ORIGINAL ARTICLE
https://doi.org/10.30773/pi.2018.10.22.1
Print ISSN 1738-3684 / On-line ISSN 1976-3026
OPEN ACCESS

Differences in Psychopathology between Offspring of Parents with Bipolar I Disorder and Those with Bipolar II Disorder: A Cross-Sectional Study

Hyeon-Ah Lee[1], Ji-Sun Kim[1], Yeon-Jung Lee[2], Nam-Hun Heo[1], Se-Hoon Shim[1] ✉, and Young-Joon Kwon[1]

[1]Department of Psychiatry, Cheonan Hospital, College of Medicine, Soonchunhyang University, Cheonan, Republic of Korea
[2]Department of Psychiatry, Seoul Hospital, College of Medicine, Soonchunhyang University, Seoul, Republic of Korea

Objective The aim of this study was to evaluate differences in psychopathology between offspring of parents with bipolar I disorder (BP-I) and those with bipolar II disorder (BP-II).

Methods The sample included 201 offspring between 6 and 17 years of age who had at least one parent with BP-I or BP-II. The offspring were diagnostically evaluated using the Korean Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version. Psychopathology and Clinical characteristics were evaluated, including lifetime DSM-5 diagnoses, depression, and childhood trauma. Lifetime DSM-5 diagnoses were also compared between schoolchildren aged 6 to 11 years and adolescents aged 12 to 17 years.

Results In lifetime DSM-5 diagnoses, offspring of parents with BP-I had significantly increased risk of developing MDD and BP-I than those with BP-II. Regarding clinical characteristics, ADHD rating scale and childhood trauma scale were significantly higher in offspring of parents with BP-I than that in those with BP-II.

Conclusion The present study supports that BP-I may be etiologically distinct from BP-II by a possible genetic liability. Our findings indicate that additional research related to bipolar offspring is needed to enhance understanding of differences between BP-I and BP-II.

Psychiatry Investig 2018;15(12):1135-1143

Key Words Bipolar I disorder, Bipolar II disorder, Offspring, Schoolchildren, Adolescent.

INTRODUCTION

Bipolar disorder is a severe mental disorder that affects aspects of an individual's behavior and function.[1-3] The chronicity of illness has long been associated with considerable global impairment and varied symptomatology.[4]

Differences and similarities in the phenomenology of bipolar I disorder (BP-I) and bipolar II disorder (BP-II) have remained subjects of continuous research interest. Their clinical distinction is of central importance if they differ etiologically in their natural course or show differential treatment responses to various treatment modalities.[5] A recent review on distinguishing characteristics between BP-I and BP-II individuals has found no differences in temperament or personality.[6,7] However, controversy remains regarding whether they differ only in severity of manic-side episodes or they also differ in etiology.

Some genetic epidemiologic studies have shown that morbid risk of BP-II is much higher in relatives of BP-II probands than in that in those of BP-I probands.[8,9] Some studies have suggested that BP-I may be etiologically distinct from BP-II by genetic liability.[10,11] In view of phenomenological and biological heterogeneity of bipolar disorder (BP), some researchers have suggested that BP-II can be distinguished from BP-I by the basics of prior course, characteristics of prior episode, and familial history.[12]

Meanwhile, previous studies have reported that offspring of patients with BP have higher risks for developing psychopathology and higher frequencies of psychiatric illness.[13,14] Additionally, family history for BP is one of predictors for developing psychiatric illness such as BP, major depressive disorder (MDD), and Attention Deficit Hyperactivity Disorder

Received: July 29, 2018 **Revised:** October 16, 2018
Accepted: October 22, 2018

✉ **Correspondence:** Se-Hoon Shim, MD, PhD
Department of Psychiatry, College of Medicine, Soonchunhyang University Cheonan Hospital, 31 Suncheonhyang 6-gil, Dongnam-gu, Cheonan 31151, Republic of Korea
Tel: +82-41-570-3853, **Fax:** +82-41-592-3804, **E-mail:** shshim2k@daum.net

(ADHD).[15,16] Despite clinical implications, few previous studies have evaluated psychopathology or clinical manifestations in offspring of parents with BP. Moreover, most previous studies have demonstrated psychopathology among offspring of parents with BP without considering bipolar subtypes. To our knowledge, there have been no studies which compare differences in psychopathology or clinical features between offspring of parents with BP-I and those with BP-II.

This study evaluated child and adolescent offspring of bipolar parents to further examine the presence of psychopathology in this population. Lifetime DSM-5[17] diagnoses and severity of mood symptoms as well as demographic characteristics, clinical characteristics, and family psychiatric history were examined. We used a relatively large clinical sample to investigate differences in these trait characteristics between offspring of parents with BP-I and those with BP-II.

METHODS

Subjects

The sample included 201 children and adolescents between 6 and 17 years of age who had at least one parent with DSM-5 BP-I or BP-II. All subjects of this study were enrolled between August 2017 and July 2018. Parents and their offspring were recruited from inpatient and outpatient units of Soonchunhyang University Hospital at Cheonan, Korea. In all families, the bipolar parent as the informant of this study was an outpatient at the time of enrollment and was euthymic at the time of assessments.

Exclusion criteria for offspring included the presence of neurological disorders, history of head injury with loss of consciousness, a family history of hereditary neurologic disorder, or any current, serious medical problems.

Informed consent was obtained from the parents or legal guardians and assent from the children and adolescent subjects in the study after an explanation of this study. This study was approved by the Institutional Review Board of Soonchunhyang University Hospital in Cheonan (IRB No. 2017-05-027).

Instruments and procedures

To ascertain socio-demographic characteristics and psychiatric family history, a detailed interview form was prepared by researchers. The offspring were diagnostically evaluated using Korean Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (K-SADS-PL-K).[18,19] K-SADS-PL-K was performed independently on both offspring and parents by a trained psychiatrist. K-SADS-PL-K is a semi-structured diagnostic interview. It was used to assess lifetime history of psychiatric disorder and confirm their diagnoses. In cases of disagreement between child and parent about the presence of a symptom, greater weight was given to parents' reports of observed behavior and children's reports of subjective experiences.[20]

To improve diagnostic accuracy, additional scales including Korean version of Mood Disorder Questionnaire Adolescent version (K-MDQ-A),[21,22] Korean version of Parent-General Behavior Inventory 10-item Manic Scale (K-P-GBI-10M)[23,24] for BP, and Korean ADHD Rating Scale (K-ARS)[25,26] for ADHD were applied. K-MDQ-A is a self-report of manic symptoms for adolescent. K-MDQ-A yielded a score for each adolescent ranging from 0 to 13. It was completed by parents about adolescent's symptoms. It demonstrated good sensitivity and specificity (0.72 and 0.81, respectively) at a cut-score of 5.[21,22] K-P-GBI-10M is a 10-item parent-report instrument ranging from 0 to 30, with higher score indicating greater severity. It was completed by parents to screen for elevated symptoms of mania.[23,24] K-ARS is used to identify the presence of ADHD and its subtype (inattention or hyperactive). K-ARS has 18 questions, of which 9 items are related to symptoms of inattention while the other 9 items are related to symptoms of hyperactivity and impulsivity as a self-report assessment.[25,26] All diagnoses were made using DSM-5 criteria. The interviewer was not blinded to the status of parents. DSM-5 diagnoses were confirmed based on consensus review by a board-certified child psychiatrist (SHS).

Offspring's subjective perception of anxiety was assessed by self-report using the Korean version of Revised Children's Manifest Anxiety Scale (K-RCMAS).[16,27,28] K-RCMAS consists of 37 questions to assesses both the degree and quality of anxiety experienced by children and adolescents. It provides a global summary score as well as three sub-scores in areas of psychological anxiety (including 10 items), worry/oversensitivity (including 11 items), social concerns/concentration (including 7 items), and a lie scale. An overall cut-off point of 19 out of 28 can be used to identify children experiencing clinically significant levels of anxiety.[16,27,28] Offspring were subjected to Korean Children's Depression Inventory (K-CDI),[29,30] a 27-item multiple choice questionnaire for measuring the severity of depression. K-CDI scores of >13 are conventionally considered a clinically meaningful cut-off score to identify significant depressive symptomatology.[29,30] Childhood trauma history was obtained using the Korean childhood trauma questionnaire (K-CTQ)[31,32] consisting of 28 items for a self-report inventory. K-CTQ measures the severity of different types of childhood trauma, including emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. Each subscale score ranges from 5 (no history of abuse or neglect) to 25 (very extreme history of abuse and neglect).[31,32]

Analyses

First, socio-demographic information of parents was compared between BP-I and BP-II. Second, socio-demographic information, lifetime DSM-5 diagnoses, and clinical characteristics of offspring were compared between offspring of parents with BP-I and those with BP-II. Lifetime DSM-5 diagnoses were also compared between schoolchildren group aged 6 to 11 years and adolescent group aged 12 to 17 years. To describe differences in psychiatric disorders between offspring of parents with BP-I and those with BP-II, two age groups were considered.

Comparison of socio-demographic and clinical variables between offspring of parents with BP-I and those with BP-II was performed by chi-square or Fisher's exact test for categorical data and t-test for continuous variables with approximately normal distribution. For continuous variables violating normal distribution, Mann-Whitney U test was applied. A two-tailed significance level was used at $p<0.05$, not adjusted for multiple comparisons. For relatedness of parental bipolar subtypes, we used logistic regression models to estimate ORs with its respective 95% confidence interval (95% CI). Age, Sex and K-CTQ score of offspring were used as covariant variables in this analysis. The odds of psychiatric disorders in offspring of parents with BP-I was compared with the odds of psychiatric disorders in offspring of parents with BP-II. All statistical analyses were performed using SPSS 21 (IBM Corp., Armonk, NY, USA).

RESULTS

Socio-demographic characteristics: parents with BP-I vs. BP-II

Characteristics of parents with BP-I and BP-II are summarized in Table 1. There were 65 parents with BP-I and 71 parents with BP-II. Of these participants, 60% of parents with BP-I and 42.3% of parents with BP-II were females. Parents with BP-I were significantly younger with slightly lower SES than parents with BP-II, although these groups did not significantly differ in educational level. Parents with BP-I had lower age at onset than parents with BP-II. However, parents with BP-I and those with BP-II did not differ in sex, occupation, or number of children.

Socio-demographic and clinical characteristics: offspring of parents with BP-I vs. BP-II

Ninety-nine offspring of parents with BP-I and 102 offspring of parents with BP-II were recruited. No families were rejected if one of the children refused to participate. Table 2 shows comparison of socio-demographic and clinical characteristics in offspring of parents with BP. Offspring of parents with BP-I were younger than offspring of parents with BP-II (p=0.006). There was no significant difference in gender between the two groups. There were no significant differences in K-MDQ-A, K-ARS-hyperactivity, K-CDI, K-RCMAS, or K-P-GBI-10M score between offspring of parents with BP-I and those with BP-II.

Overall K-ARS score was significantly higher in offspring of parents with BP-I than that in offspring of parents with BP-II (p=0.034). Offspring of parents with BP-I had significantly higher scores in overall K-CTQ scale and specific types of abuse scale (K-CTQ emotional abuse, emotional neglect and physical neglect sub-scales) than offspring of parents with BP-II (p=0.004, p=0.041, p=0.032, and p=0.003, respectively). There were no differences in physical abuse or sexual abuse sub-scale between offspring of parents with BP-I and those with BP-II (Table 2).

Table 1. Socio-demographic characteristics of patients with bipolar disorder (N=136)

	BP-I (N=65)	BP-II (N=71)	χ^2 or t	p value
	N (%) or mean (SD)			
Sex (M/F)	26/39 (40.4/60.0)	41/30 (57.7/42.3)	χ^2=4.276	0.390
Age (years)	42.9 (5.4)	46.0 (6.3)	t=-3.043	0.003*
Education (years)	12.5 (2.6)	12.1 (3.1)	t=0.722	0.471
Socioeconomic status			χ^2=8.600	0.046
High	5 (7.7)	13 (18.3)	χ^2=3.331	0.090
Middle	28 (43.1)	36 (50.7)	χ^2=0.792	0.395
Low	32 (49.2)	22 (31.0)†	χ^2=4.718	0.036*
Age of onset (years)	23.8 (7.8)	28.8 (6.7)	t=-4.007	0.000*
Currently employed	41 (63.1)	53 (74.6)	χ^2=2.128	0.145
Number of children	1.8 (0.7)	2.0 (0.9)	t=-1.882	0.062

*significance at $p<0.05$, †denotes a significant difference between BP-I and BP-II (p=0.036). BP-I: bipolar I disorder, BP-II: bipolar II disorder

Differences in DSM-5 Primary and Comorbid diagnoses between Offspring of parents with BP-I and BP-II

As shown in Table 3, 67 offspring of parents with BP-I (67.7%) and 64 offspring of parents with BP-II (62.7%) had at least one psychiatric disorder. Offspring of parents with BP-I had 2.31-fold increased risk of developing MDD (95% CI: 1.11–4.84, p=0.024) and 4.13-fold increased risk of developing BP-I (95% CI: 1.12–15.27, p=0.027) than offspring of parents with BP-II. Offspring of parents with BP-II had higher rate of BP-II, although this difference did not reach statistical significance (p=0.056).

Among 67 offspring of parents with BP-I, 33 had any depressive disorder and 17 had any bipolar disorder. Six off-

Table 2. Socio-demographic and clinical characteristics of offspring of parents with bipolar disorder

	BP-I offspring (N=99)	BP-II offspring (N=102)	χ^2 or t	p value
	N (%) or Mean (SD)			
Sex (M/F)	56/43 (56.6/43.4)	58/44 (56.9/43.1)	χ^2=0.002	0.966
Age (years)	13.1 (3.6)	14.4 (2.8)	t=-2.785	0.006*
K-P-GBI-10M	2.7 (2.9)	2.1 (2.5)	t=1.597	0.112
K-ARS	13.0 (6.8)	11.0 (6.9)	t=2.136	0.034*
K-ARS hyperactivity subscore	4.7 (4.1)	4.4 (4.0)	t=0.742	0.459
K-CDI	15.3 (6.0)	15.3 (5.6)	t=-0.013	0.989
K-RCMAS	17.5 (7.2)	16.8 (6.7)	t=0.685	0.494
K-CTQ	26.1 (1.9)	25.5 (0.9)	t=2.941	0.004*
Emotional abuse	5.0 (0.2)	5.0 (0.0)	t=2.062	0.041*
Physical abuse	5.1 (0.4)	5.1 (0.3)	t=0.691	0.490
Sexual abuse	5.0 (0.0)	5.0 (0.0)	-	-
Emotional neglect	5.6 (1.1)	5.3 (0.6)	t=2.163	0.032*
Physical neglect	5.4 (0.8)	5.2 (0.4)	t=3.042	0.003*

*significance at p<0.05. K-ARS: Korean ADHD rating scale, K-CDI: Korean children's depressive inventory, K-CTQ: Korean childhood trauma questionnaire, K-P-GBI-10M: Korean version of parent-general behavior inventory 100-item manic scale, K-RCMAS: Korean version of revised children's manifest anxiety scale

Table 3. Comparison of DSM-5 primary diagnosis and comorbidity between offspring of parents with BP-I and BP-II

	BP-I offspring (N=99) (%)	BP-II offspring (N=102) (%)	OR (95% CI)†	χ^2 or t	p value
Any psychiatric disorder	67 (67.7)	64 (62.7)	1.24 (0.70–2.22)	0.538	0.463
Affective disorder					
Depressive disorder	33 (33.3)	25 (24.5)	1.54 (0.83–2.85)	1.905	0.167
Major depressive disorder	25 (25.3)	13 (12.7)	2.31 (1.11–4.84)	5.126	0.024*
Depressive disorder, NOS	6 (8.1)	12 (11.8)	0.48 (0.17–1.34)	2.005	0.315
Dysthymia	2 (2.0)	1 (1.0)	2.08 (0.19–23.34)	9.850	0.482
Bipolar disorder	17 (16.2)	18 (17.6)	0.97 (0.47–2.01)	0.079	0.779
BP-I	11 (11.1)	3 (2.9)	4.13 (1.12–15.27)	6.900	0.027*
BP-II	5 (5.1)	13 (12.7)	0.36 (0.13–1.06)	3.648	0.056
BP, NOS	1 (1.0)	2 (2.0)	0.51 (0.05–5.72)	1.480	1.000
Anxiety disorder	25 (25.3)	19 (18.6)	1.48 (0.75–2.90)	1.290	0.256
Separation anxiety	5 (5.1)	7 (6.9)	0.72 (0.22–2.36)	0.294	0.588
ADHD	32 (32.3)	29 (28.4)	1.20 (0.66–2.20)	0.360	0.549
Tic disorder	1 (1.0)	4 (3.9)	0.25 (0.03–2.28)	2.460	0.369
Autism spectrum disorder	0 (0.0)	1 (1.0)		0.490	1.000
Disruptive behavioral disorder	12 (12.1)	11 (10.8)	1.14 (0.48–2.72)	0.089	0.766
Schizophrenia	1 (1.0)	1 (1.0)	1.03 (0.06–16.71)	0.990	1.000

*significance at p<0.05, †BP-II offspring were the referent group. Age, Sex and K-CTQ score of offspring were used as covariant variables in this analysis. CI: confidence interval, NOS: not otherwise specified, BP-I: bipolar I disorder, BP-II: bipolar II disorder, BP: bipolar disorder, ADHD: attention deficit hyperactive disorder, OR: odds ratio

spring of parents with BP-I had depressive disorder not otherwise specified, 2 had dysthymia, and 1 had bipolar disorder not otherwise specified. Among the 64 offspring of parents with BP-II, 25 had any depressive disorder, 18 had any bipolar disorder, 1 had dysthymia, and 2 had bipolar disorder not otherwise specified.

Regarding non-mood disorders, offspring of parents with BP-I had higher rate of anxiety disorder, attention deficit-hyperactive disorder, and disruptive behavior disorder, although these differences did not reach statistical significance (p=0.256, p=0.549, p=0.766, respectively).

Among offspring of parents with BP-I, 37 of the offspring with affective disorder had at least one comorbid disorder and 4 of them had two comorbid disorders. Among offspring of parents with BP-II, 27 of the offspring with affective disorder had at least one comorbid disorder and 6 of them had two comorbid disorders.

Differences in DSM-5 Primary and Comorbid diagnoses between schoolchildren and adolescents

In the analysis by age group (Table 4), schoolchildren aged 6 to 11 years had 4.35-fold increased risk of developing separation anxiety disorder (95% CI: 1.32–14.37, p=0.010). There were no significant differences in prevalence of psychiatric disorder except separation anxiety disorder between schoolchildren and adolescents. Table 4 details these findings and their statistical values.

Differences in DSM-5 Primary and Comorbid diagnoses between Offspring of parents with BP-I and those with BP-II in different age groups

As shown in Table 5, there was no significant difference in prevalence of psychiatric disorder between offspring of parents with BP-I and those with BP-II in schoolchildren group. However, there were significant differences in prevalence of MDD, BP-I, and BP-II between offspring of parents with BP-I and those with BP-II in the adolescent group. Offspring of parents with BP-I had 2.63-fold increased risk of developing MDD (95% CI: 1.17–5.90, p=0.017) and 4.29-fold increased risk of developing BP-I (95% CI: 1.11–16.54, p=0.033) than offspring of parents with BP-II while offspring of parents with BP-II had significantly higher frequencies of BP-II than offspring of parents with BP-I (p=0.043). Table 5 details these findings and their statistical values.

DISCUSSION

This study aims to examine the presence of psychopathology for offspring of parents with BP-I and those with BP-II. To our knowledge, this is the first study to compare psychiatric prevalence and clinical features in the offspring of parents with BP-I and those with BP-II and assess their potential as-

Table 4. Comparison of DSM-5 primary diagnosis and comorbidity between different age groups of offspring

	Schoolchildren (N=53) (%)	Adolescents (N=148) (%)	OR†	χ^2 or t	p value
Any psychiatric disorder	30 (56.6)	101 (68.2)	0.61 (0.32–1.16)	2.329	0.127
Affective disorder					
Depressive disorder	11 (20.8)	47 (31.8)	0.56 (0.27–1.19)	2.301	0.129
Major depressive disorder	6 (11.3)	32 (21.6)	0.46 (0.18–1.18)	2.701	0.100
Depressive disorder, NOS	5 (9.4)	13 (8.8)	1.08 (0.37–3.19)	0.020	0.887
Dysthymia	0 (0.0)	3 (2.0)	-	0.790	0.568
Bipolar disorder	10 (18.9)	25 (16.9)	1.14 (0.51–2.58)	0.106	0.745
BP-I	2 (3.8)	12 (8.1)	0.44 (0.10–2.06)	3.690	0.363
BP-II	8 (15.1)	10 (6.8)	2.45 (0.91–6.59)	3.327	0.068
BP, NOS	0 (0.0)	3 (2.0)	-	0.790	0.568
Anxiety disorder	13 (24.5)	31 (20.9)	1.23 (0.59–2.57)	0.293	0.588
Separation anxiety	7 (13.2)	5 (3.4)	4.35 (1.32–14.37)	6.716	0.010*
ADHD	12 (22.6)	49 (33.1)	0.59 (0.29–1.23)	2.022	0.155
Tic disorder	1 (1.9)	4 (2.7)	0.69 (0.08–6.34)	1.320	1.000
Autism spectrum disorder	0 (0.0)	1 (0.7)	-	0.260	1.000
Disruptive behavioral disorder	7 (13.2)	16 (10.8)	1.26 (0.49–3.24)	0.221	0.638
Schizophrenia	0 (0.0)	2 (1.4)	-	0.530	0.395

Schoolchildren: aged 6 to 11 years, Adolescents: aged 12 to 17 years. *significance at p<0.05. †Adolescents were the referent group. Sex and K-CTQ score of offspring were used as covariant variables in this analysis.
NOS: not otherwise specified, BP-I: bipolar I disorder, BP-II: bipolar II disorder, BP: bipolar disorder, ADHD: attention deficit hyperactive disorder, OR: odds ratio

Table 5. Comparison of DSM-5 primary diagnosis and comorbidity between offspring of parents with BP-I and BP-II in different age group

	Adolescents				Schoolchildren			
	BP-I offspring (N=65) (%)	BP-II offspring (N=83) (%)	OR (95% CI)†	p	BP-I offspring (N=34) (%)	BP-II offspring (N=19) (%)	OR (95% CI)†	p
Any psychiatric disorder	46 (70.8)	55 (66.3)	1.23 (0.61–2.49)	0.559	21 (61.8)	9 (47.4)	1.80 (0.58–5.59)	0.310
Affective disorder								
Depressive disorder	25 (38.5)	22 (26.5)	1.73 (0.86–3.48)	0.121	8 (23.5)	3 (15.8)	1.64 (0.38–7.11)	0.726
Major depressive disorder	20 (30.8)	12 (14.5)	2.63 (1.17–5.90)	0.017*	5 (14.7)	1 (5.3)	3.10 (0.34–28.75)	0.402
Depressive disorder, NOS	3 (4.6)	10 (12.0)	0.35 (0.09–1.34)	0.148	3 (8.8)	2 (10.5)	0.82 (0.13–5.42)	1.000
Dysthymia	2 (3.1)	1 (1.2)	2.60 (0.23–29.36)	0.582	0 (0.0)	0 (0.0)	-	-
Bipolar disorder	11 (16.9)	14 (16.9)	1.00 (0.42–2.39)	0.993	6 (17.6)	4 (21.1)	0.80 (0.20–3.30)	1.000
BP-I	9 (13.8)	3 (3.6)	4.29 (1.11–16.54)	0.033*	2 (5.9)	0 (0.0)		0.531
BP-II	1 (1.5)	9 (10.8)	0.13 (0.02–1.04)	0.043*	4 (11.8)	4 (21.1)	0.50 (0.11–2.28)	0.365
BP, NOS	1 (1.5)	2 (2.4)	0.63 (0.06–7.14)	1.000	0 (0.0)	0 (0.0)	-	-
Anxiety disorder	18 (27.7)	13 (15.7)	2.06 (0.92–4.61)	0.074	7 (20.6)	6 (31.6)	0.56 (0.16–2.01)	0.372
Separation anxiety	2 (3.1)	3 (3.6)	0.85 (0.14–5.22)	1.000	3 (8.8)	4 (21.1)	0.36 (0.07–1.83)	0.234
ADHD	23 (35.4)	26 (31.3)	1.20 (0.60–2.39)	0.603	9 (26.5)	3 (15.8)	1.92 (0.45–8.18)	0.502
Tic disorder	0 (0.0)	4 (4.8)	-	0.131	1 (2.9)	0 (0.0)	-	1.000
Autism spectrum disorder	0 (0.0)	1 (1.2)	-	1.000	0 (0.0)	0 (0.0)	-	-
Disruptive behavioral disorder	6 (9.2)	10 (12.0)	0.74 (0.26–2.16)	0.584	6 (17.6)	1 (5.3)	3.86 (0.43–34.75)	0.400
Schizophrenia	1 (1.5)	1 (1.2)	1.28 (0.08–20.88)	1.000	0 (0.0)	0 (0.0)	-	-

*significance at $p<0.05$, †BP-II offspring were the referent group. Sex and K-CTQ score of offspring were used as covariant variables in this analysis. CI: confidence interval, NOS: not otherwise specified, BP-I: bipolar I disorder, BP-II: bipolar II disorder, BP: bipolar disorder, ADHD: attention deficit hyperactive disorder, OR: odds ratio

sociation with psychopathology risk and adjustment in both groups. We found that offspring of parents with BP-I and those with BP-II showed different psychopathology and clinical manifestation.

Among these offspring, 67.7% offspring of parents with BP-I and 62.7% offspring of parents with BP-II received at least one psychiatric diagnosis, similar to rates reported in prior bipolar offspring studies.[33,34] One of these prevalence studies has demonstrated high rates (71%) of psychiatric disorders in children and adolescent aged 6 to 17 years with at least one parent diagnosed with BP-I.[33] Another study has also reported that 71.4% offspring of bipolar parents (type I and II combined) have at least one psychiatric disorder.[34] Results of this study are slightly higher than the rate (52%) found in a meta-analysis.[13] Because of methodological differences in dividing subtypes of BP in this study, we had difficulties comparing our results with previous studies.

This study showed that offspring of parents with BP-I had higher score of overall K-CTQ and sub-scores of emotional abuse, emotional neglect, and physical neglect than offspring of parents with BP-II. This result means that offspring of parents with BP-I might have experienced more stressful events than offspring of parents with BP-II. Previous studies have suggested that childhood trauma such as abuse and neglect is associated with increased risk of developing offspring's psychiatric disorder.[35,36] Bipolar offspring often have exposure to significant environmental stressors. For example, those who have a parent with BP may be prone to mood episodes, substance abuse, and hospitalizations.[37,38] Parents' dysfunctional behaviors can lead to child neglect or maltreatment.[39] Because the severity of psychiatric symptom is correlated with impairment, offspring of parents with BP-I might be more exposed to environmental stressors than offspring of parents with BP-II.[3] Further studies are needed to confirm these results.

Results from the present study suggest that the offspring of parents with BP-I compared to offspring of parents with BP-II have significantly higher prevalence of BP-I (11.1% vs. 2.9%) and MDD (25.3% vs. 12.7%). These results were comparable to those of previous studies.[8,40] We found that the offspring of parents with BP-I were themselves at significantly higher risk for BP-I, with a morbidity risk of 13.8% by age 17. These findings are similar to those of other studies (20.7%), supporting the hypothesis that relatives of probands BP-I have increased risk of suffering BP-I.[41] In early controlled studies, the risk for BP-I was reported to be in the range of 0% to 5%.[42] This prevalence rate resembles that observed in recent, uncontrolled,

high-risk studies of children in middle childhood or early adolescence.[43,44] The present study showed that the offspring of parents with BP-I had significantly higher rates of BP-I. And offspring of parents with BP-II had significantly higher rates of BP-II in adolescents, although this difference did not reach statistical significance in entire age group. The etiology and clinical course of BP are considered to be determined by genetic and environmental factors.[45] Although there are many similarities between BP-I and BP-II in symptom profiles, this study supports that these two subtypes might have different genetic transmission. Further study is needed to test this possibility.

The prevalence of depressive disorder in this study that compared between offspring of parents with BP-I and those with BP-II was similar to previous reports of high-risk studies.[13,42] In contrast, rate of depression was higher in adolescents 12 to 17 years old than that in children under 12 years. Moreover, previous longitudinal high-risk studies have demonstrated that the first manic episode is generally preceded by depressive symptoms.[20] These results suggest that some subjects in this study who presented with MDD might meet the criteria for BP in the future.

In the present study, offspring of parents with BP-II compared to offspring of parents with BP-I had higher rate of prevalence in BP-II (12.7%). This finding is similar to those of other studies on familial transmission of BP.[8,10] One of these studies has reported that familial transmission within each subtype is stronger than cross-subtype for each first-degree relative.[10] Interestingly, in our adolescent group, offspring of parents with BP-I had higher rate of prevalence of BP-I (13.8%) than offspring of parents with BP-II (3.6%). Offspring of parents with BP-II also had higher rate of prevalence in BP-II (10.8%) than offspring of parents with BP-I (1.5%) in the adolescent group whereas there is no significant difference in prevalence of BP-II between overall offspring groups. Regarding later onset age of BP-II, this result may be plausible. Additionally, this result supports previous studies suggesting that BP-I may be etiologically distinct from BP-II by a genetic liability, although it remains controversial.[10,11,46] Previous epidemiologic studies that could provide more detailed information on BP subtypes in relatives have suggested some degree of distinction between BP-I and BP-II, with relatives of BP-II probands more likely to suffer from the same BP subtype than developing BP-I.[8,9,12] However, previous studies targeted relatives of patients with BP, not their offspring. They focused on clinical manifestation of bipolar subtypes, not the prevalence.[12] This study was of academic and clinical value considering the offspring as study subject.

Regarding the distinctive nature of bipolar subtypes, several previous studies have suggested that BP-II can be phenomenologically and biologically distinguished from BP-I. In view of phenomenology, one prior report has commented that BP-I shows more extensive manic symptom whereas BP-II has more serious and complicated natures in terms of clinical course, symptomatology of episodes, and comorbidity of psychiatric disorders.[12] Moreover, in a previous genome-wide association study on 6,447 BP cases, there are significant differences in SNP heritability and genetic correlation estimations between BP-I and BP-II.[11] Previous imaging study has investigated structural brain abnormalities in BP-II and reported that BP-II compared to BP-I has different pattern of gray matter abnormalities in the frontal, temporal, and parietal regions.[47] The present study was the first evaluation of the pathology of offspring separated by bipolar subtypes. Further replicated study is needed to confirm the above suggestions.

Meanwhile, in this study, ADHD, anxiety, and disruptive behavior disorders were similar to other studies that reported high prevalence of psychopathology in high-risk group.[41,44,48] ADHD and anxiety disorders are also highly comorbid with mood disorders in offspring of bipolar parents in previous studies,[44,49] in line with results of the present study. These findings support that comorbidity with ADHD in offspring of parents with BP may be a marker of increased vulnerability to BP.[50] Interestingly, overall K-ARS score was significantly higher in offspring of parents with BP-I than that in offspring of parents with BP-II in this study. Because offspring of parents with BP-I are younger than those with BP-II, it may have affected K-ARS score. Although we couldn't exclude the influence of offspring's age in K-ARS score, we did not find any association between offspring's age and K-ARS score in comparison of schoolchildren and adolescent. This result is consistent with a previous study reporting that patients with lifetime ADHD are more likely to be diagnosed as BP-I (82.8%), but less likely to be diagnosed as BP-II (13.8%).[51] Because ADHD and mania share diagnostic criteria, ADHD have a risk of over-diagnosis. However, several studies have shown that most children with combined condition continued to meet criteria of both mania and ADHD after removing overlapping symptoms.[52,53] These results indicate that comorbidity with ADHD and BP is not a methodological artifact due to diagnostic criteria shared by two disorders.

The analysis of psychiatric disorders by age group–schoolchildren (6–11 years) and adolescents (12–17 years)–showed statistically significant difference in separation anxiety disorder (SAD) in schoolchildren. This result reflects higher prevalence of SAD in schoolchildren age.[54] The present study showed that the offspring of parents with BP-I had significantly higher rates of BP-I and offspring of parents with BP-II had significantly higher rates of BP-II in adolescents. But these results were not found in schoolchildren. It might be

because schoolchildren have not reached the age of the highest risk to develop BP and MDD.

This study has some limitations. First, our study was limited by a cross-sectional approach to define the presence of symptoms and diagnoses. Thus, studies with longitudinal outcome analyses are needed in the future. Second, despite the adequate overall sample size, some subgroups with low prevalence had relatively low numbers of individuals, limiting interpretation of such findings. Moreover, the composition of our sample had important potential biases, limiting the generalizability of our findings in relatively affluent, referred for treatment in university hospital. Information related to the course of illness and previous treatment was elicited retrospectively. Recall bias is also possible. Especially, age difference between BP-I and BP-II family may have affected recall bias. Furthermore, as noted in the methods section, parent's clinical variables such as number of episodes, number of hospitalizations and age of onset were not assessed. Additionally, the parental age was not considered as a covariate in the analysis. Finally, because most children have not reached the age of the highest risk to develop BP, the rate of BP in these children is likely to continue to increase with further follow-up.

Despite these limitations, our study was in line with recent high-risk population studies for BP and showed some evidences for establishing bipolar offspring as a high-risk cohort. Moreover, this is the first study to evaluate differences between offspring of patients with BP-I and those with BP-II. It has clinical implications as an initial attempt to evaluate the distinction of bipolar subtypes. It also provides implications for future research.

In conclusion, data from our study suggest that BP-II may not simply represent a milder form of BP-I. Our findings indicate that additional research related to offspring of parents with BP is needed to enhance our understanding of multiple dimensional differences between BP-I and BP-II. Our findings also underscore the importance of considering the developmental level of offspring in high-risk studies when examining the risk for psychopathology.

Acknowledgments

This work was supported by Soonchunhyang University.

REFERENCES

1. Judd LL, Akiskal HS. The prevalence and disability of bipolar spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. J Affect Disord 2003;73:123-131.
2. Pradhan S, Sinha V, Singh T. Psycho-social dysfunctions in patients after recovery from mania and depression. Int J Rehab Res 1999;22:303-309.
3. Judd LL, Akiskal HS, Schettler PJ, Endicott J, Leon AC, Solomon DA, et al. Psychosocial disability in the course of bipolar I and II disorders: a prospective, comparative, longitudinal study. Arch Gen Psychiatry 2005;62:1322-1330.
4. Xu G, Lin K, Rao D, Dang Y, Ouyang H, Guo Y, et al. Neuropsychological performance in bipolar I, bipolar II and unipolar depression patients: a longitudinal, naturalistic study. J Affect Disord 2012;136:328-339.
5. Dell'Osso B, Holtzman JN, Goffin KC, Portillo N, Hooshmand F, Miller S, et al. American tertiary clinic-referred bipolar II disorder compared to bipolar I disorder: more severe in multiple ways, but less severe in a few other ways. J Affect Disord 2015;188:257-262.
6. Fletcher K, Parker G, Barrett M, Synnott H, McCraw S. Temperament and personality in bipolar II disorder. J Affect Disord 2012;136:304-309.
7. Parker G, Fletcher K. Differentiating bipolar I and II disorders and the likely contribution of DSM-5 classification to their cleavage. J Affect Disord 2014;152-154:57-64.
8. Heun R, Maier W. The distinction of bipolar II disorder from bipolar I and recurrent unipolar depression: results of a controlled family study. Acta Psychiatr Scand 1993;87:279-284.
9. Andreasen NC, Rice J, Endicott J, Coryell W, Grove W, Reich T. Familial rates of affective disorder. Arch Gen Psychiatry 1987;44:461-469.
10. Song J, Kuja-Halkola R, Sjölander A, Bergen SE, Larsson H, Landén M, et al. Specificity in etiology of subtypes of bipolar disorder: Evidence from a Swedish population-based family study. Biol Psychiatry 2017 [Epub ahead of print].
11. Charney A, Ruderfer D, Stahl E, Moran J, Chambert K, Belliveau R, et al. Evidence for genetic heterogeneity between clinical subtypes of bipolar disorder. Transl Psychiatry 2017;7:e993.
12. Baek JH, Park DY, Choi JM, Kim JS, Choi JS, Ha KS, et al. Differences between bipolar I and bipolar II disorders in clinical features, comorbidity, and family history. J Affect Disord 2011;131:59-67.
13. Lapalme M, Hodgins S, LaRoche C. Children of parents with bipolar disorder: a metaanalysis of risk for mental disorders. Can J Psychiatry 1997;42:623-631.
14. Diler RS, Birmaher B, Axelson D, Obreja M, Monk K, Hickey MB, et al. Dimensional psychopathology in offspring of parents with bipolar disorder. Bipolar Disord 2011;13:670-678.
15. Faraone SV, Glatt SJ, Tsuang MT. The genetics of pediatric-onset bipolar disorder. Biol Psychiatry 2003;53:970-977.
16. Pavuluri MN, Birmaher B, Naylor MW. Pediatric bipolar disorder: a review of the past 10 years. J Am Acad Child Adolesc Psychiatry 2005;44:846-871.
17. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). Washington DC: American Psychiatric Association; 2013.
18. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. 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;36:980-988.
19. Kim YS, Cheon KA, Kim BN, Chang SA, Yoo HJ, Kim JW, et al. The reliability and validity of kiddie-schedule for affective disorders and schizophrenia-present and lifetime version-Korean version (K-SADS-PL-K). Yonsei Med J 2004;45:81-89.
20. Mesman E, Nolen WA, Reichart CG, Wals M, Hillegers MH. The Dutch bipolar offspring study: 12-year follow-up. Am J Psychiatry 2013;170:542-549.
21. Wagner KD, Hirschfeld R, Emslie GJ, Findling RL, Gracious BL, Reed ML. Validation of the Mood Disorder Questionnaire for bipolar disorders in adolescents. J Clin Psychiatry 2006;67:827-830.
22. Shim SH, Lee JH, Song JH, Nam BW, Yoon BH, Jin HY, et al. Screening with the Korean version of the mood disorder questionnaire for bipolar disorders in adolescents: Korean validity and reliability study. Clin Psychopharmacol Neurosci 2018;16:316-323.
23. Youngstrom EA, Frazier TW, Demeter C, Calabrese JR, Findling RL. Developing a 10-item mania scale from the Parent General Behavior Inventory for children and adolescents. J Clin Psychiatry 2008;69:831-839.
24. Lee HJ, Joo YH, Youngstrom EA, Yum SY, Findling RL, Kim HW. Di-

agnostic validity and reliability of a Korean version of the Parent and Adolescent General Behavior Inventories. Compr Psychiatry 2014;55:1730-1737.
25. DuPaul GJ. Parent and teacher ratings of ADHD symptoms: psychometric properties in a community-based sample. J Clin Child Adolesc Psychol 1991;20:245-253.
26. So YK, Noh JS, Kim YS, Ko SG, Koh YJ. The reliability and validity of Korean parent and teacher ADHD rating scale. J Korean Neuropsychiatr Assoc 2002;41:283-289.
27. Reynolds CR, Richmond BO. Revised Children's Manifest Anxiety Scale. Los Angeles: Western Psychological Services; 1985.
28. Cho SC, Choi JS. Development of the Korean form of the state-trait anxiety inventory for children. Seoul J Psychiatry 1989;14:150-157.
29. Kovacs M. The Children's Depression Inventory: A Self-Rated Depression Scale for School-Aged Youngsters. Pittsburgh: University of Pittsburgh School of Medicine, Department of Psychiatry, Western Psychiatric Institute and Clinic; 1983.
30. Cho SC, Lee YS. Development of the Korean form of the Kovacs' Children's Depression Inventory. J Korean Neuropsychiatr Assoc 1990;29:943-956.
31. Bernstein DP, Fink L. Childhood Trauma Questionnaire: A Retrospective Self-Report: Manual. San Antonio, TX: Psychological Corporation; 1998.
32. Yu JH, Park JS, Park DH, Ryu SH, Ha JH. Validation of the Korean Childhood Trauma Questionnaire: the practical use in counselling and therapeutic intervention. Korean J Health Psychol 2009;14:563-578.
33. Zappitelli MC, Bordin IA, Hatch JP, Caetano SC, Zunta-Soares G, Olvera RL, et al. Lifetime psychopathology among the offspring of Bipolar I parents. Clinics 2011;66:725-730.
34. 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 Disord 2007;9:828-838.
35. Dervic K, Garcia-Amador M, Sudol K, Freed P, Brent D, Mann J, et al. Bipolar I and II versus unipolar depression: clinical differences and impulsivity/aggression traits. Eur Psychiatry 2015;30:106-113.
36. Molnar BE, Buka SL, Kessler RC. Child sexual abuse and subsequent psychopathology: results from the National Comorbidity Survey. Am J Pub Health 2001;91:753-760.
37. Chang K, Steiner H, Dienes K, Adleman N, Ketter T. Bipolar offspring: a window into bipolar disorder evolution. Biol Psychiatry 2003;53:945-951.
38. Chang KD, Blasey C, Ketter TA, Steiner H. Family environment of children and adolescents with bipolar parents. Bipolar Disord 2001;3:73-78.
39. Sidebotham P, Golding J, Team AS. Child maltreatment in the "Children of the Nineties": A longitudinal study of parental risk factors. Child Abuse Negl 2001;25:1177-1200.
40. Egeland JA, Endicott J, Hostetter AM, Allen CR, Pauls DL, Shaw JA. A 16-year prospective study of prodromal features prior to BPI onset in well Amish children. J Affect Disord 2012;142:186-192.
41. Henin A, Biederman J, Mick E, Sachs GS, Hirshfeld-Becker DR, Siegel RS, et al. Psychopathology in the offspring of parents with bipolar disorder: a controlled study. Biol Psychiatry 2005;58:554-561.
42. Hammen C, Burge D, Hamilton EB, Adrian C. Longitudinal study of diagnoses in children of women with unipolar and bipolar affective disorder. Arch Gen Psychiatry 1990;47:1112-1117.
43. Duffy A, Alda M, Kutcher S, Cavazzoni P, Robertson C, Grof E, et al. A prospective study of the offspring of bipolar parents responsive and nonresponsive to lithium treatment. J Clin Psychiatry 2002;63:1171-1178.
44. Chang KD, Steiner H, Ketter TA. Psychiatric phenomenology of child and adolescent bipolar offspring. J Am Acad Child Adolesc Psychiatry 2000;39:453-460.
45. Aldinger F, Schulze TG. Environmental factors, life events, and trauma in the course of bipolar disorder. Psychiatry Clin Neurosci 2017;71:6-17.
46. Merikangas K, Cui L, Heaton L, Nakamura E, Roca C, Ding J, et al. Independence of familial transmission of mania and depression: results of the NIMH family study of affective spectrum disorders. Mol Psychiatry 2014;19:214-219.
47. Ha TH, Ha K, Kim JH, Choi JE. Regional brain gray matter abnormalities in patients with bipolar II disorder: A comparison study with bipolar I patients and healthy controls. Neurosci Lett 2009;456:44-48.
48. Carlson GA, Weintraub S. Childhood behavior problems and bipolar disorder-relationship or coincidence? J Affect Disord 1993;28:143-153.
49. Geller B, Zimerman B, Williams M, Bolhofner K, Craney JL, DelBello MP, et al. Diagnostic characteristics of 93 cases of a prepubertal and early adolescent bipolar disorder phenotype by gender, puberty and comorbid attention deficit hyperactivity disorder. J Child Adolesc Psychopharmacol 2000;10:157-164.
50. Chang K, Steiner H, Ketter T. Studies of offspring of parents with bipolar disorder. Am J Med Genet C Semin Med Genet 2003 15;123C:26-35.
51. Nierenberg AA, Miyahara S, Spencer T, Wisniewski SR, Otto MW, Simon N, et al. Clinical and diagnostic implications of lifetime attention-deficit/hyperactivity disorder comorbidity in adults with bipolar disorder: data from the first 1000 STEP-BD participants. Biol Psychiatry 2005;57:1467-1473.
52. Biederman J, Faraone S, Mick E, Wozniak J, Chen L, Ouellette C, et al. Attention-deficit hyperactivity disorder and juvenile mania: an overlooked comorbidity? J Am Acad Child Adolesc Psychiatry 1996;35:997-1008.
53. Milberger S, Biederman J, Faraone SV, Murphy J, Tsuang MT. Attention deficit hyperactivity disorder and comorbid disorder: Issues of overlapping symptoms. Am J Psychiatry 1995;152:1793-1799.
54. Abbo C, Kinyanda E, Kizza RB, Levin J, Ndyanabangi S, Stein DJ. Prevalence, comorbidity and predictors of anxiety disorders in children and adolescents in rural north-eastern Uganda. Child Adolesc Psychiatry Ment Health 2013;7:21.