increase in disruptive behavior disorders in offspring at risk for BP compared with controls, in contrast to some previous studies.⁴² This may be an issue of sample size, as a nonsignificant increase was seen. We did see increased disruptive behavior disorder (without including substance use disorders) in case offspring with mood disorders (adjusted $P=.005$; RR=4.8; 95% CI, 1.6–14.0), and we did find disruptive behavior disorders (without substance use disorders) to be predictive of later mood disorder in cases (adjusted $P=.03$; RR=3.3; 95% CI, 1.1–9.6).

Studies of offspring at risk for the development of psychiatric disorders can support 2 types of comparisons: (1) cases (at higher risk) and controls (at lower risk) and (2) cases who have become affected and cases who have not become affected. Most offspring in families with probands with BP will not develop major affective disorders themselves, and so they form a well-matched control group for those who do. However, some well offspring have not passed the age of risk by the time of assessment, and some others may carry nonpenetrant vulnerability markers. Therefore, this type of comparison tends to increase false-negative

findings but decrease false-positive findings. Such cohorts may be useful in the examination of potential endophenotypes.

We hypothesized 3 syndromes related to BP (and related mood disorders): (1) pure affective, (2) internalizing (with comorbid anxiety disorder), and (3) externalizing (with comorbid substance use/behavioral problems). Factor analysis in adult subjects with BP supports this division (P.O.M.; W. H. Coryell, MD; J. Harezlak; G. A. Marcoulides, PhD; H. L., and C. M. Steeger; unpublished data; 2011). On this basis, we assessed severity ratings of mood, anxiety, and behavioral symptoms. When at-risk subjects as a group are compared with controls, only mood ratings differentiate the groups. But when we subdivide the at-risk subjects into those who are affected and those who are unaffected, differences in severity ratings of anxiety and behavioral symptoms become evident. Anxiety and behavioral symptoms and diagnoses may then be further examined as clinical predictors of major mood disorders.

The results of the present study suggest that nonaffective childhood psychiatric diagnoses may have different significance in offspring in families with BP than they do in controls (although they are not increased in prevalence). In at-risk offspring, these disorders seem to be markers of vulnerability to later onset of major mood disorders (either BP or unipolar disorder). Specifically, childhood anxiety disorders are associated with a 3-fold increased risk of major affective disorders, and childhood externalizing disorders are associated with a 4-fold increased risk. Once a major affective disorder has begun, these data suggest that the course is likely to be more severe (although not necessarily BP) in subjects at familial risk. These observations have potential clinical significance. They reinforce the importance of family history in evaluating the meaning of diagnoses in children and adolescents, and they support a different monitoring and management strategy for children and adolescents with a positive family history of BP.

We should acknowledge the limitations of the present observations. The sampling methods are not epidemiologic, and, thus, the results may not accurately reflect population prevalences. The assessment of childhood diagnoses rests on a combination of retrospective data from child and parental observations and point-in-time data from medical records. As this study progresses, we intend to test these observations further in subjects at risk examined prospectively. We also anticipate that enrollment of larger numbers of participants will enable us to test hypotheses regarding the predictive significance of specific types of anxiety or behavioral disorders. Larger numbers should also support the differentiation of precursors of BP from precursors of major depression.

In the present series, African Americans are underrepresented in cases and overrepresented (relative to the population at the sites) in controls. We have planned a group-matching procedure for the study sample as it progresses and will preferentially recruit appropriate subjects to equalize the samples.

As an ancillary contribution of this study, we developed a modified assessment tool, the K-SADS-BP, which conforms to *DSM-IV* adult criteria for BP and other Axis I diagnoses. We believe that this offers advantages over other versions of the K-SADS in episode definition,

course of illness, and direct mapping of responses onto diagnostic criteria; the computerized version also offers efficiency in administration and data entry. The K-SADS-BP gives reliable results for multiple Axis I diagnoses (see previously herein).

In summary, we described the initial stages of an ongoing longitudinal study of subjects at risk for BP and related disorders. A specific increase in mood disorders was seen in case subjects compared with controls. Affected cases tended to have more severe and impairing disorders than did controls. Among case subjects who have become affected, diagnoses of anxiety and behavioral disorders were increased, as were consensus ratings of symptoms in those domains. Childhood diagnoses of anxiety and externalizing disorders seemed to have premonitory significance in offspring in families with probands with BP in that they presaged adolescent development of major affective disorders. Similar findings were recently reported by Duffy et al.¹⁷

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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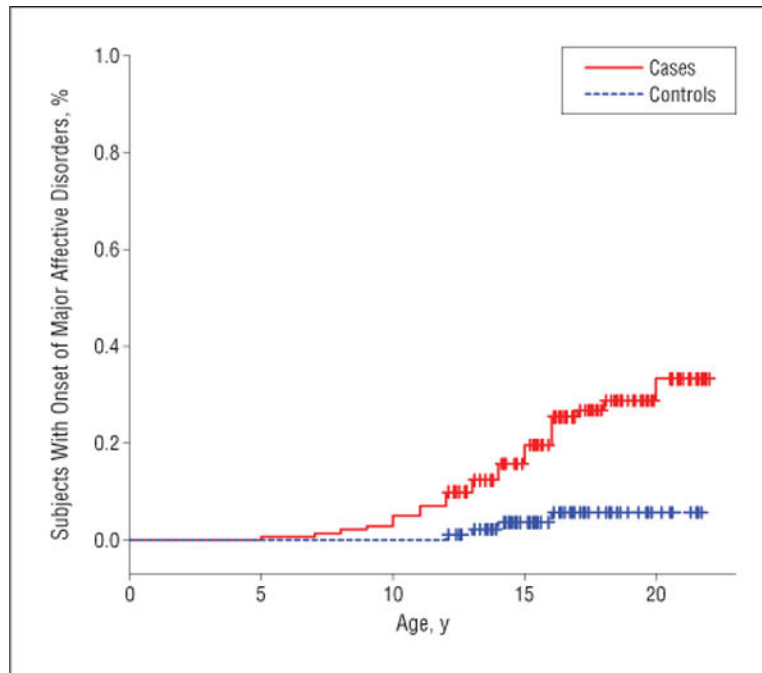


Figure 1. Onset of major affective disorders in cases (n=141) and controls (n=91). The 2 groups are significantly different by log-rank test ($P<.001$).

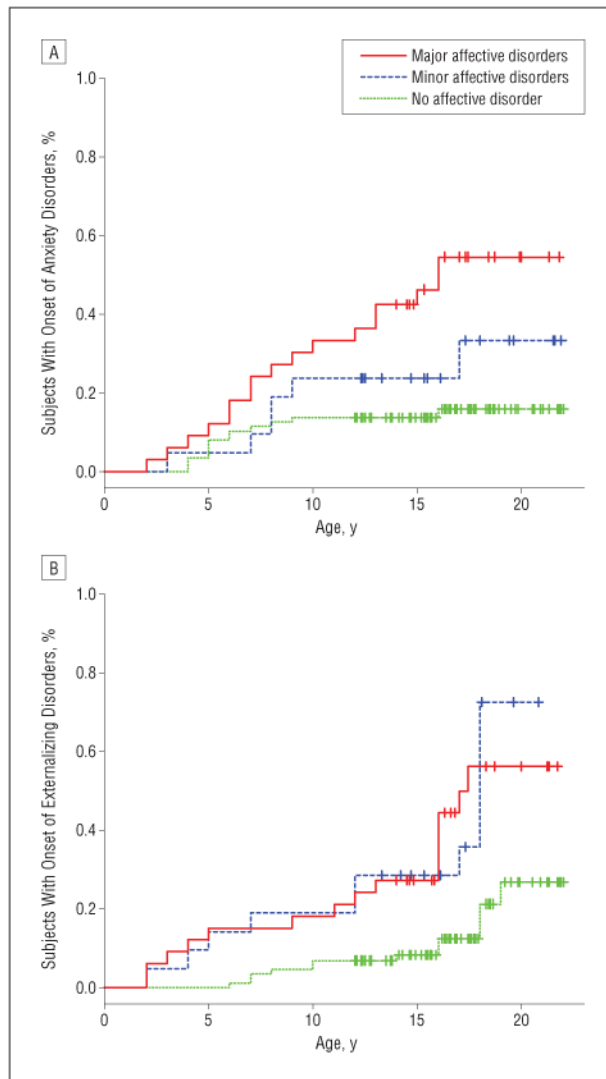


Figure 2. Onset of anxiety disorders (A) and externalizing disorders (B) in cases with major affective disorders (n=33), minor affective disorders (n=21), and no affective disorder (n=87). The 3 groups are significantly different by log-rank test ($P<.001$).

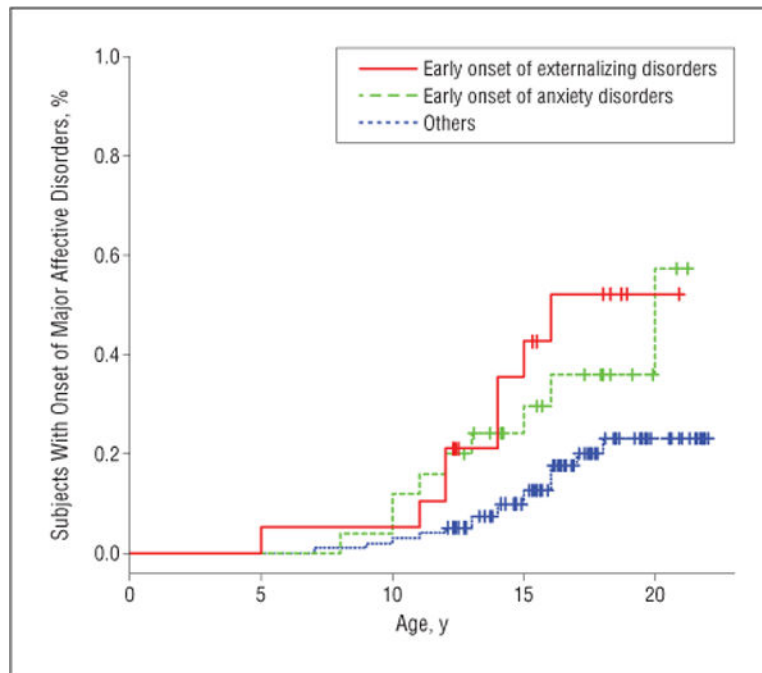


Figure 3.

Onset of major affective disorders in cases with an externalizing diagnosis by 12 years of age ($n=19$), an anxiety diagnosis by 12 years of age ($n=25$), and neither early-onset behavioral nor anxiety disorders ($n=97$). The 3 groups are significantly different by log-rank test ($P=.007$).

Table 1

Demographic and Clinical Comparison of Cases and Controls

Characteristic	Cases (n = 141)	Controls (n = 91)	P Value	Statistic
Male sex, %	48.2	52.7	.59	Exact
Age, mean (SD), y	16.7 (3.3)	16.0 (3.1)	.11	$t = 1.61$
Ethnicity, European American, %	89.4	65.9	<.001	Exact
Education, mean (SD), last year completed	10.6 (2.5)	10.1 (2.3)	.13	$t = 1.51$
Living with mother, %	87.2	93.0	.25	Exact
Living with father, %	66.7	65.3	.87	Exact
Telephone interview, %	66.9	61.5	.48	Exact
Proband occupation, mean (SD) ^a	2.6 (0.8)	2.5 (0.9)	.09	W = 4346.5
Proband with anxiety disorder, % ^b	50.8	18.1	<.001	Exact
Proband with behavioral disorder, %	77.7	27.6	<.001	Exact
Proband without anxiety or behavioral disorder, %	14.9	60.0	<.001	Exact

Abbreviations: Exact, Fisher exact test; W, Wilcoxon rank-sum test

^a Scores used for head of household's occupation were as follows: 1, executive, administrative, and managerial occupations; 2, professional specialty, writers, artists, entertainers, and athletes; 3, technicians, sales, administrative, private household, protective service, service, farm operators and managers and other farming, forestry, and fishing occupations; 4, mechanics and repairers, construction trades, extractive occupations, precision production occupations, machine operators, assemblers, and inspectors; and 5, other occupations, including transportation and material moving, handlers, equipment cleaners, helpers, and laborers.

^b Best-estimate diagnoses in case parents/probands with bipolar disorder (n = 91); Diagnostic Interview for Genetic Studies diagnoses in control parents (n = 105); minor mood disorders are combined with anxiety disorders in control parents.

Table 2

Psychiatric Disorders in Cases and Controls

Psychiatric Disorder	Subjects, No. (%)		Unadjusted P Value ^d	Statistic	Adjusted P Value ^b
	Cases (n = 141)	Controls (n = 91)			
Bipolar disorder type I	6 (4.3)	0	.08	Exact	.15 ^c
Bipolar disorder type II with recurrent depression	4 (2.8)	0	.16	Exact	.33 ^c
Single-episode major depression	14 (9.9)	3 (3.3)	.07	z = -1.4	.15
Major depression, recurrent	9 (6.4)	1 (1.1)	.09	z = -1.6	.11
Any major affective disorder	33 (23.4)	4 (4.4)	<.001	z = -3.1	.002
BPNOS	2 (1.4)	0	.52	NC	NC
Any bipolar disorder	12 (8.5)	0	.004	z = -2.7	.007
Any minor affective disorder	21 (14.9)	13 (14.3)	>.99	z = -0.6	.58
Any anxiety disorder	37 (26.2)	13 (14.3)	.03	z = -1.3	.19
Any substance use disorder	25 (17.6)	8 (8.8)	.02	z = -1.5	.12
Any ADHD	11 (7.8)	5 (5.5)	.60	z = -0.4	.67
Disruptive behavior disorder (not ADHD)	15 (10.6)	7 (7.7)	.50	z = 0.48	.63
Any externalizing disorder (ADHD, disruptive behavior, or substance use)	38 (27.0)	17 (18.7)	.16	z = -0.6	.53
No diagnosis	57 (40.4)	55 (60.4)	.003	z = 1.7	.09

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BPNOS, bipolar disorder not otherwise specified; Exact, Fisher exact test; NC, not calculated.

^aThe Fisher exact test was used to compute the unadjusted P value.

^bThe logistic regression models were implemented using generalized estimating equations to account for the familial correlation and to adjust for age, sex, and ethnicity.

^cBecause of the 0 cell count for controls, exact logistic regression models were used to adjust for age, sex, and ethnicity.

Table 3

Clinical Characteristics of Affective Episodes in Cases and Controls

Characteristic	Cases (n = 54)	Controls (n = 17)	P Value	Statistic
Major affective disorders, No. (%)	33 (61.1)	4 (23.5)	.01	Exact
Minor affective disorders, No. (%)	21 (38.9)	13 (76.5)		
Age at onset of mania, median (IQR), y	12.5 (10–14)	NA	NA	NA
Age at onset of depression, median (IQR), y	12 (10.5–15.5)	13.5 (12–14)	.53	W = 90
Age at onset of hypomania, median (IQR), y	16 (11.5–17.0)	NA	NA	NA
Multiple episodes (any polarity), No. (%)	20 (37.0)	1 (5.9)	.02	Exact
Clear episodic disorder, No. (%) ^a	16 (29.6)	2 (11.8)	>.99	Exact
Persistent affective symptoms, No. (%) ^a	10 (18.5)	1 (5.9)		
Any psychotic symptoms, No. (%)	8 (14.8)	0	.18	Exact
Mixed episodes (possible or definite), No. (%)	8/49 ^b (16.3)	0	.12	W
Rapid cycling (definite), No. (%)	1 (1.9)	0/16 ^b	>.99	Exact
Suicidal thoughts or behavior, No. (%)	23/53 ^b (43.4)	7 (41.2)	.67	W
Comorbid substance abuse, No. (%)	16/49 ^b (32.7)	3/12 ^b (25.0)	.71	W
Episode severity moderate or greater, No. (%)	38/51 ^b (74.5)	8/16 ^b (50.0)	.08	W
Significant effect on life functioning, No. (%)	22/50 ^b (44.0)	2 (11.8)	.02	Exact

Abbreviations: Exact, Fisher exact test; IQR, interquartile range; NA, not applicable; W, Wilcoxon rank-sum test.

^a Comparisons are among subjects with illness of 2 years or more (26 cases and 3 controls) because those with illness of less than 2 years would be indeterminate for these variables.

^b Where denominators are reduced by missing data, this is noted by inclusion of the true denominator.