The prevalence of psychopathology in offspring of bipolar women from a Brazilian tertiary center

Prevalência de psicopatologia em filhos de mulheres bipolares de um centro terciário brasileiro

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Abstract

Objective: *No previous study has assessed the occurrence of psychopathology in offspring of bipolar women from South America. The objective of this study was to assess the prevalence of psychopathology in offspring of bipolar mothers from Brazil compared with two control groups.* ***Method:*** *Children and adolescents aged 6 to 18 years of bipolar disorders mothers (n = 43), mothers with other mild to moderate mental disorders (n = 53) and mothers without any psychiatric disorder (n = 53) were evaluated using the Kiddie Schedule for Affective Disorders and Schizophrenia present and lifetime version, the Child Behavior Checklist and the Youth Self-Report. Raters were blind to the mothers' diagnoses, who were interviewed by means of the Structured Clinical Interview.* ***Results:*** *Bipolar offspring had twice the chance of having one or more lifetime Axis I diagnoses [prevalence ratio = 2.11 (95% CI: 1.30-3.42) and p = 0.003] and 2.8 higher risk of having a lifetime anxiety disorder [prevalence ratio = 2.83 (95% CI: 1.39-5.78) e p = 0.004] than the offspring of mothers with no mental disorder. In addition, significantly higher scores on Child Behavior Checklist thought problems and Youth Self-Report social problems, as well as anxiety/depression and internalizing problems were observed.* ***Conclusion:*** *Our results confirm previous findings suggesting higher psychiatric problems in offspring of bipolar mothers and extend them to the Brazilian society*

Descriptors: *Bipolar disorder; Psychopathology; Risk factors; Children; Adolescent*

Resumo

Objetivo: *Considerando-se a inexistência de estudos avaliando a ocorrência de psicopatologia em filhos de mães bipolares na América do Sul, este se propõe a avaliar a prevalência de psicopatologia em filhos de mulheres bipolares comparado com dois grupos-controle.* ***Método:*** *Crianças e adolescentes de 6 a 18 anos de idade, filhos de mães com transtorno bipolar (n = 43), filhos de mães com outros transtornos psiquiátricos leve a moderados (n = 53) e filhos de mães sem nenhum diagnóstico psiquiátrico (n = 53) foram avaliados usando o* Kiddie Schedule for Affective Disorders and Schizophrenia present and lifetime version*, o* Child Behavior Checklist *e o* Youth Self-Report *por entrevistadores cegos ao diagnóstico das mães, as quais foram entrevistadas por meio do* Structured Clinical Interview*.* ***Resultados:*** *Os filhos de mães bipolares tiveram duas vezes mais chance de ter um ou mais diagnósticos de Eixo I [Razão de Prevalência = 2,11 (95% IC: 1,30-3,42) e p = 0,003] e 2,8 vezes maior risco de ter transtornos de ansiedade [Razão de prevalência = 2,83 (95% IC: 1,39-5,78) e p = 0,004] ao longo da vida do que os filhos de mulheres sem transtorno mental, além de maiores escores na subescala de problemas de pensamento do* Child Behavior Checklist *e nas subescalas de problemas sociais, ansiedade/depressão e problemas de internalização do* Youth Self-Report*.* ***Conclusão:*** *Nossos resultados confirmam os achados prévios da literatura internacional que sugerem mais problemas psiquiátricos em filhos de mães bipolares e os estendem para a cultura brasileira*

Descritores: *Transtorno bipolar; Psicolopatologia; Fatores de risco; Crianças; Adolescentes*

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Introduction

There is growing recognition and interest in pediatric bipolar disorder (PBD) since it is associated with severe life quality deficits, causing great impairment in school performance, difficulty in relationships with peers and relatives, and engagement in high-risk behaviors.[1,2] In addition, the disorder is associated with a high risk of relapse and a low recovery index.[3] Perlis et al. (2004) documented in a clinical sample that subjects with onset of mood symptoms of bipolar disorder (BD) at childhood will have a more severe course associated with greater comorbidity.[4]

The study of bipolar probands is a remarkable opportunity to understand early prodromal manifestations of BD, and might be also useful in improving early diagnosis and fostering potential preventive measures. A meta-analysis of 17 studies of bipolar offspring found such individuals to be at a 2.7 times higher risk of developing a mental disorder and 4.0 times more likely to develop a mood disorder than are children of parents with no mental disorders.[5] Since 1997, cross-sectional studies have reported that approximately 50% of bipolar offspring meet criteria for at least one DSM-IV psychiatric disorder.[6]

Regarding specific psychiatric diagnoses besides mood disorders, attention-deficit hyperactivity disorder (ADHD) or significant behavioral or attentional problems have been reported in approximately 27% of bipolar offspring studied.[7] In children with strong family history of BD, the diagnosis of ADHD can be the first sign of a BD.[8] More recently, Henin et al.[9] documented a higher prevalence of anxiety disorders in bipolar offspring (36%) compared to rates detected in children of psychiatrically healthy parents (14%). These findings are concordant with those suggesting that an anxiety disorder might be an alternative pathway for the further development of BD.[7] Hirshfeld-Becker et al.[10] studied a sample of children with a mean age of 6.8 years and described significantly higher rates of disruptive behavior and anxiety disorders in bipolar offspring than in offspring of both parents with panic or major depression and parents with neither mood nor anxiety disorders. Wals et al. found that daughters of bipolar parents obtained significantly higher scores on the following CBCL scales: Total Problems, Internalizing, Externalizing, Somatic Complaints, Anxious/Depressed, Social problems, Delinquent Behavior and Aggressive Behavior; and sons of bipolar parents obtained significantly higher scores on the Total Problems, Externalizing, Thought Problems and Aggressive Behavior scales than the normative sample.[11]

There has been extensive research on adult BD in Europe, the USA and many other countries, although little research has been accomplished on child and adolescent BD outside North America and Europe. The international epidemiology and phenomenology of pediatric BD is not well known.[12,13] Nevertheless, current data suggest that pediatric BD is either fairly rare or under diagnosed outside the USA in epidemiological samples.[14]

The objective of this study was to assess the prevalence of psychopathology in a high-risk child sample from Brazil. Our main hypothesis was that bipolar offspring would present a higher rate of categorical psychiatric diagnoses and dimensional psychiatric problems than would both children of mothers without psychiatric disorders and those with only mild disorders. To the best of our knowledge, this is the first study to evaluate the prevalence of psychopathology in offspring of a sample of South American women with BD.

Method

1. Subjects

This was a cross-sectional with a controlled group study assessing bipolar mothers' offspring aged between 6 and 18 years old. Mothers were recruited between December 2004 and March 2006 from the Mood Disorders Outpatient Unit at the Institute of Psychiatry, Clinical Hospital, Medical School, Universidade de São Paulo, Brazil. Of 211 patients undergoing treatment in the Mood Disorders Outpatient Unit, 139 were females. We were able to contact 135 of these patients, 50 of whom had children aged between 6 and 18 years. We invited all eligible bipolar mothers who were under treatment. All mothers had to live in São Paulo, had to have a biological offspring between 6 and 18 years old and had to have a reconfirmed DSM-IV[15] diagnosis of BD I, II or NOS, according to the DSM-IV Structured Clinical Interview (SCID).[16] Only one randomly selected proband from each family was assessed.

The control group comprised 106 offspring of women from the General Gynecology Outpatient Service of the same University Hospital, concomitantly recruited by consecutive sampling. For psychiatric diagnosis, control group mothers were assessed using the SCID.[16] They had to live in São Paulo and had to have a biological offspring between 6 and 18 years old. The presence of BD, severe depressive episode, recurrent depressive disorder or any psychotic disorder were the exclusion criteria for this control group. All mothers signed a written informed consent and children and adolescents gave their verbal assent to participate in study. The study was approved by the hospital research ethics committee (number: 660/04).

2. Diagnostic procedures

Five extensively trained research psychiatrists and a PhD psychologist made the diagnoses using the SCID[16] for DSM-IV[15] in both groups of mothers. The current version of the SCID was translated into Portuguese[17] and a previous version translated and adapted into Portuguese had presented good reliability indices.[18]

Psychiatric disorders in children were assessed using the Brazilian version[19] of the K-SADS-PL,[20] which is a semi-structured interview allowing past and current diagnosis according to the DSM-IV[15] criteria in children and adolescents aged 6 to 18 years. The Brazilian version has shown excellent psychometric properties and similar content, along with inter-observer and test-retest reliability (Kappa-agreement = 0.87-1.00).[19] The interviews were performed individually with the parent or guardian and with the child or adolescent, and both answers were taken into account for the decision about the diagnosis. In case of discrepancy, the parent's opinion had a major weight for externalizing disorders as well as the child and adolescent's impression for the internalizing disorders. Different interviewers applied the SCID and the K-SADS-PL in each family.

The CBCL[21] was used to collect the dimensionality of symptoms with parents and the YSR[21] with adolescents (≥ 11 years old). The CBCL[21] is a questionnaire to be answered by parents or guardians of children and adolescents aged 6 to 18 years. The instrument has 138 items: 20 items related to social skills and 118 items related to behavioral problems. The behavioral problems are grouped into eight scales: anxiety/depression, withdrawal, somatic complaints, social, thought, and attention problems, and delinquent and aggressive behavior. The first three scales comprise the internalizing dimension, while the last two scales comprise the externalizing dimension. The sum of scores on all eight scales constitutes the "total problems". The Brazilian version of the CBCL was previously validated showing adequate psychometric properties.[22] The YSR has similar format and content to the CBCL, but was designed to be filled out as a self report by adolescents aged 11 years or older.[23] This instrument was previously translated into Portuguese and culturally adapted to Brazil.[24]

Table 1 - Demographic characteristics and comorbidities of mothers

	Mothers w/o PD N (%)	Mothers with others PD N (%)	Mothers with BD N (%)
Marital status * ** * **			
Married	39 (75.0)	39 (76.5)	18 (41.9)
Others	13 (25%)	12 (23.5%)	25 (58.1)
Education-years* ** * **			
0-4	9 (17.3)	10 (19.6)	6 (14)
5-8	21 (40.4)	15 (29.4)	6 (14)
≥ 9	22 (42.3)	26 (51)	31 (72)
Lifetime diagnoses			
BP I	-	-	34 (79.1)
BP II	-	-	7 (16.3)
BP NOS	-	-	2 (4.6)
Depressive Episodes	-	32 (60.4)	-
Anxiety disorders* **	-	38 (71.7)	15 (34.9)
Eating disorders*†	-	4 (7.5)	6 (13.9)
Substance abuse†	-	1 (1.9)	1 (2.3)
Substance dependence*†	-	0	5 (11.6)

BD: Bipolar disorder; PD: Psychiatriac disorder; SD: Standart deviation; Mothers could have more than one PD at the same time.
** There were significant differences (p < 0.05); ** Pearson's Chi-square Test; *** There are missing data for one Mother w/o PD and for two Mother with others PD in education and marital status variable; † Fisher Test*

In order to identify possible mania symptoms, the Young Mania Rating Scale (YMRS) was used.[25] The YMRS has proven useful in evaluating mania symptoms in children.[26] This instrument was translated and adapted to Portuguese by Vilela et al. and also showed adequate psychometric properties.[27] Family socioeconomic parameters were assessed using the Brazilian Criteria of Economic Classification *(Associação Brasileira de Empresas de Pesquisa* - ABEP).[28] The lower the total score, the lower the purchasing power of the family. The Global Assessment of Functioning (GAF)[15] was used for evaluating the mothers' psychological functioning and the Child Global Assessment Scale (CGAS)[29] was used for children functioning.

Finally, trained research psychologists administered the four subtests (Vocabulary, Block Design, Similarities, and Matrix Reasoning) of the Wechsler Abbreviated Scale of Intelligence (WASI) to estimate the IQs of the offspring.[30]

All interviewers were blind to the parents' diagnostic status and were under a child and adolescent psychiatrist's supervision.

3. Statistical analysis

Since lifetime prevalence of other psychiatric disorders was very common in mothers of the control group (50%), we decided not to exclude this group during the analyses, thereby avoiding decreased external validity and choosing a more realistic control group. Thus, we split the control group into two subgroups: 1) mothers without any psychiatric lifetime occurrence; 2) mothers with other psychiatric lifetime diagnoses.

At first, descriptive analyses were conducted, using means for continuous variables and proportions for categorical variables. Comparisons between the three groups were conducted through analysis of variance (ANOVA) for continuous outcomes (differences among groups were located by post-hoc analyses using Bonferroni) and the categorical outcomes were assessed through Pearson's Chi-square test, Pearson's Chi-square test with Yates correction and Fisher test, respecting applicability conditions of each test.

Comparisons among the three groups regarding demographic variables, and IQ scores were performed with one-way ANOVA. Multivariate Poisson Regression[31] was used to assess dichotomous outcomes adjusted for potential confounders while the ANCOVA assessed continuous outcomes. Potential confounders to be included in models were defined based on a literature review (in this study these confounders were gender, marital status, and mothers' GAF) or on a statistical definition (association with both the study factor and outcome for $p \leq 0.20$), where in the present case these confounders were age, race, schooling, socioeconomic status, and intelligence quotient of the offspring. A significance level of 0.05 was adopted for all other analyses, where all tests were two-tailed.

As proposed by Achenbach[23] and previously implemented by our group in other investigations,[32] we used the raw scores of both the CBCL and the YSR.

Results

The patient samples included three groups: a BD group with 43 patients from 50 eligible mothers (four patients, who had the same demographic and psychiatric characteristics as the role group, refused to participate and three were excluded – two had adopted children and one did not meet DSM-IV criteria for BD after reassessment). One hundred and six women without severe psychiatric disorders were enrolled and subdivided into two control groups: a) a control group without psychiatric disorder (w/o PD) (n = 53, 50%) and b) a control group with other psychiatric disorders (PD) (n = 53, 50%), including those who had one or more mild or moderate psychiatric lifetime diagnoses according to DSM-IV. The mean age of mothers w/o PD was 39.79 (SD = 5.59), with PD was 39.98 (SD = 4.44) and of bipolar mothers was 38.26 (SD = 7.66). The mean Global Assessment Function of mothers w/o PD was 91.48 (SD = 7.92), with PD was 78.45 (SD = 14.76) and of bipolar mothers was 61.74 (SD = 13.93) with a one-way ANOVA Test p value less than 0.001. Demographic characteristics and comorbidities of mothers from the three groups are described in Table 1. The variable "others" presented in Table 1

Table 2 - Demographic characteristics and intelligence quotient in offspring groups: BD offspring, and of mothers with and without psychiatric disorders

Variable	Offspring of mothers w/o PD (N = 53)	Offspring of mothers with others PD (N = 53)	Bipolar offspring (N = 43)	p value (ANOVA)
Age – mean (SD)	12.4 (3.2)	12.3 (3.4)	11.2 (3.7)	0.188
Education-years-mean (SD)	6.2 (3.1)	6.0 (3.1)	4.9 (3.2)	0.117
SEC - mean (SD)	14.1 (4.1)	13.6 (4.4)	16.3 (4.6)	0.010
Total IQ - mean (SD)	87.5 (14.2)	90.3 (13.3)	93.5 (14.3)	0.111

BD: Bipolar disorder; PD: Psychiatric disorders; SEC: Socioeconomic class; IQ: Intelligence quotient; SD:Standard deviation

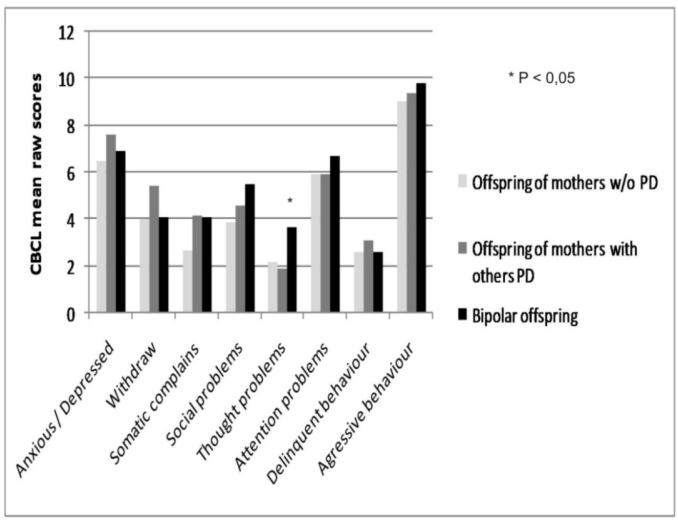

Figure 1 - CBCL mean raw scores

included separated, divorced, widows and singles.

The majority of the offspring of mothers with BD (69.8%) did not live with their biological father, in contrast with offspring from mothers with other PD (25.5%) and w/o PD (28.8%) ($p < 0.001$).

The offspring gender distribution was 29 (54.7%) females on the offspring of mothers w/o PD, 23 (43.4%) females on the offspring of mothers with PD and 25 (58.1%) females on the bipolar offspring group. The percentage of Caucasian offspring was 27 (50.9%) of mothers w/o PD, 25 (47.2%) of mothers with PD and 30 (69.8%) of bipolar mothers. Other offspring demographic characteristics are described in Table 2. There was no significant difference among groups in gender, age or ethnicity, although mothers and offspring from both control groups (with and w/o PD) belonged to families with significantly lower socioeconomic levels than did children from the BD mothers group ($p = 0.010$).

The offspring's DSM–IV prevalence of Lifetime Psychiatric Diagnoses is shown in Table 3.

Bipolar offspring had higher prevalence ratios (Poisson Regression) compared to those of mothers with and without PD in dichotomous outcomes, adjusted for potential confounders (gender, marital status, mothers' GAF, age, race, schooling, socioeconomic status, and intelligence quotient), in lifetime anxiety disorders and lifetime Axis I disorders. These results are shown in Table 4.

Additionally, when compared with the whole control group, the bipolar offspring group also had a higher prevalence ratio of disruptive disorders (including ADHD) [prevalence ratio = 3.02 (95% CI: 1.02-8.91) and $p = 0.045$] and of lifetime Axis I disorders [prevalence ratio = 1.67 (95% CI: 1.12-2.49) and $p = 0.011$].

Findings suggesting higher prevalence of anxiety disorders in bipolar offspring remained significant even after adjustment for the presence of comorbid anxiety disorder in bipolar mothers.

Considering CBCL outcomes adjusted for the same potential confounders listed above using ANCOVA, we observed a significant difference ($p = 0.038$) among groups in the CBCL thought problems scale. Mean scores of all scales of CBCL are presented in Figure 1.

Regarding the YSR, we found a significant difference in Total Problems, as well as a significant difference among the three groups in social ($p = 0.002$), anxious/depressed ($p = 0.026$) and internalizing problems ($p = 0.046$). Using Bonferroni test to localize the differences among groups, the majority of the differences were between the bipolar offspring and offspring of mothers without PD group, except for social problems that show also a difference between both offspring control groups ($p = 0.005$), with the highest means in bipolar offspring group. Mean scores in all scales of YSR are presented in Figure 2.

We did not find any relevant differences between groups in scores of YMRS or in the CGAS.

Discussion

Our findings suggest that bipolar offspring present a significantly higher prevalence of lifetime Axis I disorders and more specifically a higher prevalence of anxiety disorders than do offspring of mothers without any PD. Similarly, significant differences in prevalence of

Table 3 - Lifetime psychiatric diagnoses accordingly DSM-IV all offspring

Lifetime DSM-IV Diagnoses	Offspring of mothers w/o psychiatric disorders (N = 53)		Offspring of mothers with others mental disorders (N = 53)		Bipolar offspring (N = 43)		value
	N	%	N	%	N	%	
Any Axis I	22	41.5	31	58.5	27	62.8	0.079†††
Any mood	3	5.7	6	11.3	5	11.6	0.740‡
Depressive	2	3.8	2	3.8	2	4.7	-
Bipolar	0	0	0	0	1	2.3	-
Any Anxiety	11	20.8	21	39.6	19	44.2	0.033†††
Specific phobia	6	11.6	14	26.4	9	20.9	0.140†††
Social phobia	4	7.6	5	9.4	3	7.0	0.895†††
Separation	2	3.8	2	3.8	5	11.6	0.404‡
Panic disorder	0	0	0	0	2	4.7	-
GAD*	2	3.8	2	3.8	2	4.7	-
PTSD**	0	0	1	1.9	2	4.7	-
OCD***	2	3.8	2	3.8	2	4.7	-
ODD†	1	1.9	2	3.8	3	7.0	-
Conduct	0	0	0	0	3	7.0	-
ADHD††	3	5.7	2	3.8	5	11.6	0.521‡
Enuresis	10	18.9	8	15.1	10	23.3	0.596†††

** Generalized anxiety disorder; ** Posttraumatic stress disorder; *** Obsessive-compulsive disorder; † Oppositional defiant disorder; †† Attention deficit hyperactivity disorder; ††† Pearson's Chi-square test; ‡ Pearson's Chi-square test with Yates correction.*
Any patient could have more than one lifetime diagnosis

Table 4 - Prevalence ratio (Poisson Regression) of lifetime DSM-IV diagnoses between offspring groups

Disorders	Prevalence ratio ($CI_{95\%}$) *	p value
Lifetime axis I disorder		
Offspring of mothers w/o PD	1.00	
Offspring of mothers with PD	1.32 (0.90; 2.11)	0.141
Bipolar offspring	2.11 (1.30; 3.42)	0.003
Mood disorder		
Offspring of mothers w/o PD	1.00	
Offspring of mothers with PD	2.05 (0.32; 3.20)	0.451
Bipolar offspring	1.80 (0.26; 2.48)	0.551
Anxiety disorders		
Offspring of mothers w/o PD	1.00	
Offspring of mothers with PD	2.11 (1.09; 4.06)	0.026
Bipolar offspring	2.83 (1.39; 5.78)	0.004
Disruptive disorder with ADHD included		
Offspring of mothers w/o PD	1.00	
Offspring of mothers with PD	0.73 (0.14; 3.85)	0.711
Bipolar offspring	2.44 (0.45; 13.33)	0.304

** Adjusted for ethnicity, age, schooling, socioeconomic status, IQ, gender, marital status and Global Assessment Functioning (GAF)*

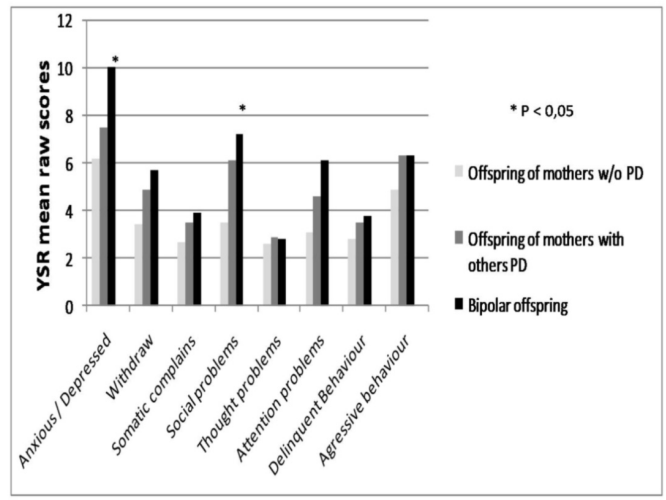

Figure 2 - YSR mean raw scores

lifetime Axis I disorders and in disruptive lifetime disorders were found comparing bipolar offspring with the entire control group.

These findings corroborate those of Henin et al.[9] that found a huge prevalence of a myriad of mental disorders including disruptive behavior disorders, separation anxiety disorder, generalized anxiety disorder, social phobia, and depression in bipolar offspring in early or middle childhood. In addition, Hirshfeld-Becker et al.[10] reported that offspring of bipolar parents had significantly higher rates of disruptive behavior and anxiety disorders than did both offspring of parents with panic or major depression disorders and offspring of parents with neither mood or anxiety disorders. Singh et al.[33] also found higher rates of psychopathology in bipolar offspring as compared to controls' offspring (respectively, 78% had at least one DSM-IV Axis I diagnosis compared to only 24% in controls).

Whilst most studies have shown a prevalence of psychopathology in bipolar offspring of around 50%,[5] our study showed that 62.8% of bipolar offspring met criteria for at least one DSM-IV lifetime diagnosis, compared to 58.5% of offspring from mothers with mild psychiatric diagnoses and 41.5% of the offspring from mothers without any psychiatric diagnosis. Of note, 9.3% of bipolar offspring and 10.4% of children of mothers from both control groups combined had a specific phobia as their sole diagnosis. Several previous studies did not classify individuals as psychiatrically ill based on the presence of simple phobia as the only diagnosis. Remarkably, we found a high prevalence of psychiatric disorders in our control group; it may be a limitation of our study but also can reflect a less selected sample. Including only healthy controls could raise differences but would not reflect a real population. Besides, it is known that in developing countries the prevalence of mental health problems is higher than in developed countries. Giel et al.[34] found that between 12% and 29% of children aged 5 to 15 years had mental health problems in four low-income countries (Sudan, Philippines, Colombia and India). Paula et al.[35] verified a prevalence of mental health problems of 24.6% in a community sample of children and adolescents aged 6 to 17 years in a city of Southeastern Brazil.

Anxiety disorders were the most prevalent diagnoses in our study, and some authors have found similarly high rates of anxiety disorders, particularly generalized anxiety disorder (GAD) and separation anxiety disorder, in bipolar offspring.[6,9] Recently, Bruckl et al.[36] have also documented that separation anxiety disorder during adolescence is a risk factor for BD in adulthood in a German community sample. Moreover, previous investigations have suggested that adolescents with anxiety disorders have a higher risk for BD than do those without anxiety disorders.[37]

We found a lifetime prevalence rate of mood disorders of 11.6% among bipolar offspring, 11.3% in offspring of mothers with other PD, and 5.7% in offspring of mothers without PD. In a meta-analysis of 17 studies, Lapalme et al.[5] reported a prevalence rate of 26.5% for mood disorders among bipolar offspring in comparison with 8.3% in offspring of parents without PD with mild disorders. The small prevalence of mood disorders found in our study might be attributed to the lower overall age of our sample, given that the onset of affective disorders frequently occurs during adolescence or in early adulthood.[5,11] The lifetime prevalence of ADHD among bipolar offspring observed in our study was 11.6%, which lies between the 5% found by Wals et al.[11] and the rate of 27% found by other studies in populations with similar characteristics.[7] BD offspring ADHD prevalence was high above the 4.7% found in the sum of control groups in our study.

Regarding dimensional measures, we found significant differences in thought problems on the CBCL, and anxious/depressed, social, and internalizing problems on the YSR between bipolar offspring and offspring of mothers without PD. Giles et al.[38] verified that bipolar offspring scored significantly higher than healthy controls on the anxious/depressed, attention problems, aggression and withdrawal subscales, and lower than bipolar youth on all scales of the CBCL except for the somatic complaints and anxious/depressed subscales. We found more internalizing symptoms in the YSR than in the CBCL, which is in accordance with the literature. Children and adolescents seem to be better informants of this kind of symptoms than are their parents.

The number of separated bipolar mothers is almost two-fold higher than that of mothers from the control groups in our sample, and the mean GAF score of bipolar mothers was significantly lower than the other mothers'. Since it is known that separated parents might represent a risk factor for psychopathology in childhood and adolescence,[39] we used marital status and GAF as potential

confounding factors in our analyses and the differences found remained statistically significant.

Of note, the majority of the literature available on preadolescent mania originates from North America. Thus, much could be learned from cross-cultural studies on this group of children.[40] This issue is even more relevant considering the huge differences reported in the prevalence of pediatric bipolar disorder between European and American countries.[13] Our study has the strength of applying international validated measures of child psychopathology in a sample from Brazil, a developing country. Other strength of our study is the use of two dimensional diagnostic tools (CBCL and YSR) and categorical diagnoses. In addition, we assessed psychopathology from different information sources – parent and child – using the K-SADS-PL.

However, this study must be interpreted in the context of some limitations. First, the relatively small sample size for some diagnoses made it difficult to exclude Type II errors when comparing the groups. Second, reliability among raters was not checked, although all were experienced clinicians with extensive training in administering the instruments, being supervised by a child psychiatrist. Third, unexpected high prevalence of mental disease was found in the control group, probably due to the tertiary center origin of the subjects or because of a possible selection bias. This fact limits the generalizability of our findings. Finally, the Portuguese translation of the WASI had not been validated yet when the study was conducted. However, any assessment bias would have affected all groups equally.

Our findings support that, in adult psychiatric settings, clinicians should bear in mind that offspring of bipolar patients are at a high risk for mental disorders. They should be prepared to refer suspect children for evaluation, especially those presenting with anxiety symptoms. It is important to adopt a more comprehensive approach comprising the patient's environment and family.

These subjects (offspring) should be prospectively followed-up to the age of the most probable onset of psychiatric disorders, particularly mood disorders, in order to verify prodromal signs of such disorders and possibly minimize or prevent suffering.

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Disclosures

Writting group member	Employment	Research grant[1]	Other research grant or medical continuous education[2]	Speaker's honoraria	Ownership interest	Consultant/ Advisory board	Other[3]
Sandra Petresco	Private practice UFPel	-	-	-	-	-	-
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Renata Krelling	Private practice	-	-	-	-	-	-
Francisco Lotufo Neto	Private practice USP	-	-	-	-	-	-
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*** Significant*
**** Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*
Note: UFPel = Universidade Federal de Pelotas; USP = Universidade de São Paulo; UFRGS = Universidade Federal do Rio Grande do Sul; CNPq = Conselho Nacional de Desenvolvimento Científico e Tecnológico; CAPES = Coordenação de Aperfeiçoamento de Pessoal de Nível Superior; FAPERGS = Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul; NASARD = National Alliance for Research on Schizophrenia and Depression; PRONEX = Programa de Apoio a Núcleos de Excelência-Ministério da Ciência e Tecnologia; SENAD = Secretaria Nacional de Políticas sobre Drogas; FIPE/HCPA = Fundo de Incentivo à Pesquisa do Hospital de Clínicas de Porto Alegre; FAPESP = Fundação de Amparo à Pesquisa do Estado de São Paulo; CEIP = Centro de Estudos do Instituto de Psiquiatria do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo; ABTB = Associação Brasileira de Transtorno Bipolar; ABP = Associação Brasileira de Psiquiatria
For more information, see Instructions for authors

References

1. Geller B, Williams M, Zimerman B, Frazier J, Beringer l, Warner KL. Prepubertal and early adolescent bipolarity differentiate from ADHD by manic symptoms, grandiose delusions, ultra-rapid or ultradian cycling. *J Affect Disord.* 1998;51(2):81-91.
2. Geller B, Craney JL, Bolhofner K, DelBello MP, Williams M, Zimerman B. One-year recovery and relapse rates of children with a prepubertal and early adolescent bipolar disorder phenotype. *Am J Psychiatry.* 2001;158(2):303-5.
3. Geller B, Craney JL, Bolhofner K, Nickelsburg MJ, Williams M, Zimerman B. Two-year prospective follow-up of children with a prepubertal and early adolescent bipolar disorder phenotype. *Am J Psychiatry.* 2002;159(6):927-33.
4. Perlis RH, Miyahara S, Marangell LB, Wisniewski SR, Ostacher M, DelBello MP, Bowden CL, Sachs GS, Nierenberg AA, STEP-BD Investigators. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). *Biol Psychiatry.* 2004;55(9):875-81.
5. Lapalme M, Hodgins S, LaRoche C. Children of parents with bipolar disorder: a meta-analysis of risk for mental disorders. *Can J Psychiatry.* 1997;42(6):623-31.
6. Chang KD, Steiner H, Ketter TA. Psychiatric phenomenology of child and adolescent bipolar offspring. *J Am Acad Child Adolesc Psychiatry.* 2000;39(4):453-60.
7. Chang K, Steiner H, Ketter T. Studies of offspring of parents with bipolar disorder. *Am J Med Genet C Semin Med Genet.* 2003;123C(1):26-35.
8. Faraone SV, Biederman J, Wozniak J, Mundy E, Mennin D, O'Donnell D. Is comorbidity with ADHD a marker for juvenile onset mania? *J Am Acad Child Adolesc Psychiatry.* 1997;36(8):1046-55.
9. Henin A, Biederman J, Mick E, Sachs GS, Hirshfeld-Becker DR, Siegel RS, McMurrich S, Grandin L, Nierenberg AA. Psychopathology in the offspring of parents with bipolar disorder: a controlled study. *Biol Psychiatry.* 2005;58(7):554-61.
10. Hirshfeld-Becker DR, Biederman J, Henin A, Faraone SV, Dowd ST, De Petrillo LA, Markowitz SM, Rosenbaum JF. Psychopathology in the young offspring of parents with bipolar disorder: a controlled pilot study. *Psychiatry Res.* 2006;145(2-3):155-67.
11. Wals M, Hillegers MH, Reichart CG, Ormel J, Nolen WA, Verhulst FC. Prevalence of psychopathology in children of a bipolar parent. *J Am Acad Child Adolesc Psychiatry.* 2001;40(9):1094-102.
12. Tramontina S, Schmitz M, Polanczyk G, Rohde LA. Juvenile bipolar disorder in Brazil: clinical and treatment findings. *Biol Psychiatry.* 2003;53(11):1043-9.
13. Soutullo CA, Chang KD, Díez-Suárez A, Figueroa-Quintana A, Escamilla-Canales I, Rapado-Castro M, Ortuño F. Bipolar disorder in children and adolescents: international perspective on epidemiology and phenomenology. *Bipolar Disord.* 2005;7(6):497-506.
14. Ford T, Goodman R, Meltzer H. The British Child and Adolescent Mental Health Survey 1999: the prevalence of DSM-IV disorders. *J Am Acad Child Adolesc Psychiatry.* 2003;42(10):1203-11.
15. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).* 4th ed. Washington, DC: American Psychiatric Association; 1994.
16. First MB, Spitzer RL, Gibbon M, Williams JBW, editors. *Structured Clinical Interview for DSM IV Axis I Disorders Patient Edition (SCID-I/P version 2.0).* New York: Biometrics Research Department, New York State Psychiatric Institute; 1996.
17. Versiani M. Entrevista clínica estruturada - DSM-IV transtornos do eixo I. Tradução da structured clinical interview for DSM-IV axis I/patient (versão 2.1). Rio de Janeiro: Programa de Ansiedade e Depressão, Instituto de Psiquiatria IPUB, UFRJ; 1996.
18. Del-Ben CM, Rodrigues CR, Zuardi AW. Reliability of the Portuguese version of the structured clinical interview for DSM-III-R (SCID) in a Brazilian sample of psychiatric outpatients. *Braz J Med Biol Res.* 1996;29(12):1675-82.
19. Brasil HHA. Desenvolvimento da versão brasileira da K-SADS-PL (Schedule for Affective Disorders and Schizophrenia for School Aged Children Present and Lifetime Version) e estudo de suas propriedades psicométricas [tese]. São Paulo: Escola Paulista de Medicina, Universidade Federal de São Paulo; 2003.
20. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N. Schedule for Affective Disorders and Schizophrenia for School-age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry.* 1997;36(7):980-8.
21. Achenbach TM, Dumenci L. Advances in empirically based assessment: revised cross-informant syndromes and new DSM-oriented scales for the CBCL, YSR and TRF: comment on Lengua, Sadowksi, Friedrich, and Fischer. *J Consult Clin Psychol.* 2001;69(4):699-702.
22. Bordin IAS, Mari JJ, Caeiro MF. Validação da versão brasileira do "Child Behavior Checklist" (CBCL) (Inventário de Comportamentos da Infância e Adolescência): dados preliminares. *Rev ABP-APAL.* 1995;17(2):55-66.
23. Achenbach TM. *Manual for the Youth Self-Report Form and 1991 profile.* Burlington: University of Vermont; 1991.
24. Duarte CS, Bordin IA. Instrumentos de avaliação. *Rev Bras Psiquiatr.* 2000;22(Supl 2):55-8.
25. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity, and sensitivity. *Br J Psychiatry.* 1978;133: 429-35.
26. Fristad MA, Gavazzi SM, Mackinaw-Koons B. Family psychoeducation: an adjunctive intervention for children with bipolar disorder. *Biol Psychiatry.* 2003;53(11):1000-8.
27. Vilela JA, Crippa JA, Del-Ben CM, Loureiro SR. Reliability and validity of a Portuguese version of the Young Mania Rating Scale. *Braz J Med Biol Res.* 2005;38(9):1429-39.
28. Associação Brasileira de Empresas de Pesquisa (ABEP). Critério de classificação econômica Brasil [on line] 2003.[cited 2008 dez 12]. Available from http://www.abep.org/codigosgerais/ABEP.CCEB.
29. Shafer D, Gould MS, Brasic J, Ambrosini P, Fisher P, Bird H, Aluwahlia S. A children's global assessment scale (CGAS). *Arch Gen Psychiatry.* 1983;40(11):1228-31.
30. Wechsler D. *Wechsler abbreviated scale of intelligence*. New York, NY: Psychological Corporation; 1999.
31. Barros AJ, Hirakata VN. Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio. *BMC Med Res Methodol.* 2003;3:21.
32. Lampert TL, Polanczyk G, Tramontina S, Mardini V, Rohde LA. Diagnostic performance of the CBCL-Attention Problem Scale as a screening measure in a sample of Brazilian children with ADHD. *J Atten Disord.* 2004;8(2):63-71.
33. Singh MK, DelBello MP, Stanford KE, Soutullo C, McDonough-Ryan, McElroy SL, Strakowski SM. Psychopathology in children of bipolar parents. *J Affect Disord.* 2007;102(1-3):131-6.
34. Giel R, de Arango MV, Climent CE, Harding TW, Ibrahim HH, Ladrido-Ignacio L, Murthy RS, Salazar MC, Wig NN, Younis YO. Childhood mental disorders in primary health care: results of observations in four developing countries. A report from the WHO collaborative Study on Strategies for Extending Mental Health Care. *Pediatrics.* 1981;68(5):677-83.
35. Paula CS, Duarte CS, Bordin IA. Prevalence of mental health problems in children and adolescents from the outskirts of Sao Paulo city: treatment needs and service capacity evaluation. *Rev Bras Psiquiatr.* 2007;29(1):11-7.
36. Bruckl TM, Wittchen HU, Hofler M, Pfister H, Schneider S, Lieb R. Childhood separation anxiety and the risk of subsequent psychopathology: results from a community study. *Psychother Psychosom.* 2007;76(1):47-56.
37. Johnson JG, Cohen P, Brook JS. Associations between bipolar disorder and other psychiatric disorders during adolescence and early adulthood: a community-based longitudinal investigation. *Am J Psychiatry.* 2000;157(10):1679-81.
38. Giles LL, DelBello MP, Stanford KE, Strakowski SM. Child behavior checklist profiles of children and adolescents with and at high risk for developing bipolar disorder. *Child Psychiatry Hum Dev.* 2007;38(1):47-55.
39. Harland P, Reijeneveld SA, Brugman E, Verloove-Vanhorick SP, Verhulst FC. Family factors and life events as risk factors for behavioural and emotional problems in children. *Eur Child Adolesc Psychiatry.* 2002;11(4):176-84.
40. Harrington R, Myatt T. Is preadolescent mania the same condition as adult mania? A British perspective. *Biol Psychiatry.* 2003;53(11):961-9.