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

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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, depression, anxiety disorders, attention-deficit hyperactivity disorder, drug abuse, personality disorders, and autism spectrum disorders.

Methods: A population-based cohort was created by linking several Swedish national registers. A total of 54,723 individuals with BPD were identified among 8,141,033 offspring from 4,149,748 nuclear families. The relative risk of BPD in relatives and the co-occurrence of other psychiatric disorders in patients with BPD 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 9.7–22.9 in individuals with BPD 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), and was 0.44 for schizophrenia.

Conclusions: The high familial risks provide 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 that BPD is in both the mood and psychotic spectra, but possibly more closely related to mood disorders.

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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 risks of BPD and explore the etiologic overlaps with other psychiatric disorders by using data from the total Swedish population (about 9 million individuals). Specifically, we aimed to: (i) provide improved estimates of familial risks and heritability for BPD; (ii) study the individual and familial co-occurrence of other psychiatric disorders for BPD; and (iii) 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 the 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 and 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 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 had biological relationships (grandparents, uncles or aunts) with their adoptee and siblings who had 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 who died or emigrated before 25 years of age. 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 five 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 patients with BPD 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 *Supplementary Table 1*).

Statistical analysis

We refer to relative risk (RR) for the measure of familial risks and co-occurrence risk throughout the paper. To estimate familial risks for BPD, we estimated the risk for relatives of individuals with BPD compared to that of 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 with 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, 10 controls were randomly selected for each BPD proband with the same strategy (i.e., matched on sex, year of birth, and living area when the proband was diagnosed BPD; and to be alive, reside in Sweden, and have no history of BPD before the date of the first diagnosis of the matched proband). Selection measures for estimates of the familial co-occurrence risks were also the same as that in the familial risks 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 OpenMx package (23, 24) in the R software (25). Then we used a bivariate Cholesky decomposition (26) to calculate the tetrachoric correlations to estimate the relative contributions of genetic and environment elements in common with BPD to the liability of another disorder (see *Supplementary Data 1* 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 five 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).

Similar to prior results, the relatives of individuals with BPD had increased risks for BPD, and risks decreased with the distance of the biological relationships ($RR_{first\text{-}degree}$ = 5.8–7.9 > $RR_{second\text{-}degree}$ = 2.2–3.3 > $RR_{third\text{-}degree}$ = 1.6). Despite the lack of sex differences for the risks in first-degree relatives, male relatives of male probands tended 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

Table 1. Familial risks for bipolar disorder (BPD) in relatives of individuals with BPD

Relation to proband	Grouping	Relatives with BPD: With BPD probands, n (%)	Relatives with BPD: Matched population controls, n (%)	RR	95% CI
Biological relationship					
First-degree					
Parent	Total	2,119 (3.1)	3,269 (0.5)	6.7	6.3–7.0
	Father	789 (2.4)	1,153 (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	1,330 (3.9)	2,123 (0.6)	6.4	6.0–6.8
	Male offspring–mother	546 (3.9)	891 (0.6)	6.3	5.8–7.0
	Female offspring–mother	784 (3.9)	1,248 (0.6)	6.5	6.0–7.0
Offspring	Total	2,119 (2.8)	3,216 (0.4)	6.8	6.4–7.1
	BPD in father	785 (2.8)	1,157 (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	1,334 (2.8)	2,065 (0.4)	6.6	6.2–7.1
	Mother proband–son	548 (2.2)	864 (0.4)	6.5	5.9–7.1
	Mother proband–daughter	786 (3.4)	1,267 (0.6)	6.4	5.9–6.9
Sibling	Total	2,142 (3.9)	3,429 (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)	1,209 (0.8)	6.6	5.9–7.2
Second-degree					
Grandparent	Total	404 (0.9)	1,797 (0.4)	2.3	2.0–2.5
Uncle/aunt	Total	620 (1.5)	2,693 (0.7)	2.3	2.1–2.5
Grandchild	Total	407 (0.5)	1,713 (0.2)	2.4	2.1–2.6
Nephew/niece	Total	619 (0.7)	2,697 (0.3)	2.3	2.1–2.5
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)	3,358 (0.4)	1.6	1.4–1.7
Unrelated					
Mating partner	Total	407 (1.0)	1,928 (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

CI = confidence interval; RR = relative risk.

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 that of paternal half-siblings but also higher than that of 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 = 578), or biological parents whose adopted-away children had BPD (n = 503) also had an increased risk of being diagnosed with BPD [RR = 5.0 (2.9–8.5) and 4.5 (2.6–7.6), respectively]. 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 been diagnosed with schizophrenia (n = 3,320), 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 depression is part of BPD and not a comorbid condition. However, we did include the estimates of RR for depression for relatives of BPD individuals, since relatives who were diagnosed with BPD were excluded. It is notable that about one-half of the patients with schizoaffective disorder were also diagnosed with BPD (n = 4,332 from a total of 10,750 individuals with schizoaffective disorder). Thus, we do not show the results for schizoaffective disorder, because it is questionable that these are distinguishable disorders in our sample.

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 *Supplementary Tables 2–8*). 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 *Supplementary Table 9*). 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 *Supplementary Tables 2–8*). 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 *Supplementary Table 8*).

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 can be found in *Supplementary Tables 10–11*). 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 one-half of the correlations overall, but higher for schizophrenia (64%), ADHD (67%) and ASD (65%).

Discussion

In this population-based study with the largest BPD cohort ever published, we found: (i) strong familial risks for BPD; (ii) strong co-occurrence risks for schizophrenia, anxiety disorders, ADHD, drug abuse, personality disorders, and ASD in individuals with BPD; (iii) 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; and (iv) that associations between BPD and these psychiatric disorders are to a large

Table 2. Risk for psychiatric disorders for individuals with bipolar disorder (BPD)

Diagnosis	Individuals with BPD n (%)[a]	Matched population controls without BPD n (%)	RR	95% CI
Schizophrenia	3,320 (6.1)	2,320 (0.4)	15.3	14.5–16.2
Anxiety disorders	14,563 (26.8)	19,614 (3.6)	10.2	9.9–10.4
ADHD	2,064 (3.8)	1,105 (0.2)	21.8	20.2–23.6
Drug abuse	5,733 (10.6)	6,761 (1.2)	9.7	9.3–10.0
Personality disorders	8,473 (15.6)	4,558 (0.8)	22.9	22.0–23.8
ASD	776 (1.4)	615 (0.1)	13.2	11.9–14.7

ADHD = attention-deficit hyperactivity disorder; ASD = autism spectrum disorders; CI = confidence interval; RR = relative risk;
[a]There were 54,328 individuals (of the total 54,723) with BPD who had available county records for county matching.

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

	Relation to proband									
	Full sibling		Maternal half-sibling		Paternal half-sibling		Adopted-away biological sibling		Adopted non-biological sibling	
Psychiatric disorder	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	NA	NA	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	NA	NA	1.5	0.6–4.0

ADHD = attention-deficit hyperactivity disorder; ASD = autism spectrum disorders; CI = confidence interval; NA = not applicable; RR = relative risk.

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

	Heritability		Non-shared environment		Shared environment	
Psychiatric disorder	Estimates (%)	95% CI	Estimates (%)	95% CI	Estimates (%)	95% CI
Bipolar disorder	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

CI = confidence interval; ADHD = attention-deficit hyperactivity disorder; ASD = autism spectrum disorders.

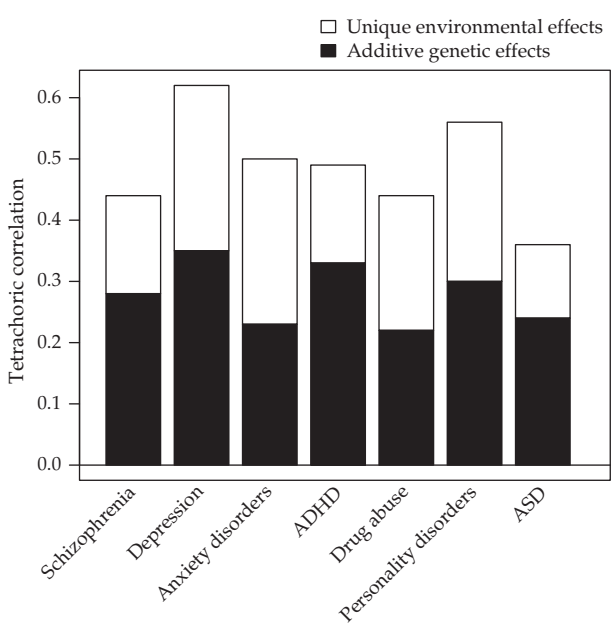

Fig. 1. Tetrachoric correlation between bipolar disorder and other psychiatric disorders. ADHD = attention-deficit hyperactivity disorder; ASD = autism spectrum disorders.

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 odds ratio (6.96) from a meta-analysis (27). 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 sibling are likely to be exposed to similar degrees 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%) (28) and the estimate from a review of psychiatric disorders (75%) (29), 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 that of another large genetic study (1) 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 an up to 100-fold increase in sample size (30-fold increase in our sample) and provide more credible assumptions about genetic covariance (30). However, sibling models might slightly underestimate the heritability in situations like assortative mating. Our estimate is lower than that from twin studies (11, 28). 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 (2, 15), and on co-occurrence with anxiety disorders—consistent with the results in Systematic Treatment Enhancement Program for Bipolar Disorder projects (31). Co-occurrences with ADHD (32, 33), personality disorders (34), drug abuse (35, 36), and ASD (37) 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 those of recently published high-quality GWAS studies (1, 2, 38). Here we also estimated the magnitude of the tetrachoric correlations (ranging between 0.37 and 0.62; see *Supplementary Table 11*), and 48–67% of these correlations were explained by shared genetic factors. Both familial co-occurrences 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 (39). 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* (39). 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 (33–52%) between BPD and other psychiatric disorders. Prenatal or perinatal complications or history of substance abuse are likely to contribute to this kind of environmental source (40).

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). Secondly, in agreement with a previous study (41), we identified a relatively high degree of assortative mating. Thirdly, RRs of co-occurrence between BPD and ASD were rather high among both biological and adoptive parents of BPD adoptees (see *Supplementary Table 8*). Although our study is the largest adoption study presented, the limited sample size and inherent assumptions (e.g., selective placement and age at adoption) constrain the possibility of drawing 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. (i) 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). (ii) 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 has BPD but is later diagnosed with schizophrenia, 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 diagnoses (i.e., when estimating the familial co-occurrence risk between BPD and another diagnoses like drug abuse, we excluded BPD probands ever diagnosed with drug abuse and siblings ever diagnosed with BPD) (*Supplementary Table 9*), and RRs remained significant. (iii) Diagnostic bias could occur if physicians were influenced by family psychiatric history in diagnostic assessments, although adoptive relationships are likely to avoid such bias. (iv) Our study used clinical diagnoses made by treating physicians. Although the specificity of these diagnoses has been validated, it is possible that the sensitivity and negative predictive value for BPD are weaker, especially in the early study period when BPD was less recognized if clinical features did not include classical grandiose-euphoric mania with psychotic features, i.e., classical bipolar I disorder. (v) In a similar vein, our study reported estimates for BPD without separating BPD subtypes because of the limited information in the National Patient Register. Future investigation of the familial risks and heritability for bipolar I and bipolar II disorder would advance knowledge and further inform the etiology for BPD and nosology for psychiatric disorders. (vi) 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 individuals with BPD, but are 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 those of recent molecular genetic studies (1, 2, 38) showing abundant pleiotropy of gene variants in psychiatry. Moreover, we showed that BPD is highly correlated with depression, highlighting the communality between BPD and depression. The precision of estimates of familial risks and the magnitude of genetic influences provides crucial parameters (i.e., estimates of the strength of genetic transmission and quantification of risk at the population level) for the design and interpretation of genetic studies and the 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

The authors of this paper do not have any commercial associations that might pose a conflict of interest in connection with this manuscript.

References

1. Cross-Disorder Group of the Psychiatric Genomics Consortium, Lee SH, Ripke S et al. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nat Genet 2013; 45: 984–994.
2. Cross-Disorder Group of the Psychiatric Genomics Consortium. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. Lancet 2013; 381: 1371–1379.
3. Steinberg S, de Jong S, Mattheisen M et al. Common variant at 16p11.2 conferring risk of psychosis. Mol Psychiatry 2014; 19: 108–114.
4. Lichtenstein P, Yip BH, Bjork C et al. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. Lancet 2009; 373: 234–239.
5. Craddock N, Sklar P. Genetics of bipolar disorder. Lancet 2013; 381: 1654–1662.
6. Kendler KS, Pedersen N, Johnson L, Neale MC, Mathe AA. A pilot Swedish twin study of affective illness, including hospital- and population-ascertained subsamples. Arch Gen Psychiatry 1993; 50: 699–700.
7. Wender PH, Kety SS, Rosenthal D, Schulsinger F, Ortmann J, Lunde I. Psychiatric disorders in the biological and adoptive families of adopted individuals with affective disorders. Arch Gen Psychiatry 1986; 43: 923–929.
8. Weissman MM, Gershon ES, Kidd KK et al. Psychiatric disorders in the relatives of probands with affective

disorders. The Yale University-National Institute of Mental Health Collaborative Study. Arch Gen Psychiatry 1984; 41: 13–21.
9. Smoller JW, Finn CT. Family, twin, and adoption studies of bipolar disorder. Am J Med Genet C Semin Med Genet 2003; 123C: 48–58.
10. Merikangas K, Yu K. Genetic epidemiology of bipolar disorder. Clin Neurosci Res 2002; 2: 127–141.
11. Barnett JH, Smoller JW. The genetics of bipolar disorder. Neuroscience 2009; 164: 331–343.
12. Tsuang MT, Winokur G, Crowe RR. Morbidity risks of schizophrenia and affective disorders among first degree relatives of patients with schizophrenia, mania, depression and surgical conditions. Br J Psychiatry 1980; 137: 497–504.
13. Taylor MA, Berenbaum SA, Jampala VC, Cloninger CR. Are schizophrenia and affective disorder related? preliminary data from a family study. Am J Psychiatry 1993; 150: 278–285.
14. Cardno AG, Rijsdijk FV, Sham PC, Murray RM, McGuffin P. A twin study of genetic relationships between psychotic symptoms. Am J Psychiatry 2002; 159: 539–545.
15. International Schizophrenia Consortium, Purcell SM, Wray NR et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature 2009; 460: 748–752.
16. Larsson H, Ryden E, Boman M, Langstrom N, Lichtenstein P, Landen M. Risk of bipolar disorder and schizophrenia in relatives of people with attention-deficit hyperactivity disorder. Br J Psychiatry 2013; 203: 103–106.
17. Sullivan PF, Magnusson C, Reichenberg A et al. Family history of schizophrenia and bipolar disorder as risk factors for autism. Arch Gen Psychiatry 2012; 69: 1099–1103.
18. Sellgren C, Landen M, Lichtenstein P, Hultman CM, Langstrom N. Validity of bipolar disorder hospital discharge diagnoses: file review and multiple register linkage in Sweden. Acta Psychiatr Scand 2011; 124: 447–453.
19. Inc SI. SAS® 9.3 Intelligence Platform: Migration Guide. Cary, NC: SAS Institute Inc., 2011.
20. Frisell T, Lichtenstein P, Langstrom N. Violent crime runs in families: a total population study of 12.5 million individuals. Psychol Med 2011; 41: 97–105.
21. Kyaga S, Landen M, Boman M, Hultman CM, Langstrom N, Lichtenstein P. Mental illness, suicide and creativity: 40-year prospective total population study. J Psychiatr Res 2013; 47: 83–90.
22. Neale MC, Maes HHM. Methodology for Genetic Studies of Twins and Families. Dordrecht: Kluwer Academic Publishers B.V., 2004.
23. Boker SM, Neale MC, Maes HH et al. OpenMx: an open source extended structural equation modeling framework. Psychometrika 2011; 76: 306–317.
24. Boker SM, Neale MC, Maes HH et al. OpenMx 1.3 User Guide. Charlottesville, VA: The OpenMx Project, 2012.
25. Team RDC. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing, 2013.
26. Loehlin JC. The Cholesky approach: a cautionary note. Behav Genet 1996; 26: 65–69.
27. Wozniak J, Faraone SV, Martelon M, McKillop HN, Biederman J. Further evidence for robust familiality of pediatric bipolar I disorder: results from a very large controlled family study of pediatric bipolar I disorder and a meta-analysis. J Clin Psychiatry 2012; 73: 1328–1334.
28. Bienvenu OJ, Davydow DS, Kendler KS. Psychiatric 'diseases' versus behavioral disorders and degree of genetic influence. Psychol Med 2011; 41: 33–40.
29. Sullivan PF, Daly MJ, O'Donovan M. Genetic architectures of psychiatric disorders: the emerging picture and its implications. Nat Rev Genet 2012; 13: 537–551.
30. Frisell T, Pawitan Y, Langstrom N, Lichtenstein P. Heritability, assortative mating and gender differences in violent crime: results from a total population sample using twin, adoption, and sibling models. Behav Genet 2012; 42: 3–18.
31. Simon NM, Otto MW, Wisniewski SR et al. Anxiety disorder comorbidity in bipolar disorder patients: data from the first 500 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry 2004; 161: 2222–2229.
32. Singh MK, DelBello MP, Kowatch RA, Strakowski SM. Co-occurrence of bipolar and attention-deficit hyperactivity disorders in children. Bipolar Disord 2006; 8: 710–720.
33. Ryden E, Thase ME, Straht D, Aberg-Wistedt A, Bejerot S, Landen M. A history of childhood attention-deficit hyperactivity disorder (ADHD) impacts clinical outcome in adult bipolar patients regardless of current ADHD. Acta Psychiatr Scand 2009; 120: 239–246.
34. Garno JL, Goldberg JF, Ramirez PM, Ritzler BA. Bipolar disorder with comorbid cluster B personality disorder features: impact on suicidality. J Clin Psychiatry 2005; 66: 339–345.
35. Regier DA, Farmer ME, Rae DS et al. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. JAMA 1990; 264: 2511–2518.
36. Cassidy F, Ahearn EP, Carroll BJ. Substance abuse in bipolar disorder. Bipolar Disord 2001; 3: 181–188.
37. Joshi G, Biederman J, Petty C, Goldin RL, Furtak SL, Wozniak J. Examining the comorbidity of bipolar disorder and autism spectrum disorders: a large controlled analysis of phenotypic and familial correlates in a referred population of youth with bipolar I disorder with and without autism spectrum disorders. J Clin Psychiatry 2013; 74: 578–586.
38. Serretti A, Fabbri C. Shared genetics among major psychiatric disorders. Lancet 2013; 381: 1339–1341.
39. Nasrallah HA. Pleiotropy of psychiatric disorders will reinvent DSM. Curr Psychiatry 2013; 12: 2.
40. Plomin R, Daniels D. Why are children in the same family so different from one another? Int J Epidemiol 2011; 40: 563–582.
41. Mathews CA, Reus VI. Assortative mating in the affective disorders: a systematic review and meta-analysis. Compr Psychiatry 2001; 42: 257–262.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Methods.
Table S1. Definition of psychiatric disorders.
Table S2. Risk for schizophrenia in relatives of individuals with BPD.
Table S3. Risk for depression in relatives of individuals with BPD.
Table S4. Risk for anxiety disorders in relatives of individuals with BPD.
Table S5. Risk for ADHD in relatives of individuals with BPD.
Table S6. Risk for drug abuse in relatives of individuals with BPD.

Table S7. Risk for personality disorders in relatives of individuals with BPD.
Table S8. Risk for ASD in relatives of individuals with BPD.
Table S9. Risk for psychiatric diseases in full siblings (without BPD) of BPD individuals (without another psychiatric disorder).
Table S10. Parameter estimates of the Cholesky factors for BPD and psychiatric disorders in bivariate Cholesky decomposition model.
Table S11. Tetrachoric correlation between BPD and psychiatric disorders in bivariate Cholesky decomposition model.