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Similar Familial Underpinnings for Full and Subsyndromal Pediatric Bipolar Disorder: A Familial Risk Analysis

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Abstract

Objectives—To examine the validity of subthreshold pediatric bipolar-I (BP-I) disorder, we compared the familial risk for BP-I disorder in child probands with full BP-I disorder, subthreshold BP-I disorder, ADHD, and non-ADHD/non-bipolar disorder controls.

Methods—Probands were youth ages 6–17 meeting criteria for BP-I disorder, full (N=239) or subthreshold (N=43), and their first degree relatives (N=687 and N=120, respectively). Comparators were youth with ADHD (N=162), controls (N=136), and their first-degree relatives (N=511 and N=411, respectively). We randomly selected 162 non-bipolar ADHD probands and 136 non-bipolar non-ADHD control probands of similar age and sex distribution to the BP-I probands from our case-control ADHD family studies. Psychiatric assessments were made by trained psychometricians using the KSADS-E and SCID structured diagnostic interviews. We analyzed rates of bipolar disorder using multinomial logistic regression.

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Results—Rates of full bipolar-I disorder significantly differed between the four groups ($\chi^2_3 = 32.72, p < 0.001$): relatives of full BP-I and relatives of subthreshold BP-I probands had significantly higher rates of full BP-I disorder than relatives of ADHD probands and relatives of control probands. Relatives of full BP-I, subthreshold BP-I, and ADHD probands also had significantly higher rates of major depressive disorder (MDD) compared to relatives of control probands.

Conclusions—Our results showed that youth with subthreshold BP-I disorder had similarly elevated risk for BP-I disorder and MDD in first-degree relatives as youth with full BP-I disorder. These findings support the diagnostic continuity between subsyndromal and fully syndromal states of pediatric BP-I disorder.

Keywords

pediatric bipolar disorder; children; familiarity; subsyndromal

Introduction

Pediatric bipolar (BP)-I disorder is a highly morbid and disabling neurobiological disorder estimated to afflict 1–2% of children. Because of its insidious onset over many years, subsyndromal manifestations of BP-I disorder often precede the child's development of the full syndromal state.¹ Studies document that subsyndromal manifestations of BP-I disorder are likely to evolve into full syndromal status over time^{2,3} and that these subthreshold states of BP-I disorder are highly morbid in their own right.⁴ Affected children with such pre-syndromal states are commonly seen in the clinic.^{5,6}

Although the modern study of pediatric bipolar disorders is in its infancy, the knowledge base surrounding the topic has grown unprecedentedly in the past 20 years.⁷ The emerging literature strongly supports the notion that a subthreshold diagnosis of pediatric BP-I disorder is prevalent and represents a source of significant morbidity and dysfunction. As early as the 1990s, Lewinsohn et al.^{4,8–10} reported that subthreshold BP-I disorder in youth affected close to 6% of their epidemiological sample, and its presence carried with it elevated impairment, comorbidity, and suicide attempts similar to full syndrome bipolar disorder. In their sample, youth with subthreshold BP-I disorder were experiencing higher levels of morbidity and disability than those with full syndromal major depression.

More recently, Axelson et al.³ reported on a large group (N=391) of high risk offspring of parents with BP-I disorder. The authors reported that 13% of these children suffered from subthreshold BP-I disorder, and its presence heralded significant morbidity. Axelson et al.¹¹ also reported in a longitudinal sample that 45% of youth with subthreshold bipolar disorder switched to full BP-I or BP-II disorder over a 5 year follow up period.

Other studies have yielded similar findings. In a longitudinal sample of ADHD youth, Biederman et al.² reported that those with subthreshold BP-I disorder in childhood were at very high risk to switch to full BP-I diagnosis in adolescence and adult years. In addition, a literature review by Uchida et al.¹² found that family history of mood disorder and subthreshold mania were predictive factors for a switch from major depression to bipolar

disorder in children initially presenting with a depressive episode. These findings support results from recent longitudinal epidemiological studies, which have documented that subthreshold psychiatric diagnoses in childhood in general are highly predictive of impairment and dysfunction in adult life.^{13, 14}

Yet, severe criticism has been leveled against subsyndromal manifestations of pediatric BP-I disorder. For example, First¹⁵ termed subthreshold diagnoses a “catch-all” category that results in “a loss of important clinical information.” Safer et al.⁵ argued that subthreshold BP-I disorder lacks reliability and raised concerns that using it in clinical practice could increase the likelihood of off-label prescribing of psychotropic medication. Rutter and Uher¹⁶ critically concluded that the subthreshold disorder diagnosis was a “rather unhelpful ‘rubbish basket’ diagnosis,” and Paris¹⁷ similarly deemed it a “waste basket for the patient who does not meet criteria for any specific diagnosis.”

While these concerns are rampant in pediatric psychiatry, the clinical relevance of subthreshold diagnoses is recognized as critically important in adult psychiatry. In a 2010 survey of 2,406 adults, subthreshold psychiatric symptoms predicted severe functional disability at follow up 18 months later.¹⁸ Further findings have revealed that children and adolescents with BD subtypes experience significantly similar functional deficits to their adult counterparts.¹⁹ Reasonably, the authors of the 2010 study concluded: “The importance of subthreshold symptoms should not be underestimated.” Angst et al have championed the use of a spectrum model of mood disorders, especially in distinguishing bipolar from unipolar disorders “as failure to recognize bipolar spectrum disorder could delay treatment and worsen prognosis.” (18) Others have argued that a ‘mood spectrum model’ is important for identifying individuals with severe psychopathology not adequately attended to in the DSM-5.²⁰

Furthermore, it has been found in meta-analyses that despite the heterogeneity of symptoms observed in youths with bipolar spectrum disorders (lending to it’s previously described “catch-all” nature), the symptoms observed in evidence-based settings have remained similar over time.²¹ In other words, bipolar symptoms in youths have been consistent over time, although they are wide-ranging. These most common symptoms are impairing and include: increased energy, irritability, mood lability, distractibility, goal-directed activity, euphoric/ elated mood, pressured speech, hyperactivity, racing thoughts, poor judgment, grandiosity, inappropriate laughter, decreased need for sleep, and flight of ideas. As Van Meter et al. explained, “Understanding the roots of this heterogeneity could broaden understanding of the complex clinical presentation of pediatric mania, and aid in diagnosis.”²¹ Therefore, the data provide evidence that studying sub-threshold patients will not cause unreliability or a loss of important clinical information, and in fact may add to the amount of clinically significant information gathered.

Given the genetic underpinnings of BP-I disorder²² and the recognition that gene expression can result in full or partial manifestations of the clinical liability, family studies can help verify the validity of subthreshold cases of pediatric onset bipolar-I disorder. Shankman et al reported on a family study of subthreshold psychiatric conditions (including subthreshold bipolar disorder) in a community sample of adolescents addressing the high rates of

familiarity with the same and other disorders in these subjects. (21) Lewinsohn et al. addressed the familiarity of subthreshold pediatric onset bipolar disorder using a brief screen of familiarity in a community sample of adolescents followed into young adulthood.⁸ The authors found similarly elevated rates of bipolar disorder in first-degree relatives of both the bipolar and subthreshold probands.⁸ Hafeman et al studied high-risk offspring of bipolar adults and found high rates of bipolar spectrum disorder, including subthreshold mania and mood lability in the high-risk children. (1)

Whether subsyndromal manifestations of pediatric BP-I disorder represent a valid clinical entity is an area of high clinical, scientific, and public health relevance. Children often present to clinical care with severe symptoms that may not meet full DSM criteria for BP-I disorder. In these cases, the subthreshold BP-I category “provides indispensable placeholders”²³ for clinicians when patients definitely need care. This issue is not surprising considering that like all psychiatric disorders, pediatric BP-I disorder emerges insidiously over time, implying that some children present to clinical care with evolving symptoms failing to meet full syndromatic status at that time.

Outside of psychiatry, medicine has long recognized the critical importance of early identification and intervention of incipient conditions. As such, the early detection of manifestations of BP-I disorder can lead to early intervention strategies that may mitigate the profound morbidity associated with the development of the full syndrome. Scientifically clarifying whether subthreshold BP-I disorder cases share genetic (and neurobiological) underpinnings with the full syndrome can provide new insight into the neurobiology of BP-I disorder. Considering the high prevalence of subthreshold BP-I disorder and its associated morbidity, clinical identification could translate into benefits for a large segment of the pediatric population at very high risk for adverse outcomes.

The primary aims of the present study were to use familial risk analysis to examine the validity of subsyndromal pediatric bipolar-I disorder. To this end, we compared the familial risk for BP-I disorder in child probands with full BP-I disorder, subsyndromal BP-I disorder, ADHD, and healthy controls. Based on the extant literature, we hypothesized that subsyndromal pediatric BP-I disorder would be as familial as the full syndrome disorder. While both Hafeman (1) and Lewinsohn (7) have addressed family history of subthreshold pediatric BP-I disorder, to the best of our knowledge, this is the first familial risk analysis study of subsyndromal pediatric BP-I disorder.

Materials and Methods

Detailed study methods have been previously described.²⁴ Briefly, families were recruited and assessed at the Clinical and Research Program in Pediatric Psychopharmacology at the Massachusetts General Hospital based on the presence of a diagnosis of a bipolar disorder in proband youth 6–17 years of age of both sexes.^{25, 26} Comparators were youth with ADHD and controls without ADHD or BP-I disorder of similar age and sex along with their first-degree relatives.^{27, 28} Comparator subjects could have other diagnoses. All studies used the same assessment methodology regardless of the disorder used to classify probands as cases. We recruited 239 full BP-I probands (687 first-degree relatives). In addition, we evaluated

43 subjects who failed to meet full BP-I criteria. These 43 subsyndromal BP-I probands and their 120 first-degree relatives were fully evaluated with identical methodology but were excluded from previous family study reports of BP-I disorder. From 522 families participating in our case-control ADHD family studies, we randomly selected 162 non-bipolar ADHD probands (511 first-degree relatives) and 136 non-bipolar non-ADHD control probands (411 first-degree relatives) so that the age and gender distribution were similar to that of the BP-I probands. ADHD probands with comorbid bipolar disorder were not included in the present analyses. All study procedures were reviewed and approved by our Institutional Review Board. After complete description of the study to the subjects, all subjects' parents or guardians signed written informed consent forms and children older than 7 years of age signed appropriate written assent forms.

Ascertainment Method

Potential BP-I probands were ascertained from our clinical service, referrals from local clinicians, or self-referral in response to advertisements in the local media. To avoid biasing our sample toward familial cases of bipolar disorder, all probands were ascertained blind to the diagnostic status of their relatives. Subjects' parents or guardians were administered a phone screen to review their child's symptoms of DSM-IV BP-I disorder. If criteria were met, they were scheduled for a face-to-face structured diagnostic interview. In addition to the structured diagnostic interview, an expert clinician (J.W.) met with each potential proband and his or her parents for a clinical interview in order to confirm the diagnosis of bipolar-I disorder using the Schedule for Affective Disorders and Schizophrenia for School-Age Children Epidemiological Version (KSADS-E) ²⁹ mania module. We have published data on the convergence of these clinical interviews with our structured interview diagnosis on the first 69 cases. We reported a 97% agreement between the structured interview and clinical diagnosis in an analysis of 69 children. ³⁰ We have also published data on the familiarity of the BP-I probands, excluding subjects who did not meet full BP-I criteria (21,22).

After completing the structured interview, 43 subjects were found to meet DSM criteria for either BP-II or BP-NOS rather than BP-I. We have defined these subjects as having "subsyndromal bipolar disorder." Bipolar-II disorder was defined according to the DSM-IV as hypomania (an abnormal mood lasting at least 4 days) and bipolar disorder NOS was defined as a severe manic mood disturbance that either did not meet DSM-IV duration criteria for hypomania or had fewer symptoms than required in criterion B (2 items required for elation and 3 for irritability).

As previously reported, ^{25, 27, 28} ADHD cases were identified from either a major academic medical center, where we selected ADHD subjects from referrals to a pediatric psychopharmacology program, or from a Health Maintenance Organization, in which ADHD subjects were selected from pediatric clinic outpatients. Controls were ascertained from outpatients referred for routine physical examinations to pediatric medical clinics at each setting, identified from their computerized records as not having ADHD. Screening procedures were similar to those described for the recruitment of the BP-I probands with the exception that we queried about ADHD (and not BP-I disorder) in the initial telephone screening, and each proband was not assessed clinically.

Diagnostic Procedures

We psychiatrically assessed the probands and their first degree relatives. Psychiatric assessments of subjects (probands and their siblings) younger than 18 years were made with the KSADS-E²⁹ and assessments of adult family members (siblings and parents) age 18 or older were made with the Structured Clinical Interview for DSM-IV (SCID),³¹ supplemented with modules from the KSADS-E to cover childhood disorders. Diagnoses were based on independent interviews with mothers and direct interviews with children older than 12 years of age. Data were combined such that endorsement of a diagnosis by either report resulted in a positive diagnosis.

Interviews with both the KSADS-E and SCID were conducted by extensively trained and supervised psychometricians with undergraduate degrees in psychology. This training involved several weeks of classroom instruction of interview mechanics, diagnostic criteria, and coding algorithms. They also observed interviews by experienced raters and clinicians and were observed while conducting interviews during the final training period. In addition, all diagnoses were reviewed by a committee of experienced, board-certified child and adolescent psychiatrists or clinical psychologists. The interviewers, as well as the committee members, were blind to the subjects' ascertainment status, ascertainment site, and data collected from other family members. We computed kappa coefficients of agreement by having experienced clinicians diagnose subjects from audiotaped interviews made by the assessment staff. Based on 500 interviews, the median kappa coefficient between raters and clinicians was 0.99. For individual diagnoses the kappa coefficients were: ADHD (0.88), conduct disorder (1.0), major depression (1.0), bipolar (0.95), separation anxiety (1.0), agoraphobia (1.0), panic (0.95), substance use disorder (1.0), and tic/Tourette's (0.89). The median agreement between individual clinicians and the clinical review committee was 0.87; for individual diagnoses, the median agreement was: ADHD (1.0), conduct disorder (1.0), major depression (1.0), bipolar (0.78), separation anxiety (0.89), agoraphobia (0.80), panic (0.77), substance use disorder (1.0), and tics/Tourette's (0.68). We did not perform a study to compute kappa coefficients of agreement for subthreshold diagnoses.

Children and adolescents were diagnosed with subsyndromal (also called 'subthreshold') bipolar disorder if they did not meet criteria according to DSM-IV for Bipolar I, but did meet criteria for Bipolar II or Bipolar, NOS. For Bipolar-I Disorder, the DSM-IV required subjects to meet criterion A for a distinct period of extreme and persistently elevated, expansive, or irritable mood lasting at least one week, plus criterion B, manifested by three (four if the mood is irritable only) of seven symptoms during the period of mood disturbance. To ensure that the criterion B symptoms were concurrent with the criterion A mood disturbance, subjects were directed to focus on the time during which the criterion A mood disturbance was at its worst. To gauge a distinct episode, our interviewers asked for a 'distinct period (of at least one week) of extreme and persistently elevated, expansive, or irritable mood' and further required that the irritability endorsed in this module is 'super' and 'extreme'. Interviewers also recorded the onset of first episode, the number of episodes, offset of last episode, and total duration of illness. Bipolar-II disorder was defined according to the DSM-IV as hypomania (an abnormal mood lasting at least 4 days) and bipolar disorder NOS was defined as a severe manic mood disturbance that did not meet DSM-IV

duration criteria for hypomania and/or had fewer symptoms than required in criterion B (2 items required for elation and 3 for irritability).

Statistical Analysis

Differences in demographic and clinical characteristics among probands were analyzed using one-way analysis of variance (ANOVA), Pearson's chi-square test, Kruskal-Wallis test followed by Dunn's test, and Poisson regression for continuous, dichotomous, ordinal, and count data, respectively. All analyses of first-degree relatives were performed using regression models with robust standard errors to account for the non-independence of the family members. Differences in demographic characteristics of first-degree relatives were assessed using linear regression, logistic regression, and ordered logistic regression for continuous, dichotomous, and ordinal data, respectively. We controlled for any demographic characteristic of the first-degree relatives that reached significance at the 0.05 alpha level. We analyzed rates of bipolar disorder using multinomial logistic regression and rates of major depressive disorder using logistic regression. All tests were two-tailed and conducted at the 0.05 alpha level. We performed all analyses using Stata® (version 14).

Results

Table 1 presents the demographic and clinical characteristics of the probands from whom we obtained first-degree relatives for our primary analysis. Control, ADHD, subthreshold BP-I, and full BP-I probands were of similar age, sex and race, but significantly differed with regards to SES, Global Assessment of Functioning (GAF) scores, and mean number of psychiatric comorbidities. ADHD and full BP-I probands were of significantly worse SES compared to control probands. GAF scores were significantly more impaired and the mean number of psychiatric disorders was higher for full BP-I probands compared to the other three groups, subthreshold BP-I probands compared to ADHD and controls probands, and ADHD probands compared to control probands.

Comparisons were made between the following groups: 684 relatives of full BP-I probands, 120 relatives of subthreshold BP-I probands, 509 relatives of ADHD probands, and 411 relatives of control probands. Demographic characteristics of the sample are presented in Table 2. All four groups were of similar age, sex, and race but significantly differed in socioeconomic status (SES). Relatives of ADHD probands and relatives of full BP-I probands were of significantly worse SES compared to relatives of control probands. Thus, all subsequent analyses were adjusted for SES.

Rates of Disorders in Relatives

As shown in Figure 1A, rates of full bipolar-I disorder significantly differed between the four groups ($\chi^2_3 = 32.72$, $p < 0.001$). Relatives of subthreshold BP-I probands and relatives of full BP-I probands had significantly higher rates of full bipolar-I disorder compared to relatives of ADHD probands and relatives of control probands. There was no statistically significant difference in the rate of BP-I disorder between the relatives of probands with subthreshold or full BP-I disorder.

There were also significant differences between the four groups in the rate of major depressive disorder ($\chi^2_3 = 48.60, p < 0.001$). Relatives of full BP-I, subthreshold BP-I, and ADHD probands had significantly higher rates of major depressive disorder compared to relatives of control probands (Figure 1B). Relatives of full BP-I probands also had a significantly higher rate of major depressive disorder compared to relatives of ADHD probands.

Discussion

Results from this familial risk analysis showed that youth with subthreshold BP-I disorder had similarly elevated risk for BP-I disorder and MDD in first-degree relatives as youth with full BP-I disorder. These findings support the diagnostic continuity between subsyndromal and fully syndromal states of pediatric BP-I disorder.

The finding of shared familial risk between subsyndromal and syndromal forms of pediatric BP-I disorder is consistent with the expected way that genetic risk factors manifest themselves. Genetic conditions, like all medical conditions, present pleomorphically with variable symptomatic expression that may be above or below arbitrary thresholds set forth by our nosology.

Although limited, the available literature on subsyndromal manifestations of pediatric BP-I disorder clearly documents that such forms of BP-I disorder are highly prevalent and highly morbid. For example, Lewinsohn et al.^{4, 8–10} documented that close to 6% of youth in the community have subsyndromal manifestations of BP-I disorder. This represents a five-fold higher rate than the 1% rate for fully syndromal BP-I disorder in the same study. Moreover, they documented that youth with subsyndromal BP-I disorder were highly impaired—even more so than youth with fully syndromal MDD. Birmaher et al.^{32, 33} reported similar results in clinical samples, documenting the high morbidity and disability associated with subsyndromal BP-I disorder.

Supporting evidence is also found in studies of high-risk children. In their³ study of offspring aged 6–18 years of parents with BP-I disorder, Axelson et al.³ documented that children at risk for BP-I disorder more frequently manifest subsyndromal manifestations of BP-I disorder than the fully syndromal state. The authors concluded that the presence of subthreshold states heralds a compromised outcome and should be the focus of clinical assessment and treatment.

In addition, the extant literature documents that the subsyndromal form of BP-I disorder represents a significant and potent risk factor for progression to full syndromal BP-I disorder over time. For example, Axelson et al.¹¹ documented that subsyndromal BP-I disorder is a significant risk for switching to full syndromal status within a short period of time. In fact, the children with subthreshold BP *plus* family history of mania were the ones at highest risk to develop BP-I/II. These authors concluded, “Efforts to identify these youth and effectively intervene may have the potential to curtail the progression of mood disorders in this high-risk population.” Likewise, Hafeman et al.¹ and Uchida et al.¹² have both reported that subsyndromal symptoms of BP-I disorder in children at risk for BP-I disorder

predict development of the fully syndromatic state, making subsyndromal diagnoses clinically and scientifically relevant. Specifically, Hafeman (1) reported that subthreshold BP as well as mood lability increased the risk for syndromal BP, in the context of having a family history of bipolar disorder (and particularly if parents had early onset BP). Axelson (3, 10) also highlighted the role of family history, finding that the children with subthreshold BP *plus* family history of mania were the ones at highest risk to progress to BP-I or BP-II.

The identification of subsyndromal manifestations of pediatric BP-I disorder has important clinical, scientific, and public health implications. Irrespective of whether subsyndromal manifestations of BP-I disorder represent early stages of BP-I disorder or a forme fruste of BP-I disorder, it is equally important to identify and address subsyndromal forms of BP-I disorder due to their associated morbidity and dysfunction, as well as their risk for conversion to fully syndromatic states, as an attempt to interrupt the progression of the illness. Targeting subsyndromal manifestations of BP-I disorder for neurobiological studies could provide critical insights as to the underlying neurobiological underpinnings of the disorder without the confounders of chronicity and treatment. Considering its high prevalence in the population, subsyndromal bipolar disorder should be targeted for preventive and early intervention efforts.

Research as to the scientific utility and predictive value of subsyndromal symptoms requires clearly operationalized criteria with prospective study. One possible definition is the criteria used in Course and Outcome of Bipolar Youth (COBY) study which required at least 4 hours of symptoms for 4 days with one symptom short of that required by DSM (1, 3, 10). Until there is a consensus, clinicians have a responsibility and imperative to treat children and adolescents presenting for treatment in the here and now. Children who lack fully syndromal states of bipolar disorder should still receive targeted treatments (including family, natural treatment and psychosocial treatments) for their mood dysregulation, which can be severely impairing, whether it progresses to a fully syndromatic state or not. The COBY study has contributed a substantial body of research supporting the morbidity associated with both fully syndromatic *and* subsyndromal bipolar disorder, including poor cognitive functioning, poor mental health utilization, and increased risk for suicidality and substance abuse. (33–38) In addition, an emerging body of treatment studies include youth with subsyndromal diagnoses (ADD our own treatment studies including preschooler Risperidone/olanzapine/quetiapine, omega-3, omega-3 inositol). For clinicians, the use of a subthreshold bipolar disorder diagnosis permits a diagnosis-targeted treatment and provides a flag of risk for an individual severely compromised by emotional dysregulation. Rather than disparage them as “rubbish,” ^{15–17} subthreshold diagnoses of bipolar disorder merit careful consideration from both the clinical and scientific community.

The present study has important strengths. To the best of our knowledge, this study represents the only controlled, blinded, direct interview family study of subsyndromal pediatric bipolar disorder to date. Our results provide strong support for the familiarity of subsyndromal bipolar disorder, which further supports the validity of subsyndromal pediatric bipolar disorder as a diagnostic entity.

Nevertheless, our findings should also be considered in the context of methodological limitations. We used samples of convenience for comparators, but all studies were performed using identical methodology. We used lay interviewers with undergraduate degrees in psychology, rather than clinician raters; however, these raters were extensively trained to high levels of inter-rater reliability. We did not compute kappa coefficients of agreement for subthreshold diagnoses. Future studies could benefit from analyses of clinician agreement regarding subsyndromal diagnoses. We only report on full BP-I diagnoses in relatives; future studies could benefit from a design which also analyzes subsyndromal diagnoses in relatives. In addition, although we did not administer structured diagnostic interviews directly to children younger than age 12, the diagnosis of bipolar disorder in probands was corroborated with clinical assessment by an expert child and adolescent psychiatrist.³⁰ Because this sample was clinically referred and primarily Caucasian, these results may not generalize to non-referred children or to families of other ethnic groups. We further acknowledge that family history is only one important element in the validation of subthreshold bipolar disorder in youth. This analysis is limited to providing family history data and does not elaborate on the clinical presentation of the probands; for example, we do not have mania and depression rating scale information for the probands. Future studies further focusing on the clinical presentation of youth with subsyndromal bipolar disorder will improve our understanding and treatment of these subjects.

Despite these limitations, results from this large family study provide compelling evidence for the familiarity of subsyndromal pediatric bipolar disorder and, thus, robust support for the consideration and treatment of this disorder in clinical practice.

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A. Full BP-I Disorder **B. Major Depressive Disorder** **Figure 1.**

Rates of full BP-I disorder and major depressive disorder among relatives of control, ADHD, subthreshold BP-I, and full BP-I probands. A. Full BP-I disorder. B. Major depressive disorder.

^aCompared to relatives of control probands. ^b Compared to relatives of ADHD probands.

*P<0.05, **P<0.005, ***P<0.001

[†]Smaller sample sizes for relatives of ADHD probands (n = 506) and relatives of full BP-I probands (n = 685).

Table 1

Demographic and clinical characteristics of probands

Characteristic	Control Probands N = 136	ADHD Probands N = 162	Subthreshold BP-I Probands N = 43	Full BP-I Probands N = 239	Test Statistic	P-Value
Age	10.7 ± 3.0	10.6 ± 3.0	11.0 ± 3.8	10.7 ± 3.3	$F_{(3,576)} = 0.19$	0.90
Sex (Male)	99 (73)	121 (75)	34 (79)	174 (73)	$\chi^2_3 = 0.88$	0.83
SES	1.5 ± 0.7	1.8 ± 1.0 ^{a**}	1.6 ± 0.7	1.8 ± 0.9 ^{d***}	$\chi^2_3 = 11.89$	0.008
Race (Caucasian)	132 (97)	160 (99)	41 (95)	224 (94)	$\chi^2_3 = 6.95$	0.07
Global Assessment of Functioning (GAF) Score [†]	70.5 ± 8.5	50.7 ± 7.3 ^{d***}	44.4 ± 6.6 ^{d***b***}	40.7 ± 5.8 ^{d***b***c**}	$F_{(3,573)} = 536.08$	<0.001
Number of Psychiatric Comorbidities	0.7 ± 0.9	3.7 ± 2.0 ^{d***}	6.1 ± 2.3 ^{d***b***}	8.0 ± 2.7 ^{d***b***c***}	$\chi^2_3 = 738.31$	<0.001

Data presented as mean ± standard deviation or *n* (%).^a Compared to control probands.^b Compared to ADHD probands.^c Compared to subthreshold BP-I probands.

* P<0.05,

** P<0.005,

* P<0.001

[†] Smaller sample sizes, Subthreshold BP-I probands: N=42; Full BP-I probands: N=237.

Table 2

Demographic characteristics of first-degree relatives

Characteristic	Relatives of Control Probands N = 411	Relatives of ADHD Probands N = 511	Relatives of Subthreshold BP-I Probands N = 120	Relatives of Full BP-I Probands N = 687	Test Statistic	P-Value
Age	31.6 ± 14.7	31.2 ± 14.7	33.3 ± 16.8	32.0 ± 15.7	$F_{(3,579)} = 1.16$	0.32
Sex (Male)	207 (50)	264 (52)	60 (50)	324 (47)	$\chi^2_3 = 6.05$	0.11
SES	1.6 ± 0.8	1.8 ± 0.9 ^{a*}	1.6 ± 0.8	1.8 ± 0.9 ^{a*}	$\chi^2_3 = 11.44$	0.01
Race (Caucasian)	404 (98)	507 (99)	117 (98)	653 (95)	$\chi^2_3 = 7.55$	0.06

Data presented as mean ± standard deviation or *n* (%).

^a Compared to relatives of control probands.

* P<0.05