A High-Risk Study of Bipolar Disorder

Childhood Clinical Phenotypes as Precursors of Major Mood Disorders

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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.

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.

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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. 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 than are children without anxiety disorders. Anxiety disorders may be increased in offspring of subjects with BP. Finally, mood disorder spectrum conditions are increased in families with a proband with BP, and BP not otherwise specified (BNOS) may predict BPI or BPII.

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. Longitudinal studies that ascertain at-risk participants and monitor them prospectively are the most effective approach for identifying specific etiologic factors. 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, 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) 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 Studies and the Family Instrument for Genetic Studies 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 1 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. 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]). 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-SADS 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 pilot 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. Detailed description of the anchor points and interviewer instructions is available online at K-SADS-BP website. The anchor points are organized into 3 domains: psychological symptoms (anxiety and behavior), diagnostic symptoms (mood), and sociodemographic variables.

Table 1. Demographic and Clinical Comparison of Cases and Controls

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

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

The K-SADS was developed for use in research projects to provide a structured interview for the assessment of affective disorders, anxiety disorders, and substance use disorders. The K-SADS is a semistructured interview designed to be used in both research and clinical settings. It is composed of a diagnosis section and a symptom section. The diagnosis section includes a series of yes/no questions that are used to determine whether a disorder is present. The symptom section includes a series of questions that are used to determine the severity of each symptom.

The K-SADS is based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). The DSM-IV is a widely used classification system for mental disorders. It is based on the concept of a syndrome, which is a group of symptoms that are associated with a particular disorder. The DSM-IV includes 10 diagnostic categories: mood disorders, anxiety disorders, obsessive-compulsive disorder, substance use disorders, eating disorders, sleep disorders, somatoform disorders, sexual and gender identity disorders, paraphilic disorders, and other specified and unspecified disorders.

The DSM-IV is used in research to classify mental disorders. It is also used in clinical settings to make diagnoses and to plan treatment. The DSM-IV is based on a number of criteria that are used to determine whether a disorder is present. The criteria include the presence of a symptom, the frequency of the symptom, and the duration of the symptom.

The K-SADS is a useful tool for research and clinical purposes. It is easy to use and it can be used to make diagnoses and to plan treatment. The K-SADS is also a useful tool for research. It can be used to compare groups of patients and to identify risk factors for mental disorders.

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tistical 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: 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 (χ² = 0.64); it also did not make a difference whether the case was interviewed by telephone or in person (χ² = 0.51). There is no difference in the distribution of multiplex and simplex families in the 3 groups (χ² = 0.74). 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 5.5 (95% CI, 1.8-16.5; 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 4.0 (95% CI, 1.8-9.3; P = .001) compared with participants with no affective disorder. 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 disor-
ders (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. Many of these disorders will have onset in adolescence (in the National Institute of Mental Health Genetics Initiative BPI sample of probands with BP and affected relatives, 45% had their first onset of major mood disorder between ages 12 and 21 years; see the study by Dick et al for ascertainment and assessment methods), but few of these subjects with BP had prepubertal onset of major mood disorder (approximately 5%-10%). See also the study by Merikangas et al 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, 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). In the present study, 3 of 141 case subjects (2.1%) and 0 of 91 controls reported mania during childhood years. Affectionally 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. 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 cases at risk 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

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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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REFERENCES


