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Bipolar disorder and its relation to major psychiatric disorders: a family- based study in the Swedish population

Running head: Bipolar disorder and psych disorders overlap

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Abstract

Objectives: Bipolar disorder (BPD) shares genetic components with other psychiatric disorders; however, uncertainty remains about where in the psychiatric spectra BPD falls. To understand the etiology of BPD, we studied the familial aggregation of BPD and co-aggregation between BPD and schizophrenia, schizoaffective disorder, depression, anxiety disorders, attention deficit/hyperactivity disorder (ADHD), drug abuse, personality disorders and autism spectrum disorders (ASD).

Methods: A population-based cohort was created by linking several Swedish national registers. 54,723 BPD individuals were identified among 8,141,033 offspring from 4,149,748 nuclear families. The relative risk of BPD in relatives and co-occurrence of other psychiatric disorders in BPD patients and their relatives were compared to those of matched population controls. Structural equation modeling was used to estimate the heritability and tetrachoric correlation.

Results: The familial risks for relatives of BPD probands were 5.8-7.9 in first degree relatives, and decreased with genetic distance. Co-occurrence risks for other psychiatric disorders were 9.7-26.4 in BPD individuals and 1.7-2.8 in full siblings of BPD probands. Heritability for BPD was estimated at 58%. The correlations between BPD and other psychiatric disorders were considerable (0.37-0.62) and primarily due to genetic effects. The correlation with depression was the highest (0.62), but was only 0.44 for schizophrenia.

Conclusions: The high familial risks provides evidence that genetic factors play an important role in the etiology of BPD, and the shared genetic determinants suggest pleiotropic effects across different psychiatric disorders. Results also indicate BPD is in both the mood and psychotic spectra, but possibly more closely related to mood disorders.

Key words: genetic epidemiology – relative risk – heritability

Introduction

Recently published studies have shown shared genetic effects between major psychiatric disorders including bipolar disorder (BPD) (1, 2), but it remains unclear where BPD falls among psychiatric disorders. BPD has long been treated as a mood disorder from traditional symptom diagnoses, but recent studies have emphasized its correlation with schizophrenia, a psychotic disorder (3-5). Estimates of familial risks and heritability help quantify the magnitude of genetic and environmental influences on BPD, and co-occurrence and correlations between BPD and other psychiatric disorders can provide crucial information about the position of BPD among major psychiatric disorders.

Twin, adoption and family studies (4-11) have shown that genes influence the familial transmission for BPD, even though questions remain regarding the magnitude of the heritability and whether sex-specific effects exist. Also, risk estimates in second and third degree relatives, spouses, and adoptive relatives of individuals with BPD have been limited.

Observed co-occurrences between BPD and several psychiatric conditions (e.g., depression (12), schizophrenia (12, 13) and schizoaffective disorder (14)) within the same individuals over time as well as in family members, are partly due to shared genetic determinants. We previously reported that about 50% of the genetic determinants overlap in BPD and schizophrenia (4), which is in line with results from genome-wide association studies (GWAS) (15). In addition, we have found evidence for shared genetic factors between BPD and attention deficit/hyperactivity disorder (ADHD) (16), as well as between BPD and autism spectrum disorders (ASD) (17). However, the co-occurrence risk estimates vary across studies (9, 10), and the relative importance of genetic factors for these overlaps has not been estimated.

Our aim was to provide reliable estimates of familial risk of BPD and explore the etiologic overlap with other psychiatric disorders by using data from the total Swedish population (N=9 million individuals). Specifically, we aimed to: (1) provide improved estimates of familial risks and heritability for BPD; (2) study the individual and familial co-occurrence of other psychiatric disorders for BPD; (3) Estimate the genetic overlaps between BPD and other psychiatric disorders to determine shared genetic and/or environmental effects.

Methods

National registers

We established a population-based national cohort through linkage of several longitudinal Swedish total population registers, using the personal identification numbers unique to each individual. The National Patient Register (NPR) captures all public psychiatric inpatient admissions in Sweden since 1973 and outpatient diagnoses since 2001. Each record contains admission and discharge dates, the main discharge diagnosis, and up to eight secondary diagnoses assigned by the attending physician in accordance with International Classification of Diseases (ICD) system. The Multi-Generation Register (MGR) enabled identification of biological and adoptive parents of all individuals registered as living in Sweden since 1961 and born in Sweden since 1932. The Swedish Twin Register covers all twins born in Sweden since 1886. The Total Population Register (TPR), Cause of Death Register and Migration Register provided information on individuals' sex, date of birth, and when and where they were alive and living in Sweden. All registries were followed from their start to 2009. Ethical approval was given by the ethics committee at Karolinska Institutet.

We identified 8,141,033 offspring clustered into 4,149,748 nuclear families. Using the NPR and TPR we found probands with BPD and the controls. Through the MGR we identified their first, second and third degree relatives, mating partners and adoptive relatives. In analyses of adoptions, we excluded adoptive parents who have biological relationships (grandparents, uncles or aunts) with their adoptee and siblings who have biological relationships (cousins) with their adoptive siblings.

For heritability analyses, we established a cohort of siblings born from 1958 to 1985 with follow-up time from 1973 to 2009, which included monozygotic (MZ) twins, dizygotic (DZ) twins, full siblings and half-siblings after exclusion of those died or emigrated before age 25. To simplify the analysis, we randomly selected one sibling pair from each sibling structure, giving priority to twins, followed by maternal siblings, paternal siblings and full siblings in order to maximize sample size in each class of sibling structure. To increase comparability, we only selected the eldest siblings born within 5 years of each other. Our cohort contained 5,773 MZ twin pairs, 17,053 DZ pairs, 35,017 maternal half-sibling pairs, 24,289 paternal half-sibling pairs and 638,295 full sibling pairs.

Disease classifications

Diagnoses were coded according to ICD-8 (1969-1986), ICD-9 (1987-1996) and ICD-10 (1997-present) using a non-hierarchical diagnostic structure. We extracted bipolar patients with high specificity from the NPR by applying a validated algorithm (18), where BPD was defined as at least two inpatient or outpatient admissions for a core BPD diagnosis (ICD-8: 296.0- 296.3, 296.8, 296.9; ICD-9: 296A-296E, 296W, 296X; ICD-10: F30, F31), with exclusion of sole diagnoses of ICD-8 296.2 (manic-depressive psychosis, depressed type) and/or ICD-9 296B

(unipolar affective psychosis, melancholic form). Schizophrenia, schizoaffective disorder, depression, anxiety disorders, ADHD, drug abuse, personality disorders and ASD were defined by one or two of their core diagnosis codes (see Table S1 in the online data supplement).

Statistical analysis

We refer to relative risk (RR) for the measure of familial risk and co-occurrence risk throughout the manuscript. To estimate familial risk for BPD, we estimated the risk of relatives to individuals with BPD compared to relatives of up to ten randomly selected individuals unaffected by BPD, matched by sex and year of birth. To ensure equal follow-up time, the control was required to be alive, reside in Sweden, and have no history of BPD before the date of the first diagnosis of the matched proband. To allow equal possibility for diagnosis of BPD, the proband and matched controls were required to live in the same county in the year when the proband was diagnosed BPD (because counties began reporting to the registry at different times). This county-matching qualification was not conducted in adoptive relationships to maximize sample size. In addition, to ensure equal time at risk, the relative of the control was also matched to the relative of the proband by biological relationship, sex, and year of birth.

For co-occurrence of other psychiatric disorders within individuals with BPD, ten controls were randomly selected for each BPD proband with the same strategy (i.e., matched on sex, year of birth, living area when the proband was diagnosed BPD; to be alive, reside in Sweden, and with no history of BPD before the date of the first diagnosis of the matched proband). Selection measures for estimates of the familial co-occurrence risk were also the same as that in the familial risk for BPD. To ensure that the observed associations in analyses were between BPD in the proband and psychiatric disorders in the relative, we excluded relatives ever diagnosed with

BPD. Furthermore, we conducted sensitivity analyses excluding the possibility of diagnoses of both disorders within individuals in full siblings. For example, when estimating the co-occurrence risk between BPD and schizophrenia, we excluded BPD probands ever diagnosed with schizophrenia and excluded siblings ever diagnosed with BPD.

We estimated the associations using conditional logistic regression models with PROC PHREG in SAS 9.3 (19). Since several correlated pairs of relatives from each family were sometimes included in the analyses, a robust sandwich estimator was used to adjust for the non-independent data structure when calculating the 95% confidence intervals (4, 20, 21).

Structural equation modeling was used to estimate the heritability. We treated the disease status as a binary variable and employed the liability-threshold model (22). For each diagnosis, we allowed for different prevalence of the outcome in the five different types of siblings, and adjusted prevalence for sex effects assumed to be identical between all sibling types. The genetic correlation was fixed to 1 for MZ twin pairs (they are genetically identical), to 0.5 for DZ twins and full siblings (they share on average 50% of their segregating genes), and to 0.25 for half-siblings. We assumed that the family environment is shared between MZ twins, DZ twins, full siblings and maternal half-siblings (the family environmental correlation was fixed to 1), but unshared between paternal half-siblings (22). We assumed that there are no epistasis or dominance deviations between genes and no interactions or correlations between genetic and environmental components. Data were first analyzed with a univariate model using the Mx program (23). Then we used a bivariate Cholesky decomposition (24) to calculate the tetrachoric correlations to estimate the relative contribution of genetic and environment elements in common with BPD to the liability of another disorder (See Methods in the online data supplement for more details).

Results

Familial risks for BPD

There were 54,723 individuals who met our criteria for BPD. We have previously presented the results for parent/offspring, sibling, half/sibling and adoptive relationships with inpatient data (4). Here we extended our previous work by including 5 more years of follow-up of inpatient data and outpatient data since 2001, and by also estimating the risks for other biological and adoptive relationships (Table 1).

{ Table 1 approximately here }

Similar to prior results, the relatives of individuals with BPD had increased risks for BPD, and risks decreased with the distance of biological relationships ($RR_{\text{first degree}}=5.8-7.9 > RR_{\text{second degree}}=2.2-3.3 > RR_{\text{third degree}}=1.6$). Despite the lack of sex differences for the risks in first-degree relatives, male relatives of male probands tend to have higher risks ($RR = 7.4-7.9$). We found a suggestive difference in RRs between maternal half-siblings and paternal half-siblings of BPD probands; among the 6,895 maternal half-siblings, 139 were diagnosed with BPD ($RR=3.3$ (2.6-4.2)), whereas 101 were diagnosed with BPD among the 8,941 paternal half-siblings ($RR=2.2$ (1.7-2.9)). Notably, the RR of maternal half-siblings was not only higher than paternal half-siblings but also for any other class of second-degree relatives. Furthermore, there was substantial evidence for assortative mating for BPD ($RR=2.1$ (1.9-2.3)). Additionally, adopted children whose biological parents had BPD ($N=503$), or biological parents whose adopted away children had BPD ($N=578$), also had increased risk of being diagnosed with BPD ($RR=4.5$ (2.6-

7.6) and 5.0 (2.9-8.5)). We also observed significantly increased, but relatively lower, risks of BPD in adoptee/adoptive parent and adoptive parent/adoptee relationships.

Co-occurrence risk for psychiatric disorders within individuals with BPD

Among the 54,723 patients diagnosed with BPD, a number of patients had at some point also had been diagnosed with schizophrenia (N=3,320), depression (N=22,433), anxiety disorders (N=14,563), ADHD (N=2,064), drug abuse (N=5,733), personality disorders (N=8,473) or ASD (N=776) (Table 2). There were substantially increased risks for all of these psychiatric disorders (RR 9.7-22.9) in individuals with BPD when compared to population controls. We did not estimate the RR for depression for individuals with BPD, because those who were diagnosed with BPD will experience depressive episodes during their lifetime. However, we did include the estimates of RR for depression for relatives of BPD probands since relatives who were diagnosed with BPD were excluded.

It is notable that about half of the patients with schizoaffective disorder were also diagnosed with BPD (N=4,332 from 10,750 individuals with schizoaffective disorder). Thus, we did not show the results for schizoaffective disorder, because it's questionable that these are distinguishable disorders in our sample.

{ Table 2 approximately here }

Co-occurrence risk for psychiatric disorders among relatives of BPD probands

Our previous studies have shown the familial aggregation between BPD and schizophrenia (4), BPD and ADHD (16) and BPD and ASD (17). This study extended investigations to depression, anxiety disorders, drug abuse and personality disorders in the first, second, third degree and adoptive relatives of BPD probands. Table 3 displays the results for different sibling types

(results for all types of relationships are shown in supplemental tables S2-S8 online). Full siblings of BPD probands had significantly increased risks for all disorders investigated (RR=1.7-2.8), and in sensitivity analyses (i.e., excluding the possibility that individuals could be diagnosed with both disorders) these co-occurrences were somewhat attenuated but still significant (RR = 1.4-2.6; see supplemental Table S9 online). Full siblings had higher risks for co-occurrence compared to half-siblings; maternal half-siblings had slightly higher risks than paternal half-siblings (except for schizophrenia). Adopted away siblings, whose biological sibling had BPD and grew up in a different family, also had increased risks for depression, anxiety disorders, drug abuse and personality disorders. Similar patterns of significantly increased risks appeared for all the disorders among first-degree relatives of BPD probands (see supplemental Table S2-S8 online). From these results, we noted high risks for ASD for adopted away biological offspring of parents with BPD (RR=5.5 (1.6-18.4)) and for adoptees of adoptive parents with BPD (RR=2.2 (1.2-3.9)) (see supplemental Table S8 online).

{ Table 3 approximately here }

Heritability

We estimated the heritability for BPD at 58%, and the remaining variance was attributed to non-shared environmental effects (Table 4). We next performed bivariate correlation analyses between BPD and other psychiatric disorders, summarized in Figure 1 (estimates of parameters and correlations in supplemental Table S10-S11 online). The tetrachoric correlations were considerable (0.37-0.62), and the highest correlation was between BPD and depression (0.62). Genetic effects accounted for approximately 1/2 of the correlations; for schizophrenia, ADHD and ASD the proportion achieved 2/3.

{Table 4 approximately here}

{Figure 1 approximately here}

Discussion

In this population-based study with the largest BPD cohort ever published, we found: (1) strong familial risks for BPD; (2) strong co-occurrence risks for schizophrenia, anxiety disorders, ADHD, drug abuse, personality disorders and ASD in individuals with BPD; (3) high familial risks for the co-occurrence for schizophrenia, depression, anxiety disorders, ADHD, drug abuse, personality disorders and ASD among family members of BPD probands; (4) associations between BPD and these psychiatric disorders are to a large extent explained by shared genetic factors. These results confirm the importance of genetic risk factors in the etiology of BPD, as well as their pleiotropic effects for other psychiatric disorders.

The estimates of familial risks for BPD align with previous family and adoption studies but have higher precision. We confirmed the excess risk for BPD among first degree relatives of BPD probands suggested by previous studies. For example, the RRs among first degree relatives (6.4-6.8) were similar to the pooled OR (6.96) from a meta-analysis (25). The results for parent/offspring, sibling, half/sibling and adoptive relationships are close, if not identical, to those from our previous work (4). We have now extended the estimates and confidence intervals for essentially all classes of relatives. The tendency for decreasing RRs with the distance of biological relationship, the higher RR for full siblings compared to maternal half-siblings (these two types of siblings are likely to be exposed to similar degree of shared environment), and the high RRs for adopted away biological relatives all suggest strong genetic effects for the

development of BPD. The estimate of heritability of BPD (58%) is lower than that in a summary of twin studies (85%) (26) and the estimate from a review of psychiatric disorders (75%) (27), but practically identical to our previous result (59%) which was based on another family model (i.e., parent/offspring model) that rests on different assumptions (4). Moreover, our result is consistent with another large genetic study (2) which offers a lower bound of heritability by using common variants from GWAS data, and our estimation, without specifying genetic variants, is likely closer to the true heritability. Compared to twin models on the same data, sibling models may yield up to a hundred-fold increase in sample size (thirty-fold increase in our sample) and provide more credible assumptions about genetic covariance (28). However, sibling models might slightly underestimate the heritability in situations like assortative mating. Our estimate is lower than that from twin studies (11, 26). Nevertheless, both these methods and molecular genetics studies (5, 11) confirm that genetic factors play a significant etiologic role.

The higher risk for BPD in maternal half-siblings compared to paternal half-siblings and the significantly increased risk for BPD in adoptees to biologically unrelated parents with BPD suggested shared environmental effects that were not evident in the heritability analyses (where shared environments were estimated at 0). This highlights the need for studies of the effects of growing up in families with parents who have BPD.

Finding increased co-occurrence risks between BPD and major psychiatric disorders within individuals was expected. Our results agree with studies on shared genetic effects with schizophrenia (1, 15), and on co-occurrence with anxiety disorders - consistent with the results in STEP-BD projects (29). Co-occurrences with ADHD (30, 31), personality disorders (32), drug abuse (33, 34) and ASD (35) were also verified.

Interestingly, we found increased risks for psychiatric disorders among the relatives of individuals with BPD (which was significant in full siblings even when individuals could not have both BPD and another disorder). These results are congruent with recently published high quality GWAS studies (1, 2, 36). Here we also estimated the magnitude of the tetrachoric correlations (ranging between 0.37 and 0.76), and 42% to 67% of these associations were explained by shared genetic factors. Both familial co-occurrence and correlations across psychiatric disorders strengthen the evidence that BPD risk genes contribute to the development of different psychiatric disorders, suggesting pleiotropy of genes contributing to psychiatric etiology and challenging the current descriptive diagnostic schema (37). In etiological and pathophysiological investigations, it may be better to break traditional diagnostic boundaries and conceptualize psychiatric disorders as syndromes of “inter-related clinical phenotypes” rather than isolating them and assigning the concept of “common comorbidity” (37). Moreover, as correlations are less affected by prevalence of diseases and provide more information in measuring associations than relative measures of risk, the highest correlation here, with depression, showed that BPD may be closer to mood disorders than psychosis among the “inter-related phenotypes”.

Non-shared environmental liability to the co-occurrence also cannot be ignored, which is evident from its considerable contribution to the correlations (33% to 58%) between bipolar and other psychiatric disorders. Prenatal or perinatal complications or history of substance abuse are likely to contribute to this kind of environmental source (38).

We also noticed some interesting features in our data meriting additional investigation. First, although no marked sex effects were found, the familial risks for male-male relationships (son-father, father-son, and male full siblings) were slightly higher than for other relationships

(female-male, male-female and female-female relationships). Second, in agreement with a previous study (39), we identified a relatively high degree of assortative mating. Third, RRs of co-occurrence between BPD and ASD were rather high both among biological and adoptive parents of BPD adoptees (see supplemental Table S8 online). Although our study is the largest adoption study presented, the limited sample size and inherent assumptions (e.g., selective placement, age at adoption) constrain the possibility for firm conclusions.

The large nationwide sample is a considerable strength. We studied medical records from the entire Swedish population spanning more than 30 years, which reduced the risk of misclassification by recall and reporting biases. Nevertheless, several limitations exist in our studies. (1) Despite the substantial advantages afforded by the population-based studies, a typical drawback is the use of non-standardized diagnoses from different physicians with different opinions across time and geographic region. However, we used a validated algorithm that has been shown to have a positive predictive value of 0.92 and low false-positive rate (18). (2) To study the co-occurrence within individuals, a non-hierarchical structure was applied in the definition of psychiatric disorders, and we did not consider the order of diagnoses. Since it is not uncommon that an individual first diagnosed with depression later develops BPD, or suffers from BPD but develops schizophrenia over time, misdiagnoses are inevitable and would affect the estimate results. We additionally estimated familial risks and co-occurrence risks with a hierarchical definition for schizophrenia, schizoaffective disorder (i.e., excluding those ever diagnosed with schizophrenia), and BPD (i.e., excluding those ever diagnosed with schizophrenia or schizoaffective disorder) and obtained similar results (data not shown). Furthermore, a sensitivity analysis was conducted for the familial co-occurrence between those psychiatric disorders and BPD among siblings excluding the possibility of assigning both

diagnosis (i.e., when estimating the co-occurrence risk between BPD and another diagnoses like drug abuse, we excluded siblings ever diagnosed with BPD; Table S9), and RRs remained significant. (3) Diagnostic bias could occur if physicians were influenced by family psychiatric history in diagnostic assessments, although adoptive relationships are likely to avoid such bias. (4) Clinical diagnosis was the diagnostic procedure of our study and because it is possible that sensitivity and negative predictive value for BPD were relatively poor in the early study period, clinical features that were more likely to be correctly diagnosed (classical grandiose-euphoric mania, psychotic features, BPD type I) during earlier time might have impacted the results. (5) In a similar vein, our study reported estimates for BPD without separating BPD subtypes because of the limited information in the Swedish National Register. Future investigation of the familial risks and heritability for BPD-I and BPD-II would advance knowledge and further inform the etiology for BPD and nosology for psychiatric disorders. (6) For some psychiatric disorders, inpatient or outpatient admissions are unusual or atypical. For example, an individual with personality disorders is unlikely to be diagnosed; however, if the individual also has BPD, he or she will be more likely to visit a physician and also, consequently, be diagnosed with personality disorders. Such biases could exist in our estimates of co-occurrence within BPD individuals, but is less likely in their relatives for whom BPD was an exclusion criterion.

Overall, we confirmed and extended the familial risk estimates for BPD and found evidence that BPD partly shares genetic causes with other psychiatric disorders. Our findings corroborate recent molecular genetic studies (1, 2) showing abundant pleiotropy of gene variants in psychiatry. Moreover, we showed that BPD is highly correlated with depression, highlighting that the communality between BPD and depression should not be forgotten. Precision of estimates of familial risks and the magnitude of genetic influences provide crucial parameters

(i.e., estimate of strength of genetic transmission, quantification of risk at the population level) for the design and interpretation of genetic studies and identification of meaningful endophenotypes. From a clinical perspective, the feature of familial risks may offer a rationale to initiate preventive family-based screening in primary care. The knowledge of co-occurrence might contribute to future nosology of psychiatric disorders through incorporation of genetic factors and other levels of information to lay the foundation for a more precise diagnostic system; thus yielding better treatments and medications for patients.

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Disclosures

All authors report no financial relationships with commercial interests.

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Table 1. Familial risks for BPD in relatives of individuals with BPD

Relative class	Relation to proband	Grouping	Relatives affected with BPD		RR	95%CI		
			With BPD probands (%)	General population controls (%)				
Biological relationship								
First degree	Parent	Total	2119 (3.1)	3269 (0.5)	6.7	6.3-7.0		
		Father	789 (2.4)	1153 (0.4)	7.0	6.4-7.5		
		Male offspring-father	364 (2.7)	474 (0.4)	7.9	7.0-8.9		
		Female offspring-father	425 (2.2)	702 (0.4)	6.1	5.5-6.8		
		Mother	1330 (3.9)	2123 (0.6)	6.4	6.0-6.8		
		Male offspring-mother	546 (3.9)	891 (0.6)	6.3	5.8-7.0		
	Offspring	Female offspring-mother	Female offspring-mother	784 (3.9)	1248 (0.6)	6.5	6.0-7.0	
			Total	2119 (2.8)	3216 (0.4)	6.8	6.4-7.1	
			BPD in father	785 (2.8)	1157 (0.4)	6.9	6.4-7.5	
			Father proband-son	362 (2.5)	486 (0.3)	7.6	6.7-8.6	
			Father proband-daughter	423 (3.1)	694 (0.5)	6.2	5.6-6.9	
			BPD in mother	1334 (2.8)	2065 (0.4)	6.6	6.2-7.1	
		Mother proband-son	Mother proband-son	548 (2.2)	864 (0.4)	6.5	5.9-7.1	
			Mother proband-daughter	786 (3.4)	1267 (0.6)	6.4	5.9-6.9	
			Sibling	Total	2142 (3.9)	3429 (0.6)	6.4	6.0-6.8
				Male proband-female sibling	464 (4.2)	795 (0.7)	5.9	5.3-6.5
				Male proband-male sibling	442 (3.9)	612 (0.6)	7.4	6.5-8.4
				Female proband-male sibling	463 (2.8)	814 (0.5)	5.8	5.2-6.4
				Female proband-female sibling	773 (4.8)	1209 (0.8)	6.6	5.9-7.2
Second degree	Grandparent	Total		404 (0.9)	1797 (0.4)	2.3	2.0-2.5	
		Uncle/aunt	Total	620 (1.5)	2693 (0.7)	2.3	2.1-2.5	
	Grandchild	Total	407 (0.5)	1713 (0.2)	2.4	2.1-2.6		
	Nephew/niece	Total	619 (0.7)	2697 (0.3)	2.3	2.1-2.5		

Table 1. (Continued)

Relative class	Relation to proband	Grouping	Relatives affected with BPD		RR	95%CI
			With BPD probands (%)	General population controls (%)		
Second degree	Half sibling	Paternal half-sibling	101 (1.1)	335 (0.5)	2.2	1.7-2.9
		Maternal half-sibling	139 (2.0)	293 (0.6)	3.3	2.6-4.2
Third degree	Cousin	Total	523 (0.6)	3358 (0.4)	1.6	1.4-1.7
Unrelated	Mating partner	Total	407 (1.0)	1928 (0.5)	2.1	1.9-2.3
Adoptive relationship						
First degree	Biological parent	Total	19 (3.8)	38 (0.9)	4.5	2.6-7.6
	Adopted away biological offspring	Total	19 (3.3)	29 (0.7)	5.0	2.9-8.5
	Adopted away biological sibling	Total	12 (7.9)	10 (1.1)	9.9	2.5-40.0
Unrelated	Adoptive parent	Total	14 (0.9)	49 (0.3)	2.8	1.7-4.8
	Adoptee	Total	14 (1.8)	44 (0.6)	3.1	1.8-5.4
	Non-biological sibling	Total	12 (2.0)	55 (1.1)	1.8	0.8-4.1

Table 2. Risk for psychiatric disorders for individuals with BPD

Diagnosis	Individuals with BPD (N=54328^a, %)	General population controls unaffected with BPD (N=543280, %)	RR	95%CI
Schizophrenia	3320 (6.1)	2320 (0.4)	15.3	14.5-16.2
Anxiety disorders	14563 (26.8)	19614 (3.6)	10.2	9.9-10.4
ADHD	2064 (3.8)	1105 (0.2)	21.8	20.2-23.6
Drug abuse	5733 (10.6)	6761 (1.2)	9.7	9.3-10.0
Personality disorders	8473 (15.6)	4558 (0.8)	22.9	22.0-23.8
ASD	776 (1.4)	615 (0.1)	13.2	11.9-14.7

^a There are 54328 BPD individuals who have county records used for county matching.

Table 3. Risk for psychiatric disorders in siblings of individuals with BPD

Relation to proband	Full sibling		Maternal half-sibling		Paternal half-sibling		Adopted away biological sibling		Adopted non-biological sibling	
	RR	95%CI	RR	95%CI	RR	95%CI	RR	95%CI	RR	95%CI
Schizophrenia	2.8	2.5-3.0	1.3	0.9-1.9	1.6	1.2-2.1	1.5	0.5-4.9	0.8	0.2-3.3
Depression	2.1	2.0-2.2	1.5	1.3-1.7	1.2	1.0-1.3	2.1	1.0-4.2	1.2	0.8-1.9
Anxiety disorders	1.8	1.7-1.8	1.3	1.2-1.5	1.2	1.1-1.3	2.1	1.2-3.9	1.1	0.7-1.6
ADHD	2.4	2.1-2.7	1.5	1.3-1.9	1.2	1.0-1.4	1.5	0.7-2.8
Drug abuse	1.7	1.6-1.8	1.3	1.1-1.5	1.2	1.0-1.3	2.6	1.3-5.2	1.5	0.9-2.4
Personality disorders	2.2	2.1-2.4	1.5	1.3-1.8	1.2	1.0-1.4	2.2	1.0-5.0	1.1	0.6-1.8
ASD	2.6	2.3-3.0	1.6	1.2-2.1	1.2	1.0-1.6	1.5	0.6-4.0

Abbreviation: Ellipsis, not applicable.

Table 4. Estimated variance components of the liability of psychiatric disorders

Psychiatric disorder	Heritability		Non-shared environment		Shared environment	
	Estimates	95%CI	Estimates	95%CI	Estimates	95%CI
BPD	58%	42%-64%	42%	36%-51%	0%	0%-8%
Schizophrenia	76%	69%-83%	24%	17%-33%	0%	0%-0%
Depression	32%	19%-40%	65%	60%-72%	3%	0%-9%
Anxiety disorders	41%	31%-43%	59%	57%-64%	0%	0%-5%
ADHD	64%	52%-71%	36%	29%-44%	0%	0%-0%
Drug abuse	58%	46%-71%	36%	29%-42%	6%	0%-12%
Personality disorders	53%	41%-57%	47%	43%-54%	0%	0%-0%
ASD	67%	23%-77%	32%	23%-55%	1%	0%-22%

Figure 1. Tetrachoric correlation between BPD and other psychiatric disorders

