Published in final edited form as:

J Am Acad Child Adolesc Psychiatry. 2010 April ; 49(4): 388–396.

Clinical, Demographic, and Familial Correlates of Bipolar Spectrum Disorders among School-aged Offspring of Parents with Bipolar Disorder

Benjamin I. Goldstein, MD, PhD,

Sunnybrook Health Sciences Centre, University of Toronto Faculty of Medicine

Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine

Wael Shamseddeen, MD, MPH,

Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine

David A. Axelson, MD,

Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine

Cathy Kalas, RN,

Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine

Kelly Monk, RN,

Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine

David A. Brent, MD,

Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine

David J. Kupfer, MD, and

Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine

Boris Birmaher, MD

Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine

Abstract

Objective—Despite increased risk, most offspring of parents with bipolar disorder (BP) do not manifest BP. The identification of risk factors for BP among offspring could improve preventive and treatment strategies. We examined this topic in the Pittsburgh Bipolar Offspring Study (BIOS).

Method—Subjects included 388 offspring, ages 7–17 years, of 233 parents with BP-I or BP-II (via the Structured Clinical Interview for DSM-IV). Offspring diagnoses were determined using the Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present and

© 2009 American Academy of Child & Adolescent Psychiatry. Published by Elsevier Inc. All rights reserved.

Corresponding author: Benjamin Goldstein, MD, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, FG-53, Toronto, Ontario, M4N-3M5, benjamin.goldstein@sunnybrook.ca.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Disclosure: Dr. Birmaher has received research support from the National Institutes of Mental Health. He serves as a consultant for Schering Plough. He receives royalties from Random House, Inc., and Lippincott Williams & Wilkins. Drs. Goldstein, Axelson, Brent, Shamseddeen, and Kupfer, and Ms. Kalas, and Ms. Monk report no biomedical financial interests or potential conflicts of interest.

Lifetime version (KSADS-PL). Analyses focused on the 41 offspring who were diagnosed with BP-I (N=9), BP-II (N=5), or BP-NOS (N=27).

Results—Offspring with BP had proband parents who were significantly younger at the time of their birth, were more likely to be female, and had lower socio-economic status, versus proband parents of offspring without BP. Parental clinical variables and obstetrical variables were not significantly associated with BP among offspring. History of physical and/or sexual abuse, exposure to antidepressants, and exposure to stimulants was significantly greater among offspring with versus without BP. There was significantly greater prevalence of attention-deficit hyperactivity disorder, anxiety disorders, oppositional-defiant/conduct disorders (ODD/CD), and exposure to stimulants and antidepressants among offspring with versus without BP. Variables significantly associated with BP among offspring in regression analyses were: older offspring age, younger parent age at birth, offspring anxiety disorders and ODD/CD, and biological co-parent with BP.

Conclusion—History of anxiety and/or disruptive behavior disorders, as well as presence of bi-lineal parental BP, is associated with elevated risk of bipolar spectrum disorders among offspring. If replicated prospectively, these findings could have implications for the diagnosis and treatment of psychopathology among BP offspring.

Keywords

bipolar disorder; high risk; offspring; familial

INTRODUCTION

There is substantial evidence that having a parent with bipolar disorder (BP) confers an increased risk of BP to child and adolescent offspring. A meta-analysis 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 parents¹. In the Pittsburgh Bipolar Offspring Study (BIOS), BP-spectrum (N=9 BP-I, N=5 BP-II, and N=27 BP-NOS) was prevalent among 10.6% of high-risk offspring and 0.8% of control offspring at intake.² The majority of offspring of parents with BP do not manifest BP cross-sectionally ($\leq 15\%$)¹. Although it is likely that higher rates of offspring BP would be identified in studies with longer duration of follow-up, it is important to note that even studies of adults who have been through the period of greatest risk for BP have found that the large majority do not suffer from BP³. Therefore, the question arises as to what are the factors associated with BP among offspring of parents with BP? Gaining insights regarding whom among offspring of parents with BP is at particularly elevated risk has important implications in terms of targeted and individualized prevention and intervention efforts.

There are several potential sources of risk that can be gleaned from studies of adults with BP and from previous studies of offspring of parents with BP and major depressive disorder (MDD). These include: older parental age and female sex^{4, 5}; environmental factors such as low birth weight, obstetrical complications (OC) and sexual or physical abuse^{6–11}; parental illness characteristics such as earlier age of onset, greater mood episode severity, mood episode recurrence, and comorbidity, and biological co-parent psychopathology^{12–17}; bi-lineal parental BP^{2, 18}; antecedent psychopathology (which predates BP) in the child such as anxiety disorders and attention-deficit hyperactivity disorder (ADHD).^{19–22} Several studies have examined for correlates of psychopathology in general among child and adolescent offspring of parents with BP. However, the few studies examining correlates of BP specifically among child and adolescent offspring of parents with BP have been constrained by small sample sizes.^{8, 17, 20} The main goal of this article is to identify variables that may be associated with increased risk of BP among child and adolescent offspring of parents

with BP. Based on the limited extant literature, we hypothesized that offspring BP would be associated with the above-noted factors.

METHOD

Subjects

Parents (Probands)—The methods for BIOS have been described in detail elsewhere². Briefly, parents with BP were recruited through advertisement (53%), adult BP studies (31%) and outpatient clinics (16%). There were no differences in BP subtype, age of BP-onset, or rates of non-BP disorders on the basis of recruitment source. Parents were required to fulfill Diagnostic and Statistical Manual, Version-IV (DSM-IV) criteria for BP-I or -II. Exclusion criteria included current or lifetime diagnoses of schizophrenia, mental retardation, mood disorders secondary to substance abuse, medical conditions, or medications, and living more than 200 miles away from Pittsburgh.

Offspring of BP parents—With the exception of children who were unable to participate (e.g., mental retardation), all offspring ages 6–18 years old 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 paper will be discussed. DSM-IV psychiatric disorders for proband parents, and biological co-parents who participated in direct interviews (30%), were ascertained through the Structured Clinical Interview-DSM-IV (SCID)²³ plus the ADHD, disruptive behavior disorders (DBD) and Separation Anxiety Disorder (SAD) sections from the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (K-SADS-PL).²⁴

The Family History-Research Diagnostic Criteria method (FH-RDC)²⁵ plus ADHD and DBD items from the KSADS was used to ascertain the psychiatric history of second-degree relatives, biological co-parents not seen for direct interview, and siblings of offspring that were too old (>18 years) to participate at intake. There was no significant difference between co-parents interviewed via SCID and those with history obtained via FH-RDC with respect to history of psychotic disorder, bipolar disorder, alcohol and substance abuse, DBD, or ADHD. On the other hand, co-parents interviewed via SCID were more likely to have history of depression (25.4% vs. 10.2%, $p<0.001$), dysthymia (5.6% vs. 1.3%, $p=0.01$), and anxiety (24.6% vs. 7.2%, $p<0.001$) as compared to parents with history obtained via FH-RDC. 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 Mania Rating Scale (K-MRS)²⁶ and the depression section of the KSADS-P were used (For these instruments see www.wpic.pitt.edu/research, under “Assessments”). As per the KSADS-PL instructions, mood symptoms that were also in common with other psychiatric disorders (e.g., 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 diagnoses were made using the DSM-IV criteria. However, to avoid diagnosing youth with “soft” BP symptoms, an operationalized and more strict DSM- BP- not-otherwise specified (NOS) diagnosis was utilized.²⁷ Youth with this more strict BP-NOS diagnosis

have a similar, but less severe clinical picture, comorbid disorders, family history, and longitudinal outcome compared to BP-I subjects.^{27, 28} Moreover, about 40% of these youth diagnosed with BP-NOS converted into BP-I or II.²⁹ With the exception of BP-NOS in children, and biological co-parents, other NOS and adjustment disorders for children or adults were not included in this paper. Given that the DSM-IV criteria for BP NOS are not specific and there are no other available criteria for this BP subtype, this study employed the operationalized COBY definition of BP NOS as follows: elevated and/or irritable mood, plus: 1) two associated DSM-IV manic symptoms (three if only irritable mood), 2) change in functioning, 3) mood and symptom duration of at least four hours within a 24-hour period, and 4) episode frequency of at least four cumulative 24-hour periods meeting the mood, symptom, and functional change criteria over the subject's lifetime. In the vast majority of cases, youth with BP-NOS in COBY did not meet criteria for BP-I or -II because of insufficient duration of symptoms rather than insufficient number of symptoms.

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

Bachelors- or masters-level interviewers completed all assessments after intensive training for all instruments and after $\geq 80\%$ agreement with a certified rater. The overall SCID and K-SADS kappas for psychiatric disorders were ≥ 0.8 .

About 90% of assessments were carried out in the subjects' homes. To ensure blindness to parental diagnoses, the interviewers who met with the parent to assess parental psychopathology were different from the interviewers who assessed their children's psychopathology. All data (adult, child, and family) were presented to a child psychiatrist for diagnostic confirmation. The child psychiatrists were also blind to the psychiatric status of the parents. When necessary, subjects' medical and psychiatric records were obtained and reviewed by their respective interviewers.

The Petersen Pubertal Developmental Scale (PDS)³⁰ was used to evaluate pubertal development. Socio-economic status (SES) was ascertained using the Hollingshead scale.³¹ Obstetrical history was ascertained from a medical history questionnaire utilized in research protocols at the Western Psychiatric Institute and Clinic. History of exposure to treatment with stimulants or antidepressants was determined via parent-report during administration of the K-SADS-PL. Parents were systematically queried about current and previous psychiatric medications. Given the central purpose in the present study of examining factors that may have predicted BP onset, analyses focused on medication exposure previous to the intake assessment. However, specific dates, dosages, and durations of treatment were not systematically ascertained. Therefore, these data cannot parse medication exposure that preceded or coincided with the onset of BP from medication exposure after the onset of BP. These data also cannot examine for an association between BP and duration or dosage of treatment.

Statistical Analyses

SPSS 15.0 and STATA 4.0 were used to conduct statistical analysis. Independent t-test, Pearson Chi-square, and Fisher exact tests were used as appropriate to examine the baseline differences between those with and without BP disorder. Variables that had p -value < 0.1 in bivariate analyses were included in a multivariate binary logistic model. Full and backward models were examined. Moreover, to adjust for sibling correlation, family was used for clustering in the multivariate analysis. This method corrects the standard errors to account for the intraclass correlation between siblings. This is done by using cluster robust standard errors. P -values < 0.05 were considered to be statistically significant.

RESULTS

The sample consisted of 388 offspring among which 41 (10.6%) had BP: 9 with BP-I, 5 with BP-II, and 27 with BP-NOS. Two hundred and sixty nine participants (69.3%) were members of sibling groups while 119 (30.7%) participants had no siblings in the study.

Characteristics of offspring

There were no significant differences between offspring with and without BP with respect to age, gender, or race (Table 1). None of the perinatal variables was significantly associated with offspring BP. On the other hand, compared to offspring without BP, those with BP were significantly more likely to have lifetime history of anxiety (53.7% vs. 22.5%, $p<0.001$), ODD/CD (53.7% vs. 15.0%, $p<0.001$), and ADHD (41.5% vs. 22.2%, $p=0.01$). In addition, offspring with BP were significantly more likely to have history of physical or sexual abuse (19.5% vs. 6.4%, $p=0.01$). Previous exposure to stimulants was associated with higher rates of BP compared to no exposure to stimulants (22.7% vs. 8.7%, $p=0.004$). Similarly, previous exposure to antidepressants was associated with higher rates of BP compared to no history of exposure to antidepressants (25.0% vs. 9.3%, $p=0.02$).

Characteristics of parents

As shown in table 2, proband parents of offspring with BP disorder were more likely to be female ($p=0.03$), younger in age ($p=0.03$), and of lower SES ($p=0.01$) compared to proband parents of offspring with no BP. There was no significant difference between the proband parents of the two groups with respect to any of the clinical variables (Table 2).

The psychiatric history of the biological co-parent was available for 315 offspring. The prevalence of BP did not differ between offspring for whom co-parent psychiatric history was or was not available. Compared to offspring without BP, those with BP were more likely to have the biological co-parent diagnosed with BP (3.3% vs. 12.9%, $p=0.01$). On the other hand, there was no significant difference between the two groups with respect to any mood disorder (24.3% vs. 29.6%, $p=0.53$), psychosis (1.0% vs. 0%, $p=0.58$), anxiety (12.6% vs. 11.5%, $p=0.88$), or SUD ($p=34.1\%$ vs. 41.9% , $p=0.38$) among the co-parents.

Multivariate analysis

A multivariate binary logistic regression was conducted and included all variables with p -values < 0.1 . Younger age of proband parent, older age among offspring, history of anxiety and ODD/CD among offspring, and co-parent BP were significantly associated with offspring BP (Table 3). Other variables included in the model, such as prior exposure to stimulants and antidepressants, were no longer significant. The analysis was repeated including all variables with p -values < 0.25 and yielded similar results. Moreover, similar results were obtained with a backward model.

Of 22 offspring with history of anxiety disorders and BP, BP onset preceded anxiety onset for 3 offspring and the order of onset was unknown for 4 offspring. Analyses excluding these cases found that offspring BP was still associated with offspring anxiety (OR; 2.8, 95% CI: 1.1–7.2, $p=0.03$). Similarly, of the 22 offspring with history of ODD/CD and BP, BP onset preceded ODD/CD onset for 3 offspring and the order of onset was unknown for 6 offspring. Analyses excluding these cases found that ODD/CD was not significantly associated with BP (OR= 2.7, 95% CI: 0.9–7.7, $p=0.07$). Since history for the biological co-parent was missing for 19% of the offspring, the multivariate analysis was repeated without controlling for co-parent BP. In this analysis, both antecedent anxiety disorders and antecedent ODD/CD remained significantly associated with BP.

DISCUSSION

This study examined correlates of BP among offspring of parents with BP, and found significant associations with several demographic and clinical characteristics. In univariate analyses, offspring with BP had proband parents who were significantly younger at the time of their birth, were more likely to be female, and had lower socio-economic status, versus proband parents of offspring without BP. Offspring with BP were also more likely to have bi-linear parental BP. Parental clinical variables and obstetrical variables were not significantly associated with BP among offspring. There was significantly greater lifetime prevalence of physical and/or sexual abuse, attention-deficit hyperactivity disorder, anxiety disorders, ODD/CD, and exposure to stimulants and/or antidepressants among offspring with versus without BP. Entering all of these variables into regression analyses showed that independent correlates of offspring BP included older offspring age, offspring ODD/CD and anxiety disorders, younger proband parent age, and the presence of a biological co-parent with BP.

These findings must be interpreted in the context of the limitations of this study. First, the young mean age of offspring indicates that the majority of the sample has yet to traverse the period of greatest risk for onset of BP. Accordingly, it is likely that a significant proportion of offspring currently categorized as not having BP will in fact go on to develop BP. This suggests that the present study may be subject to type II error (i.e. false negatives). Second, these analyses are cross-sectional such that the temporal associations between BP and anxiety disorders or ODD/CD were determined retrospectively. Similarly, history of abuse is based on retrospective recall, and the temporal association between physical or sexual abuse and onset of BP could not be determined. Obstetrical history was also obtained retrospectively, using a standard medical history questionnaire. It is possible that recall bias, including mood-related recall bias, may contribute to residual confounding. Use of a more comprehensive obstetrical history interview may have mitigated this limitation. Third, despite the fact that this is the largest study to date on this topic, we were unable to examine for subtype-specific (i.e. BP-I vs. BP-II vs. BP-NOS) correlates. Most offspring with BP had BP-NOS, and it is uncertain whether the same findings would apply to a sample of primarily BP-I offspring. Fourth, limited information was available regarding pharmacologic treatment or adverse events as they relate to BP onset among offspring. Data from the present study cannot parse medication exposure that preceded or coincided with the onset of BP from medication exposure after the onset of BP. As such, these data cannot address the important question of whether antidepressants and/or stimulants trigger or uncover BP among high-risk offspring³². Fifth, this study did not examine biological correlates of risk for BP. Studies examining the structural and functional neuro-anatomic as well as genetic predictors of offspring BP will be forthcoming.

Given that the majority of high-risk offspring with BP in BIOS (66%) were diagnosed with BP-NOS, it is important to briefly summarize recent findings regarding this subtype of BP. Sub-threshold BP, prevalent among approximately 5% of adolescents in the general population, is impairing and shares more similarities than differences with BP-I and BP-II.^{33, 34} Using the same narrower and more specific definition of BP-NOS employed in the current study, the COBY study found that there were no significant differences between 438 youth with BP-I (N=255; 58%) versus BP-NOS (N=153; 35%) in terms of age of onset, duration of illness, lifetime comorbidities, suicidal ideation, major depressive episodes, family psychiatric history, or type of manic symptoms²⁸. However, youth with BP-I had more severe manic symptoms, greater functional impairment, and higher rates of hospitalization, psychosis, and suicide attempts compared to youth with BP-NOS. Longitudinal data indicate that BP-NOS as defined in COBY and BIOS is an episodic illness comprised of distinct hypomanic episodes of short duration, and is distinct from the

phenotype described as “severe mood dysregulation”.³⁵ Finally, longitudinal data from the COBY study indicate that during 4 years of follow-up, nearly 40% of youth with BP-NOS converted into BP-I. Taken together, these findings suggest the importance of including BP-NOS in the present study, both because of its similarity with BP-I and BP-II and because of the high risk of conversion into these disorders.

Recent population-based studies have found that older paternal and maternal age is associated with increased risk of BP among offspring, although those studies did not examine parents with BP specifically.^{4, 36} In contrast, the present study found that lower parental age, primarily maternal, was associated with increased risk of offspring BP. The reason for this discrepancy is unclear. One possible explanation is that the association between offspring BP and age of paternity and maternity may differ for parents with versus without BP. However, another possibility is that early parenthood confers and/or reflects a diathesis toward suboptimal environments for children. For example, pregnancy during adolescence has been associated with reduced financial and marital stability, reduced responsiveness to infants, and less positive child-rearing attitudes and/or behavior.^{37, 38} The finding that having both parents with BP confers particularly elevated risk of offspring BP is consistent with previous findings from adults¹⁸.

This study found no significant association between offspring BP and OCs or birth-weight. Singh and colleagues examined OCs among 36 offspring of parents with BP and 27 offspring of controls.⁷ They found that OCs were significantly more common among high-risk offspring, however there was no significant association between psychopathology and OCs among offspring. Similarly, Pavuluri and colleagues examined perinatal risk factors, developmental milestones, traumatic brain injury, medical illness, and medical hospitalization among 33 children with BP and ADHD, 37 with BP only, and 28 controls.⁸ Other than family history of BP, only perinatal risk factors differed significantly between groups. Moreover, there was a 6-fold increased odds of BP for each additional risk factor. Therefore, both of these studies by Singh and colleagues and Pavuluri and colleagues found that OCs were significantly more prevalent among offspring of parents with BP compared to offspring of non-BP parents. However, Singh and colleagues found no significant association between OCs and psychopathology among offspring of BP parents whereas Pavuluri and colleagues did find a significant association between OCs and BP among offspring of BP parents. It is difficult to compare subjects in BIOS, who were ascertained based on their parents' illness, to those reported by Pavuluri and colleagues, who were ascertained based on their own symptoms. Moreover, different measures were used to ascertain OCs in the two studies. However there may be other reasons for this discrepancy given that there was not even a trend toward an association between BP and OCs in the much larger BIOS sample. It is important to note that studies of adults with BP have also yielded heterogeneous findings.^{39, 40}

The finding that exposure to stimulants or to antidepressants was associated with BP in univariate analyses is noteworthy in light of previous concerns that such exposure may increase the risk of BP³². Replication of this finding is required, as the current study is constrained by the above-mentioned limitation that temporal association between medication exposure and BP onset could not be determined, and because this finding did not persist after controlling for the other variables in the multivariate analyses. Nonetheless, in the interim, clinicians who treat offspring of parents with BP (or who treat BP patients who have children) may consider the possibility that the risk-benefit ratio of psycho-stimulants and selective serotonin reuptake inhibitors, first-line treatments for ADHD and anxiety disorders respectively, is not the same for these children and adolescents as it is for the general population.

The finding that history of physical or sexual abuse was more common among offspring with BP converges with previous studies reporting that abuse is prevalent among up to 50% of adults with BP and is associated with earlier onset of BP.^{11, 41, 42} As acknowledged above, longitudinal analyses will be required to determine the temporal association between abuse and onset of BP.

There were no significant between-group differences between the proband parents with regard to clinical variables. A number of studies have examined characteristics of MDD among parents that may confer increased risk of MDD among their offspring, including MDD severity, recurrence, duration, suicide attempts, and psychiatric comorbidities.^{14- 43-45} Grigoriu-Serbanescu and colleagues found that offspring functioning was associated with the severity of BP in the parents, presence of psychopathology in the non-BP parent, number of manic and/or mixed episodes, and earlier age of parent BP onset.¹⁵ However, that study did not determine correlates of BP among offspring. Chang and colleagues examined factors univariately associated with BP among 60 offspring of parents with BP, finding a trend toward lower parental BP onset age among offspring with (10.7 years) versus without (16.7 years; $p=0.07$) BP.¹⁷ They also found that parental comorbid ADHD was significantly more common among offspring with (56%) versus without (17%) BP. Parental clinical predictors of offspring BP may emerge during longitudinal follow-up of the BIOS cohort.

Several studies have examined childhood psychopathology that may presage BP, including ADHD⁴⁶⁻⁴⁸, ODD/CD^{49, 50}, and anxiety disorders^{50, 51}. Duffy and colleagues found that 30% of offspring of parents with BP who initially manifested sleep or anxiety disorders went on to develop BP.⁵² Retrospective studies indicate that childhood anxiety disorders and ODD/CD are more common among adults with BP compared to controls⁵³, and youth-onset anxiety disorders have been associated with elevated rates of BP in adulthood.⁵⁴ Previous studies have found starkly contradictory findings regarding ADHD. One study reported a 28.5% conversion rate from ADHD into BP-I over 6-year prospective follow-up⁴⁸. Another study reported a 0% conversion rate among 91 males who had been followed-up for a mean of 16 years.⁴⁷ Also, co-segregation of BP and ADHD within families has been reported.⁵⁵ In BIOS, univariate analyses showed more ADHD in the BP offspring of parents with BP. The effects of ADHD were no longer significant after adjusting for confounding variables, suggesting that other factors such as comorbid ODD/CD and/or anxiety disorders accounted for the association between ADHD and BP. Future prospective studies from the BIOS sample will specifically examine the relationship between ADHD and other disorders and the onset of BP.

In conclusion, despite its limitations, this study extends the literature regarding correlates of BP among offspring of parents with BP. Because most BP offspring will not manifest BP, these correlates may help to increase the precision of predicting BP in this population. Clearly, replication based on longitudinal data from this and other samples will be required before these findings can reliably be used to inform clinical decisions. Genetic and endophenotypic predictors of BP among offspring of BP parents are also needed, and studies regarding these biological variables in the BIOS sample will be forthcoming.

Acknowledgments

This work was supported by NIMH grants MH60952 (primary investigator, Boris Birmaher, MD).

REFERENCES

1. Lapalme M, Hodgins S, LaRoche C, Lapalme M, Hodgins S, LaRoche C. Children of parents with bipolar disorder: a metaanalysis of risk for mental disorders. *Canadian Journal of Psychiatry* 1997 Aug;42(6):623-631.

2. Birmaher B, Axelson D, Monk K, et al. Lifetime Psychiatric Disorders in School-aged Offspring of Parents With Bipolar Disorder: The Pittsburgh Bipolar Offspring Study. *Archives of General Psychiatry* 2009;66(3):287–296. [PubMed: 19255378]
3. Goodwin, FK.; Jamison, KR. *Manic Depressive Illness*. New York: Oxford University Press; 2007. Genetics; p. 411–461.
4. Frans EM, Sandin S, Reichenberg A, Lichtenstein P, Langstrom N, Hultman CM. Advancing Paternal Age and Bipolar Disorder. *Archives of General Psychiatry* 2008;65(9):1034–1040. [PubMed: 18762589]
5. Helzer JE, Winokur G. A Family Interview Study of Male Manic Depressives. *Archives of General Psychiatry* 1974;31(1):73–77. [PubMed: 4835987]
6. Nomura Y, Wickramaratne PJ, Pilowsky DJ, et al. Low birth weight and risk of affective disorders and selected medical illness in offspring at high and low risk for depression. *Comprehensive Psychiatry* 2007 Sep-Oct;48(5):470–478. [PubMed: 17707257]
7. Singh MK, DelBello MP, Soutullo C, Stanford KE, McDonough-Ryan P, Strakowski SM. Obstetrical complications in children at high risk for bipolar disorder. *Journal of Psychiatric Research* 2007 Oct;41(8):680–685. [PubMed: 16698037]
8. Pavuluri MN, Henry DB, Nadimpalli SS, O'Connor MM, Sweeney JA. Biological Risk Factors in Pediatric Bipolar Disorder. *Biological Psychiatry* 2006;60(9):936–941. [PubMed: 16806102]
9. Wals M, Reichart CG, Hillegers MHJ, et al. Impact of birth weight and genetic liability on psychopathology in children of bipolar parents. *Journal of the American Academy of Child & Adolescent Psychiatry* 2003 Sep;42(9):1116–1121. [PubMed: 12960712]
10. Fuller, Torrey E.; Rawlings, RR.; Ennis, JM.; Merrill, DD.; Flores, DS. Birth seasonality in bipolar disorder, schizophrenia, schizoaffective disorder and stillbirths. *Schizophrenia Research* 1996;21(3):141–149. [PubMed: 8885042]
11. Levitan RD, Parikh SV, Lesage AD, et al. Major Depression in Individuals With a History of Childhood Physical or Sexual Abuse: Relationship to Neurovegetative Features, Mania, and Gender. *American Journal of Psychiatry* 1998;155(12):1746–1752. [PubMed: 9842786]
12. Laroche C, Sheiner R, Lester E, et al. Children of parents with manic-depressive illness: a follow-up study. *Canadian Journal of Psychiatry* 1987 Oct;32(7):563–569.
13. Rice J, Reich T, Andreasen NC, et al. The familial transmission of bipolar illness. *Archives of General Psychiatry* 1987 May;44(5):441–447. [PubMed: 3579495]
14. Keller MB, Beardslee WR, Dorer DJ, Lavori PW, Samuelson H, Klerman GR. Impact of severity and chronicity of parental affective illness on adaptive functioning and psychopathology in children. *Archives of General Psychiatry* 1986 Oct;43(10):930–937. [PubMed: 3753160]
15. Grigoriu-Serbanescu M, Christodorescu D, Jipescu I, Totoescu A, Marinescu E, Ardelean V. Psychopathology in children aged 10–17 of bipolar parents: Psychopathology rate and correlates of the severity of the psychopathology. *Journal of Affective Disorders* 1989;16(2–3):167–179. [PubMed: 2522116]
16. Duffy A, Alda M, Kutcher S, Fusee C, Grof P. Psychiatric Symptoms and Syndromes Among Adolescent Children of Parents With Lithium-Responsive or Lithium-Nonresponsive Bipolar Disorder. *American Journal of Psychiatry* 1998 March 1;155(3):431–433. [PubMed: 9501760]
17. Chang KD, Steiner H, Ketter TA. Psychiatric Phenomenology of Child and Adolescent Bipolar Offspring. *Journal of the American Academy of Child & Adolescent Psychiatry* 2000;39(4):453–460. [PubMed: 10761347]
18. Gershon ES, Hamovit J, Guroff JJ, et al. A Family Study of Schizoaffective, Bipolar I, Bipolar II, Unipolar, and Normal Control Proband. *Arch Gen Psychiatry* 1982 October 1;39(10):1157–1167. [PubMed: 7125846]
19. Anne D, Martin A, Leah C, Robert M, Paul G. The early manifestations of bipolar disorder: a longitudinal prospective study of the offspring of bipolar parents. *Bipolar Disorders* 2007;9(8): 828–838. [PubMed: 18076532]
20. Hillegers MH, Reichart CG, Wals M, Verhulst FC, Ormel J, Nolen WA. Five-year prospective outcome of psychopathology in the adolescent offspring of bipolar parents. *Bipolar Disorders* 2005;7(4):344–350. [PubMed: 16026487]

21. Shaw JA, Egeland JA, Endicott J, Allen CR, Hostetter AM. A 10-year prospective study of prodromal patterns for bipolar disorder among Amish youth. *Journal of the American Academy of Child & Adolescent Psychiatry* 2005 Nov;44(11):1104–1111. [PubMed: 16239857]
22. Johnson JG, Cohen P, Brook JS, Johnson JG, Cohen P, Brook JS. Associations between bipolar disorder and other psychiatric disorders during adolescence and early adulthood: a community-based longitudinal investigation. *American Journal of Psychiatry* 2000 Oct;157(10):1679–1681. [PubMed: 11007724]
23. Spitzer RL, Williams JB, Gibbon M, et al. The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. *Archives of General Psychiatry* 1992 Aug;49(8):624–629. [PubMed: 1637252]
24. Kaufman J, Birmaher B, Brent D, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): Initial Reliability and Validity Data. *Journal of the American Academy of Child & Adolescent Psychiatry* 1997;36(7):980–988. [PubMed: 9204677]
25. Andreasen NC, Endicott J, Spitzer RL, et al. The family history method using diagnostic criteria. Reliability and validity. *Archives of General Psychiatry* 1977 Oct;34(10):1229–1235. [PubMed: 911222]
26. Axelson D, Birmaher BJ, Brent D, et al. A preliminary study of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children mania rating scale for children and adolescents. *Journal of Child & Adolescent Psychopharmacology* 2003;13(4):463–470. [PubMed: 14977459]
27. Birmaher B, Axelson D, Strober M, et al. Clinical course of children and adolescents with bipolar spectrum disorders. *Archives of General Psychiatry* 2006 Feb;63(2):175–183. [PubMed: 16461861]
28. Axelson D, Birmaher B, Strober M, et al. Phenomenology of children and adolescents with bipolar spectrum disorders. *Archives of General Psychiatry* 2006 Oct;63(10):1139–1148. [PubMed: 17015816]
29. Birmaher B, Axelson D, Goldstein B, et al. Four-Year Longitudinal Course of Children and Adolescents With Bipolar Spectrum Disorders: The Course and Outcome of Bipolar Youth (COBY) Study. *Arch Gen Psychiatry* 2009 July 1;166(7):795–804.
30. Petersen AC, Crockett L, Richards M, Boxer A. A self-report measure of pubertal status: Reliability, validity, and initial norms. *Journal of Youth and Adolescence* 1988;17(2):117–133.
31. Hollingshead, A. Four-factor Index of Social Status. New Haven: Yale University; 1975.
32. Reichart CG, Nolen WA. Earlier onset of bipolar disorder in children by antidepressants or stimulants? An hypothesis. *Journal of Affective Disorders* 2004 Jan;78(1):81–84. [PubMed: 14672801]
33. Lewinsohn PM, Klein DN, Seeley JR, Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity, and course. *Journal of the American Academy of Child & Adolescent Psychiatry* 1995 Apr;34(4):454–463. [PubMed: 7751259]
34. Kessler RC, Avenevoli S, Green J, et al. National comorbidity survey replication adolescent supplement (NCS-A): III. Concordance of DSM-IV/CIDI diagnoses with clinical reassessments. *Journal of the American Academy of Child & Adolescent Psychiatry* 2009 Apr;48(4):386–399. [PubMed: 19252450]
35. Leibenluft E, Rich BA. *Pediatric Bipolar Disorder* 2008:163–187.
36. Menezes PR, Lewis G, Rasmussen F, et al. Paternal and maternal ages at conception and risk of bipolar affective disorder in their offspring. *Psychological Medicine* 2006;23:1–9.
37. Zuravian SJ. Child maltreatment and teenage firstbirths: a relationship mediated by chronic sociodemographic stress? *American Journal of Orthopsychiatry* 1988;58:91–103. [PubMed: 3344804]
38. Bolton, FG. *The Pregnant Adolescent: Problems of Premature Parenthood*. Beverly Hills, CA: Sage Publications; 1980.

39. K. Kinney D, Yurgelun-Todd DA, Tohen M, Tramer S. Pre- and perinatal complications and risk for bipolar disorder: a retrospective study. *Journal of Affective Disorders* 1998;50(2-3):117-124. [PubMed: 9858071]
40. Browne R, Byrne M, Morris M, et al. Labour and delivery complications at birth and later mania: An Irish case register study. *British Journal of Psychiatry* 2000 April 1;176(4):369-371. [PubMed: 10827886]
41. Leverich GS, McElroy SL, Suppes T, et al. Early physical and sexual abuse associated with an adverse course of bipolar illness. *Biological Psychiatry* 2002 Feb 15;51(4):288-297. [PubMed: 11958779]
42. Garo JL, Goldberg JF, Ramirez PM, Ritzler BA. Impact of childhood abuse on the clinical course of bipolar disorder. *British Journal of Psychiatry* 2005 Feb;186:121-125. [PubMed: 15684234]
43. Williamson DE, Birmaher B, Axelson DA, Ryan ND, Dahl RE. First episode of depression in children at low and high familial risk for depression. *Journal of the American Academy of Child & Adolescent Psychiatry* 2004 Mar;43(3):291-297. [PubMed: 15076262]
44. Warner V, Mufson L, Weissman MM, Warner V, Mufson L, Weissman MM. Offspring at high and low risk for depression and anxiety: mechanisms of psychiatric disorder. *Journal of the American Academy of Child & Adolescent Psychiatry* 1995 Jun;34(6):786-797. [PubMed: 7608053]
45. Beardslee WR, Keller MB, Seifer R, et al. Prediction of adolescent affective disorder: effects of prior parental affective disorders and child psychopathology. *Journal of the American Academy of Child & Adolescent Psychiatry* 1996 Mar;35(3):279-288. [PubMed: 8714315]
46. Biederman J, Faraone S, Milberger S, et al. A prospective 4-year follow-up study of attention-deficit hyperactivity and related disorders. *Archives of General Psychiatry* 1996 May;53(5):437-446. [PubMed: 8624187]
47. Mannuzza S, Klein RG, Bessler A, et al. Adult outcome of hyperactive boys. Educational achievement, occupational rank, and psychiatric status. *Archives of General Psychiatry* 1993 Jul;50(7):565-576. [PubMed: 8317950]
48. Tillman R, Geller B, Tillman R, Geller B. Controlled study of switching from attention-deficit/hyperactivity disorder to a prepubertal and early adolescent bipolar I disorder phenotype during 6-year prospective follow-up: rate, risk, and predictors. *Development & Psychopathology* 2006;18(4):1037-1053. [PubMed: 17064428]
49. Biederman J, Petty CR, Dolan C, et al. The long-term longitudinal course of oppositional defiant disorder and conduct disorder in ADHD boys: findings from a controlled 10-year prospective longitudinal follow-up study. *Psychological Medicine* 2008 Jul;38(7):1027-1036. [PubMed: 18205967]
50. Kim-Cohen J, Caspi A, Moffitt TE, Harrington H, Milne BJ, Poulton R. Prior juvenile diagnoses in adults with mental disorder: developmental follow-back of a prospective-longitudinal cohort. *Archives of General Psychiatry* 2003 Jul;60(7):709-717. [PubMed: 12860775]
51. Johnson JG, Cohen P, Brook JS. Associations between bipolar disorder and other psychiatric disorders during adolescence and early adulthood: a community-based longitudinal investigation. *American Journal of Psychiatry* 2000 Oct;157(10):1679-1681. [PubMed: 11007724]
52. Duffy A, Alda M, Crawford L, Milin R, Grof P. The early manifestations of bipolar disorder: a longitudinal prospective study of the offspring of bipolar parents. *Bipolar Disorders* 2007 Dec;9(8):828-838. [PubMed: 18076532]
53. Henin A, Biederman J, Mick E, et al. Childhood antecedent disorders to bipolar disorder in adults: a controlled study. *Journal of Affective Disorders* 2007 Apr;99(1-3):51-57. [PubMed: 17045657]
54. Goldstein BI, Levitt AJ. Prevalence and correlates of bipolar I disorder among adults with primary youth-onset anxiety disorders. *Journal of Affective Disorders* 2007;103(1-3):187-195. [PubMed: 17328960]
55. Faraone SV, Biederman J, Mennin D, Wozniak J, Spencer T. Attention-deficit hyperactivity disorder with bipolar disorder: a familial subtype? *Journal of the American Academy of Child & Adolescent Psychiatry* 1997 Oct;36(10):1378-1387. [see comment]. discussion 1387-1390. [PubMed: 9334551]

Table 1

Characteristics of high-risk offspring with vs. without bipolar disorder

	Non BP N=347	BP N=41	p-value
Demographics:			
Age (years)	11.9 ± 3.7	12.8 ± 3.1	0.08
Gender (female)	163 (47.0%)	25 (61.0%)	0.09
Race (white)	284 (81.8%)	32 (78.0%)	0.55
Perinatal:			
Weight at birth (lbs)	7.0 ± 1.4	7.0 ± 1.3	0.67
Drugs during pregnancy	29 (8.4%)	5 (12.2%)	0.39
Smoking during pregnancy	106 (30.8%)	15 (36.6%)	0.48
Psychotropic medication			0.61
during pregnancy	34 (10.8%)	5 (11.8%)	
Normal delivery	229 (66.8%)	27 (65.9%)	1.00
Trouble at birth	41 (12%)	5 (12.2%)	1.00
Trouble breathing	38 (11.3%)	3 (7.9%)	0.78
Other troubles	77 (22.4%)	9 (22%)	1.00
Comorbidity:			
Anxiety	78 (22.5%)	22 (53.7%)	<0.001
ODD/CD	52 (15.0%)	22 (53.7%)	<0.001
ADHD	77 (22.2%)	17 (41.5%)	0.01
SUD	13 (3.7%)	3 (7.3%)	0.28
Physical/Sexual Abuse	22 (6.4%)	8 (19.5%)	0.01
Medication exposure:			
Stimulants	30 (8.7%)	9 (22.7%)	0.004
Antidepressants	32 (9.3%)	10 (25.0%)	0.02

Note: Continuous variables are presented as mean standard deviation while categorical variables are presented as frequency and percentage.

BP = Bipolar disorder; ODD/CD = oppositional defiant disorder/conduct disorder; ADHD = attention-deficit / hyperactivity disorder; SUD = substance use disorder

Table 2

Parental characteristics of high-risk offspring with vs. without bipolar disorder

	Non BP N=347	BP N=41	p-value
Demographics:			
Age (years)	39.2 ± 7.3	36.6 ± 5.8	0.03
Age at child's birth (years)	27.3 ± 5.9	23.8 ± 4.6	<0.001
Gender (Female)	283 (81.6%)	39 (95.1%)	0.03
SES	34.9 ± 14.2	30.0 ± 11.4	0.01
Race (white)	300 (86.5%)	33 (80.5%)	0.33
Clinical Status			
Lowest GAF	34.1 ± 13.9	35.0 ± 13.6	0.70
BP type (BPI)	228 (65.7%)	25 (61%)	0.55
Rapid cycling	84 (24.2%)	12 (29.3%)	0.48
Age of onset	19.5±8.5	18.0±8.4	0.30
Any suicide attempts	173 (50.4%)	18 (43.9%)	0.51
Any psychiatric hospitalization	117 (33.7%)	9 (22.0%)	0.13
Psychosis	5 (1.4%)	0 (0.0%)	1.00
Comorbidity			
Anxiety	238 (68.6%)	34 (82.9%)	0.06
SUD	212 (61.1%)	26 (63.4%)	0.77
ADHD	88 (25.4%)	10 (24.4%)	1.00
ODD	84 (24.2%)	13 (31.7%)	0.34
Conduct disorder	70 (20.2%)	10 (24.4%)	0.53

Note: Continuous variables are presented as mean standard deviation while categorical variables are presented as frequency and percentage.

BP = Bipolar disorder; SES = socio-economic status; GAF = global assessment of functioning; SUD = substance use disorder; ADHD = attention-deficit / hyperactivity disorder; ODD = oppositional defiant disorder

Table 3

Multivariate analysis examining offspring bipolar disorder

	OR	p-value	95% CI
Proband			
Age at child's birth	0.92	0.02	0.86–0.99
Gender	1.79	0.50	0.33–9.69
SES	1.00	0.89	0.97–1.04
Anxiety	2.09	0.23	0.63–6.92
Offspring			
Age	1.18	0.01	1.04–1.33
Gender	1.42	0.50	0.51–4.00
Anxiety	3.43	0.01	1.34–8.77
ADHD	1.05	0.94	0.30–3.69
ODD/CD	4.84	0.002	1.83–12.83
History of abuse	1.03	0.96	0.34–12.83
Medication exposure			
Stimulants	1.37	0.62	0.39–4.77
Antidepressants	1.34	0.66	0.36–4.96
Other parent with BP	3.30	0.04	1.04–10.49

Note: BP = bipolar disorder; SES = socio-economic status; ADHD = attention-deficit / hyperactivity disorder; ODD/CD = oppositional defiant disorder/conduct disorder; OR = Odds Ratio