Risks of Coaggregation of Major Psychiatric Disorders Among First-Degree Relatives of Patients With Bipolar I and Bipolar II Disorder:

Evidence From a Nationwide Population-Based Study

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ABSTRACT

Background: Etiologic differences between bipolar I disorder (BD-I) and bipolar II disorder (BD-II) have been challenged recently, and family epidemiologic studies may elucidate the matter. Nevertheless, it remains unclear whether BD-I and BD-II display different familial aggregation patterns within each bipolar disorder subtype and coaggregation with other psychiatric disorders.

Method: Per the Taiwan National Health Insurance Research Database (N = 23,258,175), patients with bipolar disorder were classified as having BD-I or BD-II based on the history of psychiatric hospitalization for a manic episode. During the study period (2001–2011), 184,958 first-degree relatives (FDRs) of patients with BD-I and BD-II were identified. By comparing patients with 1:4 age-, sex-, and kinship-matched samples without BD-I/BD-II probands, the relative risks (RRs) of major psychiatric disorders were estimated.

Results: FDRs of BD-I probands had a significantly higher risk of BD-I than those of BD-II probands (BD-I proband: RR = 15.80 vs BD-II proband: RR = 5.68, $P < .001$). The risk of BD-II was similar between FDRs of BD-I and BD-II probands (BD-I proband: RR = 6.48 vs BD-II proband: RR = 5.89, $P = .1161$). Familial aggregation was greater within each BD subtype than among cross-subtypes. Furthermore, FDRs of BD-I probands had an increased risk of schizophrenia (BD-I probands: RR = 5.83 vs BD-II probands: RR = 2.72, $P < .001$); FDRs of BD-II probands had a higher likelihood of attention-deficit/hyperactivity disorder (BD-II probands: 2.36 vs BD-I probands: 1.93, $P = .0009$).

Conclusions: The risk of psychiatric disorders is higher among the FDRs of patients with either BD-I or BD-II. Furthermore, the familial specificity of BD-I and BD-II assessed in this study may further the current understanding of etiologic boundaries between bipolar disorder subtypes.

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Bipolar I disorder (BD-I) and bipolar II disorder (BD-II) are severe, chronic, and relapsing-remitting mental disorders.[1–3] Relative to BD-I, BD-II is characterized by patients' having only hypomanic episodes rather than full manic episodes. BD-II is characterized by frequent recurrences of depressive, hypomanic, and cycling/mixed episodes, potentially causing a comparable degree of psychosocial disability as that of BD-I.[1–3] The recognition of BD-II in the formal diagnostic system is considered a major development in the classification of mental disorders, enhancing medical awareness and promoting the development of different treatment strategies from those for BD-I.[4,5]

High transmission and coaggregation of bipolar disorder within a family have been well documented in previous family and registry studies.[6–8] Family studies have suggested the transmission of BD-I and BD-II among first-degree relatives (FDRs),[9–12] but this finding has been partially challenged by several recent family studies.[13,14] Gershon et al[12] reported that the relatives of BD-I probands had similar risks of BD-I and BD-II, and the risk of BD-II among relatives of BD-I and BD-II probands displayed no significant difference. Coryell et al[11] reported that a higher proportion of relatives of BD-II probands were diagnosed with BD-II than with BD-I; however, relatives of patients with BD-I displayed no differences in the proportions having BD-I or BD-II diagnoses. By contrast, a Swedish registry study[15] reported that the risk of BD-I was significantly higher among relatives of BD-I rather than BD-II probands but further identified no significant difference in the BD-II risk between the relatives of BD-I and BD-II probands. Furthermore, Merikangas et al[13] and Vandeleur et al[14] reported no familial aggregation for BD-II. These studies may have had some methodological deficiencies that limit their generalizability, such as small selected samples, limited kinship (ie, only

Clinical Points

- First-degree relatives (FDRs) of bipolar I disorder (BD-I) probands had a higher risk of BD-I than those of bipolar II disorder (BD-II) probands.
- The risk of BD-II remained unchanged between the FDRs of BD-I and BD-II probands.
- The FDRs of BD-I probands had a higher risk of schizophrenia, and those of BD-II probands had a higher risk of attention-deficit/hyperactivity disorder.

siblings or offspring), inclusion of only Caucasians, and biases from identification and recall.

Epidemiologic and genome-wide association studies (GWASs) have evaluated the cross-transmission of BD to other psychiatric disorders.[6,16–19] Song et al[6] and Chen et al[16] reported the familial coaggregation of bipolar disorder with other major psychiatric disorders, including schizophrenia, major depressive disorder (MDD), autism spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD) among Caucasians and Asians. However, studies comparing the differences in familial coaggregation with other psychiatric disorders, especially beyond schizophrenia and bipolar disorder, between the FDRs of patients with BD-I and BD-II are lacking.[12,15] Etiologic differences between BD-I and BD-II have been challenged in the last few years because of the lack of specific biological underpinnings.[20,21] Hence, family epidemiologic studies may reveal the boundaries between BD-I and BD-II.

In this study, we used the Taiwan National Health Insurance Research Database (NHIRD) with the entire nationwide population to compare the risks of schizophrenia, BD-I, BD-II, MDD, ASD, ADHD, anxiety disorder, and obsessive-compulsive disorder (OCD) among FDRs of patients with BD-I and BD-II, including parents, offspring, siblings, and twins. We hypothesized that FDRs of BD-I and BD-II probands are at a higher risk of the aforementioned psychiatric disorders and that the risks of familial coaggregation of specific psychiatric disorders differ between the two bipolar disorder subtypes.

METHODS

Data Source

Taiwan's National Health Insurance (NHI) is a compulsory universal single-payer health insurance program established in 1995. It provides comprehensive medical care coverage to almost the entire nationwide population (approximately 23 million individuals). The coverage rate of NHI was approximately 99.6% at the end of 2010. The National Health Research Institute (NHRI) audits and releases its database (NHIRD) for research purposes. Comprehensive data on the insured subjects in the NHIRD include details regarding demographics (birth date, sex, residential location, income status, and family relationship) and medical claims data (inpatient and outpatient care, prescriptions, and medical diagnoses). Before releasing the data for research purposes, the NHRI assigns a unique and anonymous identifier to all individuals to protect their privacy, thus facilitating follow-up evaluation of all individuals. The *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) was applied to diagnose diseases during the study. To identify the major psychiatric disorders, we used a specialized dataset of mental disorders, including the psychiatric medical records between January 1, 2001, and December 31, 2011, for all insured subjects. Using the method of Cheng et al[22] and Kuo et al,[23] we reconstructed genealogy from the recorded family kinships in the NHIRD, as previously described.[22,23] The Taipei Veterans General Hospital Institutional Review Board reviewed and approved this study protocol. The NHIRD has been extensively used in numerous epidemiologic studies in Taiwan.[22,24–26]

Inclusion Criteria and Disease Definitions

Individuals diagnosed with bipolar disorder (*ICD-9-CM* codes 296 except 296.2, 296.3, 296.9, and 296.82) by board-certified psychiatrists at least twice between January 1, 2001, and December 31, 2011, were classified as patients with bipolar disorder. Because a specific diagnostic code of BD-II is not available in the *ICD-9-CM* code system, we defined bipolar disorder patients with the history of psychiatric hospitalization for manic episode or mixed episode (*ICD-9-CM* codes: 296.0, 296.1, 296.4 296.6, 296.81) as the BD-I subgroup.[15] The others were assigned as the BD-II subgroup. Hierarchical diagnosis was applied for BD subtypes, according to which patients with BD-II could not be diagnosed with BD-I at any time during the entire study period. All psychiatric disorders were diagnosed at least twice by board-certified psychiatrists based on their clinical judgment and comprehensive diagnostic interviews.

Definition of the Control Group and Evaluation of Covariates

A 1:4 case-control matched cohort was used to decrease the confounding effects of age, sex, and types of familial relations, in accordance with our previous study.[22] For example, a 35-year-old woman with a BD-I father would be matched with four 35-year-old women without BD-I fathers. If this woman had two types of familial relationships, such as mother-daughter and brother-sister relationships, she would be considered under each of these relationships and matched twice. The patient demographics of age, sex, income status, and area of residence in 2010 are summarized in Table 1, and all characteristics were adjusted in our study. The area of residence was classified into 5 categories based on urbanization levels.

Definition of Outcomes

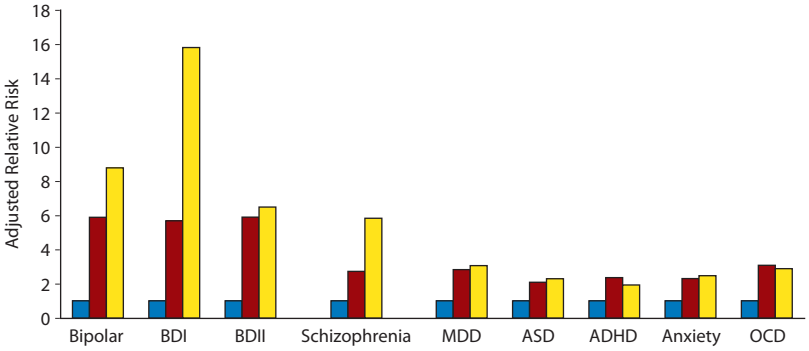
Both FDRs (parents, offspring, and siblings) of BD-I and BD-II probands and controls were evaluated to determine their risk of major psychiatric disorders. Those diagnosed with schizophrenia (*ICD-9-CM* code 295), BD-I, BD-II, MDD (*ICD-9-CM* codes 296.2 and 296.3), ASD (*ICD-9-CM* code 299), ADHD (*ICD-9-CM* code 314), OCD (*ICD-9-CM*

Table 1. Characteristics of FDRs of BD-I/BD-II Patients and Their Matched Cohort[a]

	BD-I Cohort			BD-II Cohort		
Characteristic	FDRs of BD-I Patients (n = 45,185)	Matched BD-I Control Cohort (n = 180,740)	*P* Value	FDRs of BD-II Patients (n = 139,773)	Matched BD-II Control Cohort (n = 559,092)	*P* Value
Age, mean (SD), y	35.62 (18.70)	35.62 (18.70)		34.30 (18.63)	34.30 (18.63)	
Male	22,355 (49.47)	89,420 (49.47)		69,657 (49.84)	278,628 (49.84)	
Monthly income, US $			**<.001**			**<.001**
0–500	32,627 (72.20)	128,112 (70.88)	**<.001**	101,637 (72.72)	398,588 (71.29)	**<.001**
501–800	7,991 (17.69)	31,969 (17.69)	.9890	22,700 (16.24)	96,900 (17.33)	**<.001**
≥801	4,567 (10.11)	20,659 (11.43)	**<.001**	15,436 (11.04)	63,604 (11.38)	**.0004**
Place of residence			**<.001**			**<.001**
1 (urban)	15,381 (34.03)	64,760 (35.83)	**.0011**	51,728 (37.01)	199,538 (35.69)	**<.001**
2	14,399 (31.87)	56,878 (31.47)	.1041	44,966 (32.17)	177,093 (31.68)	**.0004**
3	6,529 (14.45)	27,899 (15.44)	**<.001**	18,324 (13.11)	86,738 (15.51)	**<.001**
4	5,390 (11.93)	20,341 (11.25)	**<.001**	16,521 (11.82)	62,383 (11.16)	**<.001**
5 (rural)	3,216 (7.12)	10,241 (5.67)	**<.001**	7,782 (5.57)	31,486 (5.63)	.3525
Unknown	270 (0.60)	621 (0.34)	**<.001**	452 (0.32)	1854 (0.33)	.6314

[a]Values are shown as n (%) unless otherwise noted. Boldface indicates a statistically significant difference.
Abbreviations: BD-I = bipolar I disorder, BD-II = bipolar II disorder, FDR = first-degree relative.

Figure 1. The Comparison of Adjusted Relative Risk Between First-Degree Relatives of BD-I and BD-II Patients for Each Psychiatric Disorder



	Bipolar	BDI	BDII	Schizophrenia	MDD	ASD	ADHD	Anxiety	OCD
Matched Controls	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
FDR of BD-II	5.88	5.68	5.89	2.72	2.83	2.09	2.36	2.30	3.08
FDR of BD-I	8.77	15.80	6.48	5.83	3.06	2.29	1.93	2.47	2.88
P for BD-I vs BD-II	< .001	< .001	.1161	< .001	.0212	.4741	.0009	.0017	.4826

Abbreviations: ASD = autism spectrum disorder, ADHD = attention-deficit/hyperactivity disorder, BD-I = bipolar I disorder, BD-II = bipolar II disorder, FDR = first-degree relative, MDD = major depressive disorder, OCD = obsessive-compulsive disorder.

code: 300.3), and anxiety disorder (*ICD-9-CM* code 300.0 except 300.3 and 300.4) by board-certified psychiatrists at least twice were considered to constitute prevalence cases.

Statistical Analysis

Independent *t* tests and Pearson χ^2 tests were used to evaluate the demographic differences between the FDRs of BD-I/BD-II probands and matched cohorts (ie, age-, sex-, and familial kinship–matched controls without BD-I/BD-II probands) for continuous variables and categorical variables, respectively. The prevalence of major psychiatric disorders in case and matched cohorts was estimated. Risk was defined by the ratio of cases of each psychiatric disorder (numerator) to the number of FDRs with BD-I/BD-II probands or matched cohorts (denominator).

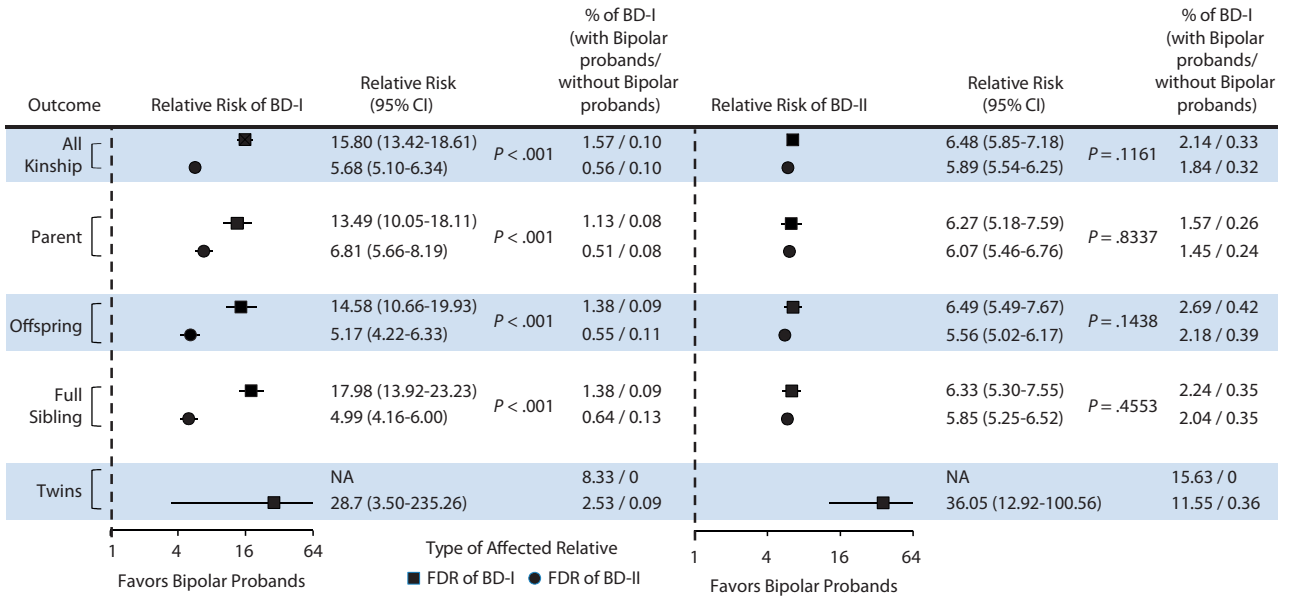
To assess familial transmission of bipolar disorder subtypes and familial coaggregation between bipolar disorder subtypes and other psychiatric disorders, adjusted relative risks (RRs) and 95% confidence intervals (CIs) were used to evaluate the risks of the major psychiatric disorders among the FDRs of BD-I and BD-II probands relative to their matched cohorts after adjustment for age, sex, urbanization, and income. To estimate the specific association between familial aggregation and cross-aggregation between bipolar disorder subtypes based on each kinship type (parents, offspring, full siblings, and twins), the adjusted RRs of bipolar disorder subtypes for each kinship type were determined. The clustering effect may have been a factor in this study owing to measurements being obtained from multiple subjects in a family, but to manage the clustering effect, modified Poisson regression analysis with robust variance estimation was used to estimate the RRs for clustered data.[27,28] Subanalyses were performed to estimate the effect of sex on the risks of the major psychiatric disorders between the FDRs of BD-I/

Table 2. Adjusted Relative Risk of Different Psychiatric Disorders Between FDRs With BD-I/BD-II Probands and Their Matched Cohort[a]

	BD-I Cohort			BD-II Cohort		
Psychiatric Disorder	FDRs of BD-I Patients (n = 45,185)	Matched BD-I Control Cohort (n = 180,740)	Adjusted RR* (95% CI)	FDRs of BD-II Patients (n = 139,773)	Matched BD-II Control Cohort (n = 559,092)	Adjusted RR* (95% CI)
Schizophrenia	1,311 (2.90)	906 (0.50)	**5.83 (5.35–6.34)**	1,916 (1.37)	2,847 (0.51)	**2.72 (2.57–2.88)**
Bipolar disorder	1,680 (3.72)	785 (0.43)	**8.77 (8.06–9.55)**	3,366 (2.41)	2,323 (0.42)	**5.88 (5.58–6.20)**
BD-I	711 (1.57)	180 (0.10)	**15.80 (13.42–18.61)**	789 (0.56)	556 (0.10)	**5.68 (5.10–6.34)**
BD-II	969 (2.14)	605 (0.33)	**6.48 (5.85–7.18)**	2,577 (1.84)	1,767 (0.32)	**5.89 (5.54–6.25)**
MDD	1,876 (4.15)	2,531 (1.40)	**3.06 (2.88–3.26)**	5,242 (3.75)	7,634 (1.37)	**2.83 (2.73–2.93)**
ASD	126 (0.28)	222 (0.12)	**2.29 (1.84–2.85)**	377 (0.27)	716 (0.13)	**2.09 (1.85–2.37)**
ADHD	535 (1.18)	1,171 (0.65)	**1.93 (1.74–2.15)**	2,243 (1.60)	3,953 (0.71)	**2.36 (2.23–2.48)**
Anxiety	4,218 (9.33)	7,306 (4.04)	**2.47 (2.37–2.57)**	12,140 (8.69)	22,351 (4.00)	**2.30 (2.25–2.35)**
OCD	229 (0.56)	348 (0.20)	**2.88 (2.44–3.40)**	760 (0.60)	1057 (0.19)	**3.08 (2.80–3.38)**

[a]Values are shown as n (%) unless otherwise noted. Boldface indicates a statistically significant difference.
*Adjusted for age, urbanization, and income level.
Abbreviations: ASD = autism spectrum disorder, ADHD = attention-deficit/hyperactivity disorder, BD-I = bipolar I disorder, BD-II = bipolar II disorder, FDR = first-degree relative, MDD = major depressive disorder, OCD = obsessive-compulsive disorder, RR = relative risk.

Figure 2. Forest Plot for the Relative Risk of Bipolar I and Bipolar II in Different Kinship Relationships Between First-Degree Relatives of Bipolar I and Bipolar II Patients



Abbreviations: BD-I = bipolar I disorder, BD-II = bipolar II disorder, FDR = first-degree relative.

BD-II probands and matched cohorts. Furthermore, to compare the risk of each psychiatric disorder, the difference in adjusted RRs between groups (ie, relatives of patients with BD-I or BD-II) or between male and female individuals was assessed.

Two additional sensitivity analyses were performed to minimize the potential confounding effects in our study, and the robustness of our findings was assessed. In Model 1, psychiatric disorders that were diagnosed by psychiatrists at least 3 times indicated improved diagnostic validity and stability. In Model 2, to eliminate the comorbid effects of BD-I/BD-II with those of other psychiatric disorders, FDRs diagnosed with BD-I/BD-II were excluded. All tests were 2-tailed, and results with $P < .05$ were considered statistically significant. Bonferroni correction with a revised threshold of P value (.05/18) was used in the multiple comparisons for our main findings to prevent inflation of type I errors. All statistical analyses were performed using SPSS Version 21.0 for Windows (IBM; Armonk, New York) and SAS Version 9.2 (SAS Institute; Cary, North Carolina).

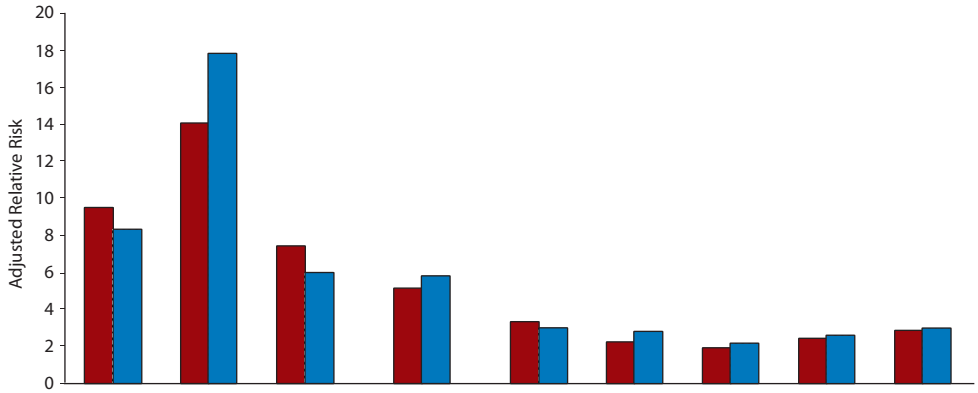
Data availability. As participants did not consent for their data to be publicly shared, even anonymized, data will be made available only to potential collaborators with ethical approval after they submit a research proposal to Bureau of the NHI (https://nhird.nhri.org.tw/).

RESULTS

A study flowchart is included in Supplementary Figure 1. In the entire Taiwanese population, 28,568 patients with

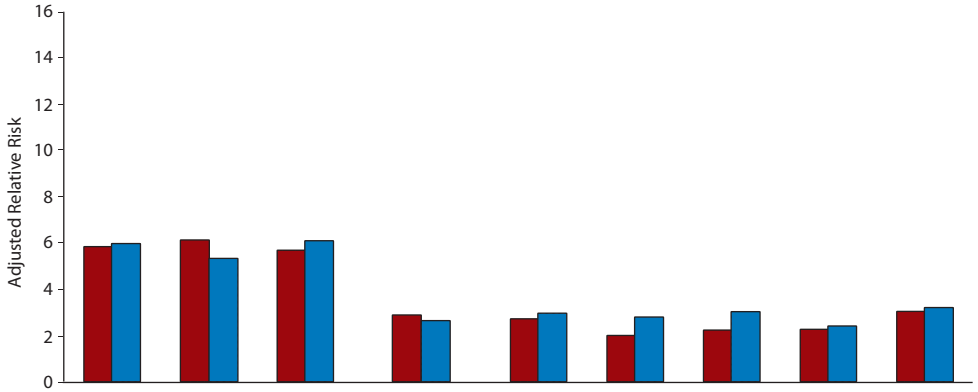
Figure 3. Comparison of Adjusted Relative Risk Between Male FDRs and Female FDRs With Each Psychiatric Disorder for the (A) Bipolar I Cohort and (B) Bipolar II Cohort

A.



	Bipolar	BD-I	BD-II	Schizophrenia	MDD	ASD	ADHD	Anxiety	OCD
Male FDR of BD-I	9.46	14.03	7.39	5.09	3.28	2.18	1.87	2.38	2.81
Female FDR of BD-I	8.28	17.81	5.94	5.76	2.95	2.75	2.12	2.55	2.94
P for male vs female	.1280	.1490	.0428	.8667	.0926	.3447	.2141	.1502	.8151

B.



	Bipolar	BD-I	BD-II	Schizophrenia	MDD	ASD	ADHD	Anxiety	OCD
Male FDR of BD-II	5.81	6.09	5.65	2.84	2.68	1.96	2.19	2.22	3.00
Female FDR of BD-II	5.94	5.30	6.06	2.60	2.92	2.75	2.99	2.37	3.16
P for male vs female	.6629	.2242	.2588	.1267	.0331	.0157	< .001	.0157	.6360

Abbreviations: ASD = autism spectrum disorder, ADHD = attention-deficit/hyperactivity disorder, BD-I = bipolar I disorder, BD-II = bipolar II disorder, FDR = first-degree relative, MDD = major depressive disorder, OCD = obsessive-compulsive disorder.

BD-I and 69,591 patients with BD-II were related to 45,185 and 139,773 FDRs, respectively (Table 1). FDRs of both BD-I and BD-II probands were more likely to have other major psychiatric disorders, including schizophrenia, BD-I, BD-II, MDD, ASD, ADHD, anxiety disorder, and OCD than were the matched cohort (Table 2). All adjusted RRs of aforementioned major psychiatric disorders in FDRs of BD-I and BD-II probands compared with the controls still indicated significance with the Bonferroni correction. Furthermore, FDRs of BD-I probands were at a considerably higher risk of BD-I than BD-II (BD-I: RR = 15.80; 95% CI, 13.42–18.61 vs BD-II: RR = 6.48; 95% CI, 5.85–7.18). Conversely, FDRs of BD-II probands were at a higher risk of BD-II than BD-I (BD-II: RR = 5.89; 95% CI, 5.54–6.25 vs BD-I: RR = 5.68; 95% CI, 5.10–6.34). For BD-I risk, FDRs of BD-I probands had a significantly (and much) higher risk of BD-I than FDRs of BD-II probands (RR = 15.80 vs 5.68, $P < .001$). For BD-II risk, no differences between the FDRs of BD-I and BD-II probands (RR = 6.48 vs 5.89, $P = .1161$) were observed, although both groups displayed significantly higher risks than the matched controls (Figure 1). Familial aggregation and cross-aggregation for BD-I and BD-II in various kinships are outlined in Figure 2 and are similar to the aforementioned results.

In comparing the familial coaggregation of bipolar disorder subtypes with that of other major psychiatric disorders, FDRs of BD-I probands were at a significantly greater risk of schizophrenia (BD-I probands: RR = 5.83,

BD-II probands: RR = 2.72; $P < .001$), MDD (BD-I: RR = 3.06, BD-II: RR = 2.83; $P = .0212$), and anxiety disorder (BD-I: RR = 2.47, BD-II: RR = 2.30; $P = .0017$) than were FDRs of BD-II probands. The risk of ASD and OCD did not differ markedly between the two groups (ASD: BD-I: RR = 2.29 vs BD-II: RR = 2.09; $P = .4741$; OCD: BD-I: RR = 2.88 vs BD-II: RR = 3.08; $P = .4826$). Compared with the FDRs of BD-I probands, those of BD-II probands were more likely to have a higher RR of ADHD (BD-II: RR = 2.36 vs BD-I: RR = 1.93; $P = .0009$; Table 2 and Figure 1). Regarding the risks of schizophrenia, BD, BD-I, ADHD, and anxiety disorder, the comparisons between FDRs of BD-I and those of BD-II probands also achieved the statistically significant difference after Bonferroni correction.

Subgroup analyses were performed to evaluate the effect of sex on familial coaggregation of major psychiatric disorders between the FDRs of patients with BD-I and BD-II (Figures 3A and 3B as well as Supplementary Tables 1 and 2). Male FDRs of BD-I probands exhibited a significantly higher risk of BD-II than did female FDRs; otherwise, both male and female FDRs displayed similar risks of other psychiatric disorders (Figure 3A). However, in the BD-II cohort, the risks of MDD, ASD, ADHD, and anxiety disorder were significantly elevated in female FDRs compared with male FDRs (Figure 3B).

Finally, sensitivity analyses, performed to evaluate the robustness of our findings, revealed that the FDRs of both BD-I and BD-II probands were at an elevated risk of BD-I and BD-II and other psychiatric disorders compared with the matched controls. Notably, in Model 1, more stringent inclusion criteria were used to define psychiatric disorders, yielding consistent findings (Supplementary Table 3). In Model 2, we excluded those FDRs diagnosed with bipolar disorder and still identified elevated risks of other psychiatric disorders in FDRs of BD-I and BD-II probands, indicating an independent effect of having probands with bipolar disorder subtypes on the increased risk of other psychiatric disorders (Supplementary Table 4).

DISCUSSION

This population-based cohort study of more than 23 million Taiwanese individuals demonstrated increased risks of schizophrenia, BD-I, BD-II, MDD, ADHD, ASD, OCD, and anxiety disorder among the FDRs of BD-I and BD-II probands. Familial aggregation of the same bipolar disorder subtypes (BD-I to BD-I, BD-II to BD-II) was stronger than the cross-coaggregation of two BD subtypes (BD-I to BD-II, BD-II to BD-I) among the FDRs. Different familial coaggregation patterns of BD-I and BD-II with other psychiatric disorders were observed, such as higher risks of schizophrenia and bipolar disorder in FDRs of BD-I probands, but higher risk of ADHD in FDRs of BD-II probands. In addition to the difference in symptom severity between BD-I and BD-II based on the current diagnostic concept, current findings may further imply the distinct etiologic boundaries between BD-I and BD-II. Our results support the findings of previous registry database studies and certain GWASs that have reported that BD-I/BD-II may have some overlapping pathomechanisms with those of other psychiatric disorders and be transmitted among family members with various diagnoses.[6,15,16,18,19]

In our results, we identified familial aggregation of BD-I and BD-II in FDRs, and, thus, our results are in accord with those of other family studies.[9–12] Familial transmission was stronger within the same BD subtype (BD-I to BD-I, BD-II to BD-II) than between different BD subtypes (BD-I to BD-II, BD-II to BD-I). In this study, the FDRs of patients with BD-II were at a higher risk of BD-II than BD-I, which was reconfirmed through sensitivity analyses, in line with the literature.[12] Furthermore, the FDRs of patients with BD-I exhibited a substantially elevated likelihood of being diagnosed with BD-I compared with BD-II, also in accord with relevant family studies.[13–15] Notably, two family studies have suggested no specificity of BD-II aggregation and cross-transmission from BD-I to BD-II in a family compared with the controls; however, GWASs have reported that the estimated genetic correlation between BD-I and BD-II was 0.78.[6,15,29] Our findings and results from the Swedish register-database study may confirm the familial aggregation of BD-II and the cross-aggregation of BD-I and BD-II, which may support the diagnostic validity of BD-II.[15,30]

Other studies, however, have found evidence of genetic heterogeneity between BD-I and BD-II.[29–31] BD-I and BD-II may have some unique genetic determinants resulting in different genetic susceptibility across various psychiatric disorders in a family. For example, a stronger genetic correlation has been reported between BD-I and schizophrenia,[29,30] concurrent with our findings of a significantly higher risk of schizophrenia among the FDRs of BD-I rather than BD-II probands. Song et al[15] reported the coaggregation of BD-I (odds ratio [OR] = 2.5; 95% CI, 2.0–3.2) but not BD-II (OR = 1.3; 95% CI, 0.9–1.9) with schizophrenia among siblings. However, FDRs of both BD-I or BD-II probands were at an increased risk of schizophrenia, concurrent with Charney et al,[29] who reported a significantly higher risk of BD-II probands' having schizophrenia risk alleles compared with controls. The risk difference of MDD between bipolar disorder subtypes was noted initially but did not survive after Bonferroni correction in our study. A recent GWAS reported a stronger correlation of MDD with BD-II than with BD-I,[30] but the results from current study and the study by Song et al[15] suggested a similar MDD risk between the FDRs of BD-I and BD-II probands. The inconsistency may be related to the different study target samples: the "patients" per se in GWASs but the "FDRs" in the register-database studies.[15]

Song et al[15] reported that siblings of patients with BD-II were at a slightly higher risk of anxiety disorder than those of patients with BD-I. However, we identified a similar risk of anxiety disorder between the FDRs of BD-I and BD-II probands, likely owing to more stringent diagnostic criteria for anxiety disorder in this study (*ICD-9-CM* codes 300 except 300.3 and 300.4) than in Song et al (300 except

300.4).[15] Notably, the OCD risk was slightly higher among FDRs of BD-II probands than those of BD-I probands, although the difference between ORs was not significant. To our knowledge, this study is the first to report that FDRs of both BD-I and BD-II probands are at an increased risk of OCD. Our results were robust and consistent when subjected to sensitivity analysis that excluded FDRs diagnosed with BD-I/BD-II, implying an independent effect of BD-I/II on the OCD risk in a family. A gene set enrichment analysis suggested that dopamine system– and ion channel–related genes, such as *CACNA1C*, *GRIA1*, *DRD2*, *NOS1*, *SLC18A1*, *HTR2A*, and *GRIK2*, are involved in the pathogenesis of OCD and bipolar disorder.[32] However, the distinct or shared genetic correlation of BD-I and BD-II with OCD warrants further investigation.

Finally, the present results are concurrent with those of previous GWASs on the genetic overlap between bipolar disorder, ADHD, and ASD.[6,16–19,29,33–35] In particular, numerous studies have confirmed the hereditary association between bipolar disorder and ADHD, including several shared clinical features, high co-occurrence among individuals, bidirectional cross-transmission between bipolar disorder and ADHD in a family, and single nucleotide polymorphism–based genetic correlation.[16,17,33,34] The Cross-Disorder Group of the Psychiatric Genomics Consortium[19] suggested that 5 major psychiatric disorders—namely, schizophrenia, bipolar disorder, MDD, ASD, and ADHD—may share overlapping genetic susceptibility. This study determined that female FDRs of BD-II probands were at a higher risk of ASD and ADHD than were male FDRs of BD-II probands. However, the effect of sex on the risk of ADHD and ASD was not observed in the BD-I cohort (Figures 3A and 3B). Nonetheless, further studies are required to determine whether the FDRs, especially female individuals, of patients with BD-II are at an increased risk of ADHD and ASD.

This study has several limitations. First, only those individuals who sought medical services and treatment are included in the NHIRD database. Therefore, the prevalence of these psychiatric disorders may be underestimated. However, this concern may be minimized owing to the high coverage rate and affordable fees for medical services of Taiwan NHI and the high accessibility of medical services in Taiwan. Second, despite the fact that structured diagnostic interviews may not be surely applied to each subject in the database as in previous register-database and GWASs,[15,19,22,36,37] major psychiatric disorders were diagnosed by the board-certified psychiatrist at least twice in our study, yielding improved diagnostic validity. Third, the definitions of BD-I and BD-II may be arbitrary in current study because the specific code of BD-II was not available in the *ICD-9-CM* coding system. In our study, we followed the BD-II definition of Song and colleagues' study[15] and defined those who were never hospitalized for a manic or mixed episode as the BD-II subgroup. Although accurate diagnosis of BD-II was still a difficult challenge in clinical practice,[38] further study with the structured diagnostic interviews may be necessary to validate our findings. Fourth, twins were defined based on the same birth date and same mother in current study. Information of monozygotes or dizygotes was not available in NHIRD. Furthermore, the NHIRD did not provide some information, including education levels, lifestyles, and environmental factors; hence, we could not estimate their influence.

In conclusion, to our knowledge, this empirical cohort study is the first to study an Asian population to confirm the familial coaggregation of BD-I and BD-II with other psychiatric disorders—namely, schizophrenia, MDD, ASD, ADHD, anxiety disorder, and OCD. This study determined that familial aggregation of the same bipolar disorder subtypes was stronger than the cross-coaggregation between the two bipolar disorder subtypes. In addition, different risk distribution of psychiatric disorders between FDRs of BD-I and BD-II probands may imply the diagnostic validity of BD-II. The present comprehensive findings may facilitate genetic counseling in clinical practice and the development of distinct preventive interventions during the early stages of psychiatric disorders among the FDRs of BD-I and BD-II probands. Further cross-disorder GWASs are required to complement the limited data on the unique and shared genetic bases between the different bipolar disorder subtypes and other major psychiatric disorders.

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Supplementary Material

Article Title: Risks of Coaggregation of Major Psychiatric Disorders Among First-Degree Relatives of Patients With Bipolar I and Bipolar II Disorder: Evidence From a Nationwide Population-Based Study

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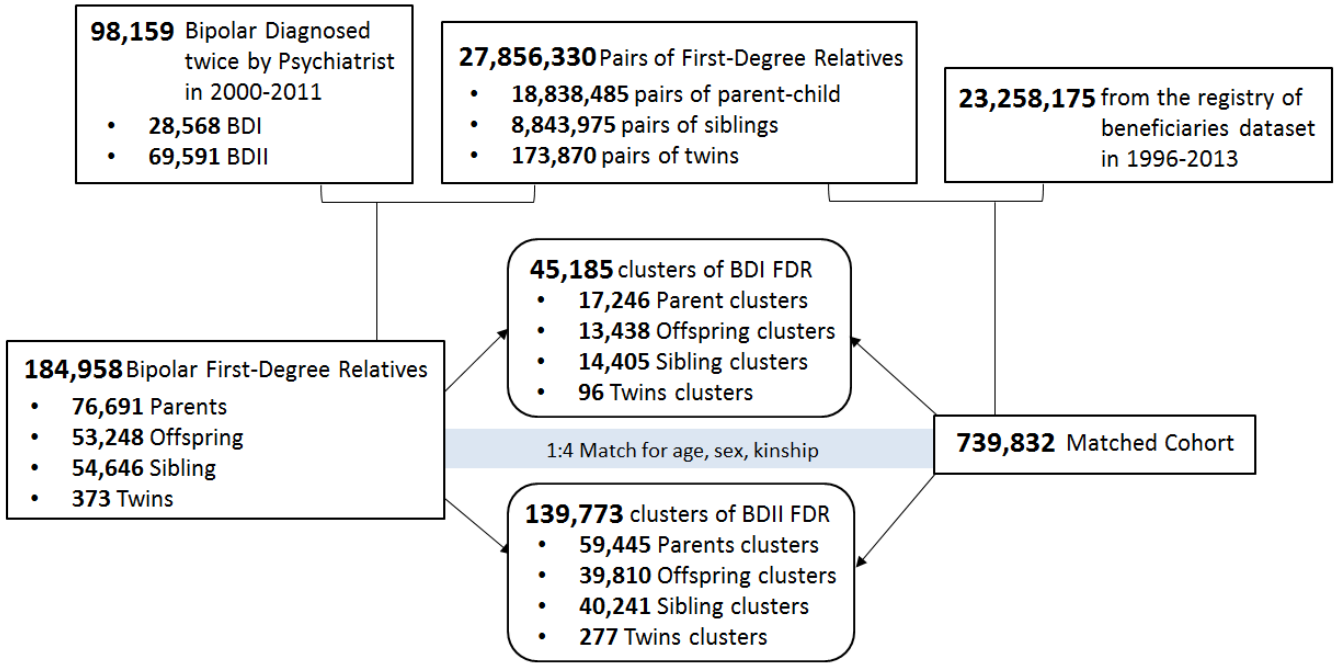
Supplementary Figure 1. Study flow-chart



Supplementary Table 1. Adjusted relative risk of different psychiatric disorders between male FDRs with BD-I/BD-II proband and their male matched cohort

Case Number	BD-I Male Cohort			BD-II Male Cohort			p-value for comparison
	FDR of BD-I patients (n=22355)	Matched BD-I control cohort (n=89420)	Adjusted RR‡ (95%C.I.)	FDR of BD-II patients (n=69657)	Matched BD-II control cohort (n=278628)	Adjusted RR‡ (95%C.I.)	
SCZ	666 (2.98)	458 (0.51)	***5.09 (5.24, 6.64)***	1012 (1.45)	1444 (0.52)	***2.84 (2.62, 3.08)***	***<0.001***
BD	759 (3.40)	328 (0.37)	***9.46 (8.31, 10.77)***	1477 (2.12)	1031 (0.37)	***5.81 (5.36, 6.30)***	***<0.001***
BDI	336 (1.50)	96 (0.11)	***14.03 (11.18, 17.61)***	416 (0.60)	275 (0.10)	***6.09 (5.23, 7.09)***	***<0.001***
BDII	423 (1.89)	232 (0.26)	***7.39 (6.29, 8.67)***	1061 (1.52)	756 (0.27)	***5.65 (5.14, 6.21)***	***0.0050***
MDD	710 (3.18)	887 (0.99)	***3.28 (2.97, 3.63)***	1888 (2.71)	2861 (1.03)	***2.68 (2.53, 2.84)***	***0.0008***
ASD	96 (0.43)	179 (0.20)	***2.18 (1.70, 2.80)***	292 (0.42)	598 (0.21)	***1.96 (1.71, 2.26)***	0.5171
ADHD	411 (1.84)	935 (1.05)	***1.87 (1.66, 2.11)***	1662 (2.39)	3163 (1.14)	***2.19 (2.06, 2.33)***	***0.0046***
Anxiety	1763 (7.89)	3118 (3.49)	***2.38 (2.24, 2.53)***	5050 (7.25)	9487 (3.40)	***2.22 (2.14, 2.30)***	0.0601
OCD	117 (0.52)	180 (0.20)	***2.81 (2.23, 3.55)***	378 (0.54)	534 (0.19)	***3.00 (2.63, 3.42)***	0.5788

‡ : Adjusted for age, urbanization, income level; a: proportion(BDI)=the number of BDI/the number of BDI+BDII; b: proportion(BDII)=the number of BDII/the number of BDI+BDII.

Abbreviation: SCZ. Schizophrenia; BD, bipolar disorder; MDD, major depressive disorder; ASD, Autism spectrum disorder; ADHD, Attention Deficit Hyperactivity Disorder; OCD, obsessive-compulsive disorder; FDR, First Degree Relative; C.I. ,confidence interval; RR, relative risk.

Supplementary Table 2.

Adjusted relative risk of different psychiatric disorders between female FDRs with BD-I/BD-II proband and their female matched cohort

Case Number	BD-I Female Cohort			BD-II Female Cohort			p-value for comparison
	FDR of BD-I patients (n=22830)	Matched BD-I control cohort (n=91320)	Adjusted RR‡ (95%C.I.)	FDR of BD-II patients (n=70116)	Matched BD-II control cohort (n=280464)	Adjusted RR‡ (95%C.I.)	
SCZ	645 (2.83)	448 (0.49)	***5.76 (5.10, 6.50)***	904 (1.29)	1403 (0.50)	***2.60 (2.39, 2.82)***	***<0.001***
BD	921 (4.03)	457 (0.50)	***8.28 (7.40, 9.26)***	1889 (2.69)	1292 (0.46)	***5.94 (5.54, 6.38)***	***<0.001***
BDI	375 (1.64)	84 (0.09)	***17.81 (14.05, 22.57)***	373 (0.53)	281 (0.10)	***5.30 (4.53, 6.19)***	***<0.001***
BDII	546 (2.39)	373 (0.41)	***5.94 (5.20, 6.78)***	1516 (2.16)	1011 (0.36)	***6.06 (5.60, 6.57)***	0.7792
MDD	1166 (5.11)	1644 (1.80)	***2.95 (2.73, 3.18)***	3354 (4.78)	4773 (1.70)	***2.92 (2.79, 3.05)***	0.7928
ASD	30 (0.13)	43 (0.05)	***2.75 (1.74, 4.36)***	85 (0.12)	118 (0.04)	***2.75 (1.74, 4.36)***	0.9087
ADHD	124 (0.54)	236 (0.26)	***2.12 (1.70, 2.64)***	581 (0.83)	790 (0.28)	***2.99 (2.68, 3.33)***	***0.0059***
Anxiety	2455 (10.75)	4188 (4.59)	***2.55 (2.42, 2.68)***	7090 (10.11)	12864 (4.59)	***2.37 (2.30, 2.44)***	***0.0235***
OCD	112 (0.49)	168 (0.18)	***2.94 (2.31, 3.73)***	382 (0.54)	523 (0.19)	***3.16 (2.77, 3.61)***	0.5827

‡ : Adjusted for age, urbanization, income level; a: proportion(BDI)=the number of BDI/the number of BDI+BDII; b: proportion(BDII)=the number of BDII/the number of BDI+BDII.

Abbreviation: SCZ. Schizophrenia; BD, bipolar disorder; MDD, major depressive disorder; ASD, Autism spectrum disorder; ADHD, Attention Deficit Hyperactivity Disorder; OCD, obsessive-compulsive disorder; FDR, First Degree Relative; C.I. ,confidence interval; RR, relative risk.

Supplementary Table 3. Sensitivity test for psychiatric diagnosis given by board-certified psychiatrists at least three times (model 1)

	ARR‡ for Male (95%C.I.)			ARR‡ for Female (95%C.I.)			ARR‡ for All (95%C.I.)		
	BD-I Cohort	BD-II Cohort	P -value for comparison	BD-I Cohort	BD-II Cohort	P -value for comparison	BD-I Cohort	BD-II Cohort	P-value for comparison
SCZ	6.06 (5.35, 6.86)	2.85 (2.62, 3.10)	***<0.001***	5.68 (5.01, 6.43)	2.53 (2.32, 2.76)	***<0.001***	5.86 (5.37, 6.40)	2.69 (2.53, 2.86)	***<0.001***
BD	9.52 (8.3, 10.91)	6.02 (5.53, 6.56)	***<0.001***	9.02 (7.99, 10.19)	6.14 (5.69, 6.62)	***<0.001***	9.24 (8.43, 10.12)	6.09 (5.75, 6.44)	***<0.001***
BDI	13.46 (10.88, 16.65)	5.92 (5.15, 6.81)	***<0.001***	15.41 (12.50, 19)	5.56 (4.84, 6.39)	***<0.001***	14.46 (12.45, 16.78)	5.74 (5.20, 6.33)	***<0.001***
BDII	6.96 (5.80, 8.34)	6.01 (5.40, 6.68)	0.1726	6.13 (5.24, 7.16)	6.31 (5.77, 6.91)	0.7456	6.46 (5.74, 7.27)	6.18 (5.77, 6.62)	0.5222
MDD	3.36 (3.02, 3.74)	2.73 (2.56, 2.90)	***0.0009***	2.95 (2.71, 3.20)	2.95 (2.81, 3.10)	0.9894	3.09 (2.90, 3.30)	2.87 (2.76, 2.98)	***0.0449***
ASD	2.27 (1.75, 2.95)	2.13 (1.83, 2.48)	0.7108	3.13 (1.85, 5.28)	3.32 (2.45, 4.49)	0.8504	2.41 (1.92, 3.04)	2.32 (2.03, 2.65)	0.7955
ADHD	1.78 (1.56, 2.03)	2.32 (2.17, 2.48)	***0.0004***	2.43 (1.89, 3.10)	3.31 (2.92, 3.74)	***0.0446***	1.91 (1.70, 2.14)	2.51 (2.37, 2.66)	***<0.001***
Anxiety	2.44 (2.25, 2.65)	2.41 (2.30, 2.53)	0.7358	2.77 (2.58, 2.97)	2.56 (2.46, 2.67)	0.0576	2.62 (2.48, 2.76)	2.49 (2.42, 2.57)	0.0949
OCD	2.82 (2.21, 3.60)	2.99 (2.61, 3.43)	0.6769	2.69 (2.09, 3.47)	3.17 (2.76, 3.65)	0.2627	2.77 (2.32, 3.30)	3.08 (2.79, 3.40)	0.2772

‡ : Adjusted for age, sex, urbanization, income level

Abbreviation: SCZ. Schizophrenia; BD, bipolar disorder; MDD, major depressive disorder; ASD, Autism spectrum disorder; ADHD, Attention Deficit Hyperactivity Disorder; OCD, obsessive-compulsive disorder; FDR, First Degree Relative; C.I., confidence interval; ARR, adjusted relative risk.

Supplementary Table 4. Sensitivity analysis for excluding FDRs having BD (model 2)

	ARR‡ for Male (95%C.I.)			ARR‡ for Female (95%C.I.)			ARR‡ for All (95%C.I.)		
	BD-I Cohort	BD-II Cohort	P -value for comparison	BD-I Cohort	BD-II Cohort	P -value for comparison	BD-I Cohort	BD-II Cohort	P-value for comparison
SCZ	4.46 (3.88, 5.12)	2.26 (2.06, 2.49)	***<0.001***	4.61 (4.01, 5.3)	2.07 (1.87, 2.28)	***<0.001***	4.53 (4.11, 5.00)	2.17 (2.02, 2.32)	***0.0001***
BD	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
BDI	--	--	--	--	--	--	--	--	--
BDII	--	--	--	--	--	--	--	--	--
MDD	2.56 (2.29, 2.87)	2.29 (2.14, 2.45)	0.0987	2.47 (2.27, 2.69)	2.56 (2.43, 2.69)	0.5365	2.50 (2.33, 2.68)	2.45 (2.36, 2.55)	0.6115
ASD	1.89 (1.45, 2.46)	1.72 (1.48, 2.00)	0.5412	1.94 (1.13, 3.34)	2.30 (1.69, 3.14)	0.6351	1.90 (1.50, 2.41)	1.81 (1.58, 2.07)	0.7217
ADHD	1.82 (1.61, 2.05)	2.06 (1.94, 2.19)	0.0679	1.96 (1.56, 2.47)	2.85 (2.55, 3.18)	***0.0034***	1.86 (1.67, 2.07)	2.22 (2.10, 2.35)	***0.0033***
Anxiety	2.13 (2.00, 2.27)	2.04 (1.97, 2.12)	0.2149	2.33 (2.21, 2.47)	2.19 (2.12, 2.26)	***0.0461***	2.24 (2.15, 2.34)	2.12 (2.07, 2.17)	***0.0205***
OCD	2.04 (1.56, 2.67)	2.49 (2.15, 2.88)	0.2110	2.33 (1.77, 3.07)	2.64 (2.27, 3.06)	0.4710	2.18 (1.80, 2.64)	2.55 (2.30, 2.83)	0.1597

‡ : Adjusted for age, sex, urbanization, income level

Abbreviation: SCZ. Schizophrenia; BD, bipolar disorder; MDD, major depressive disorder; ASD, Autism spectrum disorder; ADHD, Attention Deficit Hyperactivity Disorder; OCD, obsessive-compulsive disorder; FDR, First Degree Relative; C.I., confidence interval; ARR, adjusted relative risk.