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A population-based heritability estimate of bipolar disorder – In a Swedish twin sample

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ABSTRACT

Twin- and family studies have shown variations in the heritability estimates of bipolar disorder (BPD). The current study uses an updated statistical methodology for heritability estimation in BPD by taking available time of follow-up into account while controlling for co-variates. We identified monozygotic and dizygotic same and different sex twins with BPD (n = 804) or unaffected from BPD (n = 91,604) from the Swedish Twin Register and the National Patient Register. We applied structural equational modeling with inversed probability weighting to estimate the heritability, taking into account censoring and truncation of data. Sex-limitation models were constructed to analyze qualitative or quantitative sex-differences in BPD. Heritability for BPD was 60.4% (95% Confidence Interval: 50.3–70.5) after age, sex, left-hand truncation and censoring of the data was taken into account. A larger proportion of females were affected from BPD (females 62.2%; males 37.8%, $p < 0.001$), but no sex-difference in BPD heritability was found, nor any sex-specific genetic effects. We demonstrated a robust 60% heritability for BPD with no evidence of sex-specific genetic effects on disease liability.

1. Introduction

Bipolar disorder (BPD) is a psychiatric disorder characterized by recurrent mood swings with episodes of mania or hypomania and depression (Grande et al., 2016). The lifetime prevalence for the subtypes of BPD type I (BPD I, manic and depressive episodes), and BPD type II (BPD II, hypomanic and depressive episodes) is around 1% (Grande et al., 2016; Merikangas et al., 2011; Phillips and Kupfer, 2013). Typically, age at onset occurs in the early 20s (Grande et al., 2016; Merikangas et al., 2011), but there may be a delay between illness onset and diagnosis due to difficulties to predict whether a depressive episode will develop into BPD (Baldessarini et al., 2007; Phillips and Kupfer, 2013). BPD is heritable, and twin- and family studies have shown variations in concordance rates as well as heritability estimates ranging from 58% to 87% (see Table 1 for an overview of previous twin studies, Cardno et al., 1999; Edvardsen et al., 2008; Kendler et al., 1995; Kieseppa et al., 2004; McGuffin et al., 2003; Song et al., 2015). However, genome-wide association studies (GWAS) have estimated the heritability in BPD to around 20–40% (Lee et al., 2011; Manolio et al., 2009; Pettersson et al., 2018). Similar patterns of lower GWAS based heritability estimates as compared to the traditional twin modeling have been observed for other disorders such as autism (Anney et al., 2017) and schizophrenia (Cross-Disorder Group of the Psychiatric Genomics, 2013). One possible explanation to the discrepancy is that the heritability estimates derived from GWAS are based on common genetic variation and do not take into account rare genetic variants such as deletions or duplications of the genome that may affect the risk for disease (Geschwind and Flint, 2015).

Sex-specific differences in the genetic architecture for psychiatric disorders are of importance (Ober et al., 2009), but it is not known whether sex differences contribute to the genetic risk in BPD. Epidemiological studies have shown that the incidence for BPD is higher in females than in males (Ferrari et al., 2016; Pedersen et al., 2014), while other studies found no differences between sexes (Diflorio and Jones, 2010; Merikangas et al., 2011). In one study, males had an earlier age at onset for BPD (Kennedy et al., 2005), while another study found no sex-specific difference related to age at onset (Kawa et al., 2005). The incidence of BPD I was found to be greater in males and the incidence of

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Table 1
Casewise concordance rates and heritability estimates in previous twin studies on bipolar disorder (BPD).

Study	Concordant BPD pairs, n		Casewise concordance rate		Heritability estimates			Diagnostic methods and types of diagnoses
	MZ	DZ	MZ	DZ	A	C	E	
Song et al. (2015)	–	–	–	–	0.58	0	0.42	Register study based on ICD-diagnoses for BPD, not including schizoaffective disorder.
Edvardsen et al. (2008)	8	2	0.38	0.08	0.77	–	0.23	DSM-III-R criteria by interviews. Rates presented for BPD type I and BPD type II.
Kieseppa et al. (2004)	6	2	0.75	0.11	0.67	0.25	0.08	DSM-IV criteria by interviews. Rates presented for broad affective spectrum including schizoaffective disorder.
McGuffin et al. (2003)	30	37	0.40	0.05	0.85	0	0.15	DSM-III-R criteria by interviews. Rates presented for BPD, narrow definition.
Cardno et al. (1999)	11	3	0.44	0.09	0.87	–	0.13	DSM-III-R criteria by interviews. Rates presented for diagnosis of mania and hypomania.
Kendler et al. (1995)	–		0.39	0.05	0.79	–	0.21	Register information and questionnaire, ICD-8. Rates presented for bipolar illness, narrow spectrum.
Bertelsen et al. (1977)	32	11	0.58*	0.20*	–	–	–	Diagnosis obtained from interviews. Results presented for the diagnosis manic-depressive disorder.

BPD = Bipolar disorder, MZ = Monozygotic, DZ = Dizygotic, A = heritability, C = shared environment, E = unique environment, ICD = International Classification of Diseases, DSM = Diagnostic and Statistical Manual of Mental Disorders, R = Revised.

Bertelsen, A., Harvald, B., Hauge, M., 1977. A Danish twin study of manic-depressive disorders. Br J Psychiatry 130, 330–351.
Cardno, A.G., Marshall, E.J., Coid, B., Macdonald, A.M., Ribchester, T.R., Davies, N.J., Venturi, P., Jones, L.A., Lewis, S.W., Sham, P.C., Gottesman, II, Farmer, A.E., McGuffin, P., Reveley, A.M., Murray, R.M., 1999. Heritability estimates for psychotic disorders: the Maudsley twin psychosis series. Arch Gen Psychiatry 56 (2), 162–168.
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Kendler, K.S., Pedersen, N.L., Neale, M.C., Mathe, A.A., 1995. A pilot Swedish twin study of affective illness including hospital- and population-ascertained subsamples: results of model fitting. Behav Genet 25 (3), 217–232.
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Song, J., Bergen, S.E., Kuja-Halkola, R., Larsson, H., Landen, M., Lichtenstein, P., 2015. Bipolar disorder and its relation to major psychiatric disorders: a family-based study in the Swedish population. Bipolar Disord 17 (2), 184–193.

* Pairwise concordance rates.

BPD II was greater in females (Merikangas et al., 2011), and females had a higher risk for rapid cycling over time (Erol et al., 2015). Studies have also found sex-differences in brain structures (Mitchell et al., 2018; Shi et al., 2018) and neurocognitive function in BPD (Tournikioti et al., 2017).

Using monozygotic (MZ) and dizygotic (DZ) twin pairs is a powerful way to estimate the proportion of genetic variance that contribute to disease susceptibility (Boomsma et al., 2002). The standard statistical method to estimate the heritability by using twins is the liability-threshold model (Neale MC, 2004). However, the liability-threshold model does not take into account individuals that are still at risk for disease at the end of the observation time (i.e., right-censored individuals) which potentially could bias the heritability estimate. Furthermore, individuals with disease-onset before the establishment of the diagnostic registers may introduce a problem with left-truncation. One way to deal with the problems of truncation of data and censored observations is to include the model of inverse probability weighting (IPW, Holst et al., 2016a,b) as has been previously used for estimating the heritability of schizophrenia (Hilker et al., 2018), but also in the research field of cancer (Mucci et al., 2016).

From a translational research perspective, that includes future molecular genetic studies it is of importance to achieve as precise heritability estimates as possible taking into account censoring, truncation mechanisms as well as potential sex-differences. The purpose of this study is to provide more accurate heritability estimates and to analyze the influence from sex on the genetic liability for BPD. We here use a nation-wide sample of same-sex MZ and DZ twins as well as different-sex DZ twins identified through the Swedish Twin Register (STR) and the National Patient Register (NPR). We apply an updated statistical method taking into account truncation of data and censoring aspects. First, we estimate the concordance rate and heritability of BPD taking censoring into account. Second, we investigate the potential influence of quantitative (i.e., different heritability estimates between males and females) and qualitative (i.e., different genes that contribute to the heritability estimates between males and females) sex-specific effects on the genetic liability for BPD.

2. Methods

2.1. Ethics

Ethical approval was granted by the Regional Ethics Review Board in Stockholm.

2.2. Study population and Swedish national registers

This is a population-based twin study with information retrieved from STR (Magnusson et al., 2013) on all twins in Sweden that were born between 1940 and 2005. The total study population consisted of 92,408 twin individuals that were followed from 1967 until December 31, 2012. The STR regularly obtains register information from the National Board of Health and Welfare through the unique personal identity number which is used as a key identifier when linking several Swedish registers (Ludvigsson et al., 2009). In this study, we retrieved diagnostic information from the NPR which started in 1964 and contains all inpatient diagnoses, and 75–80% of all outpatient diagnoses from 1987 and 2001 respectively (Ludvigsson et al., 2011). The NPR was previously validated, with a positive predictive value of 85–95% (Ludvigsson et al., 2011). Information on sex and year of birth was retrieved from the Swedish Medical Birth Register (National Board of Health and Welfare), and information on death was retrieved from the Swedish Cause of Death Register (Brooke et al., 2017).

2.3. Disease classifications

Discharge diagnoses were recorded in the NPR according to the

Swedish versions of the International Classification of Diseases (ICD) (Smedby B, 2006) In this study, BPD was defined as the lifetime diagnosis in the ICD-10 (F30, F31), ICD-9 (296) and ICD-8 (296). The included cases in this study correspond to BPD I, BPD II and BPD unspecified. The bipolar diagnoses in the NPR was previously validated (Sellgren et al., 2011). In addition, our research group conducted a study in which twins with a register diagnosis of BPD from the NPR went through a clinical interview procedure showing that 92% of the twins were correctly diagnosed as BPD (Johansson et al., 2019). Age at onset for BPD was defined as the age when the BPD diagnosis first appeared in the register.

2.4. Zygostiy determination

In the STR zygosity is mainly ascertained through questions based on intra-pair physical similarities in childhood (Magnusson et al., 2012). The accuracy of similarity-based zygosity assignment has been found to be around 98% in the STR and an independent validity test of the similarity-based zygosity in same sex DZ pairs using genotype data found a corresponding accuracy of 97.4% (95% CI: 96.6–98.2%, Magnusson et al., 2012).

2.5. Statistical analyses

Baseline descriptive statistics included frequencies and percentages for count variables and mean and standard deviation (SD) for continuous variables. Pearson chi-square test or Student's *t*-test were applied to investigate differences between individuals with and without any BPD diagnosis. Age at onset is presented in individuals born in 1969 or later as those individuals would be 18 years or younger in 1987 when the NPR had reached a satisfactory nation-wide coverage of all inpatient diagnoses. We estimated the casewise concordance rates with 95% confidence intervals (CIs) among MZ and DZ twins. The casewise rates are applicable to twin individuals, and not twin pairs, and may be compared to the prevalence or the cumulative incidence in a population (McGue, 1992). To measure the degree of agreement in diagnostic status among the twin pairs, tetrachoric correlations were estimated.

There are some assumptions for the twin modeling which need to be considered before applying the structural equation models and these are, in general, twins can be generalizable to the general population, gene-environment interactions are minimal for the trait of interest, the assumption of random mating in the population. Further assumptions are that common environmental effects are shared to the same extent among MZ and DZ pairs, and for additive genetic effects, the correlation is assumed as 1.0 between MZ pairs and 0.5 between DZ pairs.

Structural equation models using the liability-threshold approach were applied to estimate the contribution of additive genetic (A), common (or shared) environmental (C) and unique environmental (E) factors to the variance in one trait by minimizing the goodness-of-fit statistic between the observed and predicted covariance matrices. When estimating the heritability of BPD it is essential to deal with the bias that a large proportion of the study participants are still at risk for developing the disease by the end of follow-up. In survival analysis, this is called censoring, meaning that complete information of the study participants are missing. By using an implementation of IPW (Holst et al., 2016a,b) one can overcome this bias by adding a weight to each complete observation (i.e., cases with the disease and deaths) based on the information from the censored data. To model the correct weights, the follow-up periods needs to be the same in both zygosity groups. Therefore, we can estimate the concordance rates and heritability until the age of the last observed concordant pair in both groups.

We fitted a full ACE model (i.e. a model including A, C, and E sources of variance and covariance) to the data as: 1) crude model, 2) accounted for censoring, 3) accounted for censoring and truncation, 4) adjusted for sex and birth year, 5) accounting for censoring and adjusting for sex and birth year and 6) accounting for censoring, adjusting for sex and birth year, and accounting for truncation.

Sex-limitation models (Neale et al., 2006) were constructed to investigate the potential influence of sex-specific effects on the genetic liability to BPD quantitatively (i.e., any differences in the magnitude of heritability between males and females) and qualitatively (i.e., any differences in which genes that contributes to the heritability between males and females). A saturated model was fitted to the data. We proceeded to fit an ACE model with sex-differences and the sex-differences were then subsequently excluded in additional models. We also tested models where influences from C were excluded. We compared these models to the saturated model using likelihood ratio tests, and Akaike information criterion (AIC) was used to identify the most parsimonious model among all models considered. For assumptions testing we used likelihood ratio tests to assess whether prevalence differed by twin order, zygosity, or sex (Supplementary Table 1). The prevalence was not statistically significantly different within sex between twin order and zygosity. However, females had a statistically significantly higher prevalence for BPD than men. Hence, we proceeded to fit quantitative genetic models, where the thresholds (and thus the prevalence) was assumed different by sex.

Data analyses were carried out using the mets-package version 1.2.2 (Holst and Scheike, 2017), and the OpenMx-package version 2.9.6 (Neale et al., 2016) in the software R version 3.4.1 (Team, 2017).

3. Results

3.1. Description of the sample

We followed a total number of 92,408 twin individuals (39,870 complete twin pairs and 12,668 not complete pairs) born between the years of 1940 and 2005. From this cohort we identified 804 (0.9%) individual twins with a diagnosis of BPD and 91,604 unaffected twins (Table 2). Zygosity was unknown in 4350 (4.7%) of the unaffected twins and in 40 (5.0%) of the BPD twins (Table 2). There were more females (500; 62.2%) than males (304; 37.8%) with BPD ($p < 0.001$). A larger proportion of the twins diagnosed with BPD were born between the years 1940–1949 and 1950–1955 than in the other birth year categories ($p < 0.001$, Table 2). There were no statistically significant differences in the proportion of MZ and DZ twin pairs ($p = 0.089$) between the twins with BPD and those who were unaffected, but the proportion of not complete twin pairs was significantly higher in the

Table 2
Sample characteristics.

	Not affected N (%)	Bipolar disorder N (%)	*P*-value[†]
	91,604 (99.1)	804 (0.9)	
Sex			
Male	43,882 (47.9)	304 (37.8)	
Female	47,722 (52.1)	500 (62.2)	< 0.001
Birth year	NA	BP	
1940–1949	17,209 (18.8)	274 (34.1)	
1950–1959	15,052 (16.4)	242 (30.1)	
1960–1969	10,277 (11.2)	96 (11.9)	
1970–1979	10,078 (11.0)	86 (10.7)	
1980–1989	10,728 (11.7)	72 (9.0)	
1990–2005	28,260 (30.9)	34 (4.2)	< 0.001
Zygosity			
MZ	27,830 (30.4)	229 (28.5)	
DZ same sex	30,543 (33.3)	301 (37.4)	
DZ opposite sex	28,881 (31.5)	234 (29.1)	
Unknown	4350 (4.7)	40 (5.0)	0.089
From complete twin pairs			
Not complete	12,526 (13.7)	142 (17.7)	
Complete	79,078 (86.3)	662 (82.3)	0.001

Note: MZ = monozygotic, DZ = dizygotic. Column percentages presented.
[†] P-values from Pearson χ^2-tests.

Table 3
Observed concordance and discordance, complete pairs only.

	Concordant healthy pairs	Discordant pairs	Concordant bipolar pairs	Concordance rate (95% CI)	Tetrachoric correlation (95% CI)
MZ	12,574	153	21	0.22 (0.14–0.29)	0.66 (0.56–0.75)
MZ female	6889	95	16	0.25 (0.15–0.35)	0.69 (0.58–0.80)
MZ male	5684	58	5	0.15 (0.03–0.26)	0.58 (0.39–0.77)
DZ	25,066	408	17	0.08 (0.04–0.11)	0.39 (0.29–0.49)
DZ female	6894	152	7	0.08 (0.03–0.14)	0.37 (0.21–0.54)
DZ male	6672	98	4	0.08 (0.01–0.15)	0.40 (0.19–0.60)
DZ female-male	11,500	158	6	0.07 (0.02–0.12)	0.40 (0.23–0.56)

Note: CI = confidence interval, MZ = monozygotic, DZ = dizygotic.

pairs affected from BPD ($p < 0.001$, Table 2). Males had a significantly younger BPD onset age than females in those who were born in 1969 or later (males: mean 24.1 years, SD 8.3; females: mean 27.5 years SD 7.4, $p = 0.003$).

3.2. Concordance rates and heritability for BPD

The casewise concordance rate and tetrachoric correlations were higher in magnitude in the MZ twins compared with the DZ twins (Table 3), and the casewise concordance rate for MZ and DZ twins over time were also well above the cumulative incidence for BPD (Fig. 1), indicating genetic influences. We fitted an ACE liability threshold model to the data using different approaches of handling truncation and censoring (Table 4). When we compared the "traditional" model adjusting for sex and birth year (Model 4, Table 4), with the present model which in addition to adjusting for sex and birth year accounted for censoring and truncation of data (Model 6, Table 4), the heritability estimates changed from 56.7% (Model 4, Table 4) to 60.4% (Model 6). Overall, the estimates changed very little when the full model (Model 6, Table 4) was compared with the 'traditional' model (Model 4, Table 4). All models yielded non-significant estimates for the common environment (C, Table 4).

3.3. Sex-differences in the genetic liability for BPD

We found that a significantly larger proportion of the females were affected from BPD (Table 2) and MZ females had a higher tetrachoric correlation for BPD than MZ males (Table 3). In the full ACE sex-limitation model (not accounting for truncation and censoring) the A, C, and E estimates differed somewhat between females and males, but the CIs overlapped throughout. There was no indication of qualitative sex differences. All investigated models had a statistically non-significant reduction in fit compared to the saturated model. Among all models, the AE model without any sex-differences was the best-fitting model according to AIC. In the AE model common genetic influences accounted for 65.6% of the variance in liability for BPD in both sexes, and unique environment accounted for 34.4% (Table 5).

Overall, the analysis revealed no significant sex-differences in the genetic liability for BPD and no significant differences regarding the heritability for BPD in males and females (i.e., qualitative or quantitative sex-differences, Table 5, Supplementary Table 2).

4. Discussion

This is the first population-based twin-study estimating the heritability of BPD by using an updated statistical approach in which censoring and the truncation of data was taken into account (Edvardsen et al., 2008; Kendler et al., 1995; Kieseppa et al., 2004; McGuffin et al.,

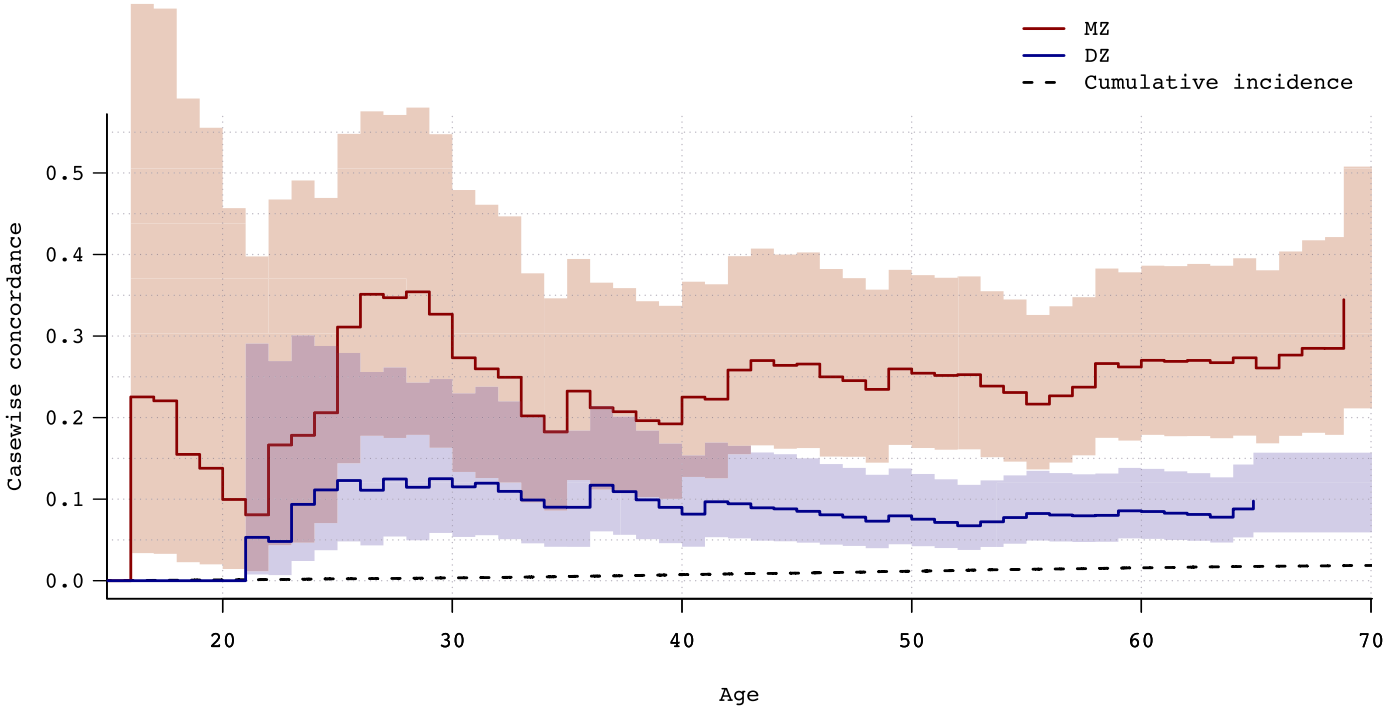

Fig. 1. Casewise concordance rates over age and the cumulative incidence for bipolar disorder. MZ = monozygotic twin, DZ = dizygotic twin.

Table 4
Heritability analyses of bipolar disorder using different approaches of handling truncation and censoring.

	Model 1: Crude analysis	Model 2: Accounted for censoring	Model 3: Accounted for censoring and truncation	Model 4: Adjusted for sex and birth year[†]	Model 5: Accounted for censoring. Adjusted for sex and birth year[†]	Model 6: Accounted for censoring and truncation. Adjusted for sex and birth year[†]
Bipolar disorder						
A	55.6% (28.9–82.3)	54.9% (23.1–86.7)	57.7% (30.1–85.2)	56.7% (28.2–85.2)	50.2% (17.9–82.5)	60.4% (50.3–70.5)
C	11.1% (0.0–33.1)	12.0% (0.0–37.6)	10.4% (0.0–33.2)	6.6% (0.0–29.9)	9.1% (0.0–35.9)	0.0% (0.0–0.0)
E	33.3% (24.4–42.1)	33.1% (22.8–43.5)	32.0% (23.0–40.9)	36.7% (27.2–46.2)	40.7% (30.3–51.0)	39.6% (29.5–49.7)

Note: Prevalences of disorder assumed to be equal between zygosities. Models fitted with "mets"-package in R. A = heritability, C = shared environment, E = unique environment. Confidence intervals have been truncated to not span below 0.

[†] Birth year in categories as in Table 1.

2003; Song et al., 2015). In addition, we applied a sex-limitation model to examine potential qualitative or quantitative sex-differences in the genetic liability for BPD, which to our knowledge has not been analyzed before in such an extensive sample. Our results show that additive genetic effects explained 60.4% of the variance in the liability for BPD, when sex and year of birth was adjusted for and censoring and truncation of data was taken into account. Further, we did not find any evidence for sex-differences in the genetic liability for BPD.

The present casewise concordance rates for the MZ twins and the heritability estimates in BPD were lower as compared to most previous reports. For example, heritability analyses based on British twin data reached heritability estimates above 80% (Cardno et al., 1999; McGuffin et al., 2003), one Finish study reached an estimate of 67% (Kieseppa et al., 2004), and one Norwegian study, yielded heritability estimates ranging from 57% to 77% (Edvardsen et al., 2008). In those previous reports, participants had been recruited for clinical interviews, in contrast to the present study that is based on a population-based sample. Inviting participants for interview procedures should provide more accurate diagnostics as compared to register diagnoses, but could lead to sampling biases, for example over recruitment of severe BPD probands resulting in higher concordance rates. A previous meta-analysis concluded that studies with lower MZ concordance rates may be attributed to the use of register-based data in comparison to when cases are ascertained through e.g. interviews (Walker et al., 1991). Furthermore, in two of the above mentioned studies the diagnoses of affective psychosis (Cardno et al., 1999) or schizoaffective disorder (Kieseppa et al., 2004) were included along with BPD, thus representing different phenotypes than in the present study.

The heritability estimate in the present study is very similar to previous twin or sibling studies on the STR using the "traditional" liability threshold model. In one study from 1995, the heritability was 64% in twins with BPD or depression (Kendler et al., 1995). In the most recent study from 2015, the heritability for BPD was 58%. In this study, the estimates were based on a sample including twins, but also first and second-degree relatives that contributed with most of the information to these estimates (Song et al., 2015). Furthermore, in a study using siblings and half-siblings from the Swedish NPR, heritability estimates of 55% or 59% were achieved for BPD, depending on whether a hierarchal or non-hierarchal diagnostic approach was used (Lichtenstein et al., 2009).

Similar to previous heritability results on schizophrenia (Hilker et al., 2018) we found that the approach taking left-hand truncation and right-hand censoring into account led to similar estimates as with the classical liability-threshold approach. While it should be investigated on a case-by-case basis, we believe that the classic method is likely to be suitable for quantitative genetic analysis within the field of psychiatric research. If the measure of association between relatives, i.e. the tetrachoric correlation, is stable over age (meaning that the heritability is not moderated be age), we should be able to assess individuals at any obtained age and get the same estimate. If we, as in the classical approach, combine measures where individuals had different follow-up times, and accounted for this by adjusting the expected prevalence for birth year (under assumption of little emigration or death), we should obtain approximately the same estimate. Additionally, for most psychiatric disorders, the first observed register diagnosis carries uncertain information on age at onset, because symptoms and impairments are likely to have existed prior to the first diagnosis. Subsequently, even if there exist age-specific heritability, register-based data will result in sources of error. Another factor of importance is changes in prevalence of a disorder in different birth cohorts, which may have an impact on the relation between age at first register diagnosis and the actual date of onset. All of these issues are likely to be present in population-based register data on psychiatric disorders, and the use of diagnostic data for other purposes than lifetimes-ever interpretations should be carried out with caution. This may be the reason why we do not observe different heritability estimates when we compare the IPW liability-threshold approach with the classic liability-threshold approach. These arguments may not be valid for diseases where the time of diagnosis is more informative or where diagnostic practice has not changed over time (e.g. cancer).

Using the NPR to identify diagnosed individuals may lead to problems with left-hand truncation of data, as a proportion of the BPD cases may have been diagnosed before the initiation of the NPR. The NPR started in 1964 for inpatient data in some of the counties in Sweden but was not complete until in 1987. With the present statistical model, we were able to take into account the left-hand truncation; however, when we compared the models with and without accounting for censoring and truncation of data the heritability estimates changed only marginally. This may indicate that the traditional model for heritability estimation is satisfactory for this type of data, but there is also a possibility that left-hand truncation of the data is not a coverage problem in the Swedish NPR.

We found that overall BPD was more prevalent in females, with a male to female prevalence ratio of 0.6, which is partially in line with one recent global study on BPD where the male to female prevalence ratio was 0.8 (Ferrari et al., 2016). Further, in a nation-wide study from Denmark, the cumulative incidence and lifetime risk for BPD was higher in females (Pedersen et al., 2014), although other studies found no sex-differences in the occurrence of BPD (Diflorio and Jones, 2010). Previous studies also indicate that males and females express BPD differently. For example, males were more likely to have BPD I, and females were more likely to have BPD II or the rapid cycling type of BPD (Diflorio and Jones, 2010; Merikangas et al., 2011). Other gender differences observed are that females with BPD had a higher medical comorbidity burden than men with BPD (Patel et al., 2018). Considering the previously observed sex-differences, we analyzed sex-differences in the genetic liability for BPD, but we did not find any strong support for differences. This adds to the view that the genetic risk for BPD is similar between males and females, but the symptoms are expressed differently across sexes, which may possibly influenced by hormonal effects such as estrogen (Meinhard et al., 2014; Nguyen and Low, 2012), but also socio-cultural differences may . Subsequently, variations in the expression of a disease between males and females does not conclude that disparately expressed phenotypes arise from different genetic origins.

Table 5
Standard analyses. Sex-limitation. Adjusted for sex and birth year (same birth year categories as in Table 1).

Model	AIC	p	h^2 female Estimate (95% CI)	c^2 female Estimate (95% CI)	e^2 female Estimate (95% CI)	h^2 male Estimate (95% CI)	c^2 male Estimate (95% CI)	e^2 male Estimate (95% CI)	r_{fm} Estimate (95%CI)
Saturated	−167,800.64	NA	NA	NA	NA	NA	NA	NA	NA
aceQuantQual	−167,811.32	0.723	63.0% (29.3–96.7)	4.5% (0.0–33.2)	32.5% (21.2–43.8)	50.0% (0.0–101.9)	9.0% (0.0–51.9)	41.0% (23.1–58.9)	1.000 (0.149–1.000)
aceQual	−167,814.65	0.816	59.7% (25.8–93.7)	5.0% (0.0–34.1)	35.3% (25.4–45.1)	59.7% (25.8–93.7)	5.0% (0.0–34.1)	35.3% (25.4–45.1)	1.000 (0.231–1.000)
aceQuant	−167,813.32	0.806	63.0% (35.2–90.8)	4.5% (0.0–26.9)	32.5% (21.3–43.8)	50.0% (0.2–99.7)	9.0% (0.0–49.0)	41.0% (23.1–58.8)	1.000 (1.000–1.000)
ace	−167,816.65	0.874	59.7% (31.1–88.3)	5.0% (0.0–28.1)	35.3% (25.5–45.1)	59.7% (31.1–88.3)	5.0% (0.0–28.1)	35.3% (25.5–45.1)	1.000 (1.000–1.000)
aeQuantQual	−167,815.04	0.848	68.2% (57.5–78.8)	0.0% (NA)	31.8% (21.2–42.5)	60.8% (44.7–77.0)	0.0% (NA)	39.2% (23.0–55.3)	1.000 (0.417–1.000)
aeQual	−167,816.47	0.862	65.6% (56.7–74.5)	0.0% (NA)	34.4% (25.5–43.3)	65.6% (56.7–74.5)	0.0% (NA)	34.4% (25.5–43.3)	1.000 (0.433–1.000)
aeQuant	−167,817.04	0.899	68.2% (57.6–78.7)	0.0% (NA)	31.8% (21.3–42.4)	60.8% (44.9–76.7)	0.0% (NA)	39.2% (23.3–55.1)	1.000 (1.000–1.000)
ae	*−167,818.47*	*0.907*	*65.6% (56.8–74.3)*	*0.0% (NA)*	*34.4% (25.7–43.2)*	*65.6% (56.8–74.3)*	*0.0% (NA)*	*34.4% (25.7–43.2)*	*1.000 (1.000–1.000)*

Note: AIC = Akaikes Information Criterion. P = p-value for likelihood ratio test against saturated model. h^2 = heritability. c^2 = shared environment. e^2 = non-shared environment. r_{fm} = the genetic correlation between male and female additive genetics, estimated using opposite sexed dizygotic twin pairs. NA = not applicable, 95% CI, 95% confidence interval. Saturated = saturated model. aceQuantQual = ACE-model with qualitative and quantitative sex differences. aceQual = ACE-model with qualitative sex differences. aceQuant = ACE-model with quantitative sex differences. ace = ACE-model without sex differences. AE-models named similarly. Models fitted with "OpenMx"-package in R. Wald-type confidence intervals using the delta method. Model in italics represent most parsimonious model according to AIC. Confidence intervals have been truncated to not span below 0 or above 100 (when applicable).

The major strength of this study is that we included one of the largest nation-wide twin sample in the world. By using the IPW method, we were able to take into account the truncation of data, time at risk, censoring effects and we were able to adjust for sex and year of birth. Prospectively collected data minimized the risk of recall bias since the data was routinely collected blind to the hypothesis of this study. Limitations include that the proportion of not complete pairs were higher for the BPD twins than not affected individuals. In the incomplete twin pairs, we do not know the status of the co-twin and this could potentially lead to an underestimation of the heritability for BPD, if concordant twin pairs are more likely to be incomplete. As the BPD diagnoses were based on registry data from the NPR and not on e.g. clinical interviews, uncertainties of the diagnoses may have been introduced, particularly considering that the Swedish NPR did not allow us to differentiate between BPD I and BPD II. Other diagnostic difficulties include whether the occurrence of depressive episodes will develop into BPD later on, or whether suicidal death was due to BPD yet undiscovered. However, the IPW method taking censoring into account and adjusting for year of birth have, at least in part, compensated for this. Notably, despite using a nation-wide sample of twins we did not have enough power to detect influences from the common environment (C) in our heritability analysis. To overcome this problem extending the sample size with transnational studies are desirable in future research.

We here present heritability estimates for BPD using a novel approach taking available time of follow-up into account while controlling for sex and year of birth. The BPD heritability of 60.4% was similar to the traditional twin-modeling methods on register-based data. Our data lends, together with studies on first and second-degree relatives, credence to a heritability of 55–60% in BPD. Although the prevalence and symptom profiles of BPD vary between males and females, we did not find any evidence for sex-specific genetic effects on disease liability, which indicates that other than genetic factors contribute to the sex-differences in disease expression. The relatively low heritability estimates for BPD as compared to other psychiatric disorders such as schizophrenia and autism, emphasize the importance of continued research on environmental and protective factors in BPD. The study is of significance for future genetic studies within the field searching for common as well as rare variants of importance for BPD risk.

Declaration of Competing Interest

Dr. Cannon is a consultant to Boehringer Ingelheim Pharmaceuticals and Lundbeck A/S. All other authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplementary materials

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