Article

High Concordance of Bipolar I Disorder in a Nationwide Sample of Twins

Tuula Kieseppä, M.D.

Timo Partonen, M.D., Ph.D.

Jari Haukka, Ph.D.

Jaakko Kaprio, M.D., Ph.D.

Jouko Lönnqvist, M.D., Ph.D.

Objective: The few studies of bipolar I disorder in twins have consistently emphasized the genetic contribution to disease liability. The authors report what appears to be the first twin study of bipolar I disorder involving a population-based twin sample, in which the diagnoses were made by using structured, personal interviews.

Method: All Finnish same-sex twins (N=19,124) born from 1940 to 1957 were screened for a diagnosis of bipolar I disorder as recorded in the National Hospital Discharge Register between 1969 and 1991 or self-reported in surveys of the Finnish Twin Cohort in 1975, 1981, and 1990. Thirty-eight pairs were thereby identified and invited to participate in the study; the participation rate was 68%. Lifetime diagnoses were made by using the Structured Clinical Interview for DSM-IV. The authors calculated probandwise and pairwise concordances and correlations in liability and applied biometrical model fitting.

Results: The probandwise concordance rates were 0.43 (95% CI=0.10 to 0.82) for monozygotic twins and 0.06 (95% CI=0.00 to 0.27) for dizygotic twins. The correlations in liability were 0.85 and 0.41, respectively. The model with no familial transmission was rejected. The best-fitting model was the one in which genetic and specific environmental factors explained the variance in liability, with a heritability estimate of 0.93 (95% CI=0.69 to 1.00).

Conclusions: The high heritability of bipolar disorder was demonstrated in a nationwide population-based twin sample assessed with structured personal interviews.

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Twin studies of bipolar disorder have frequently shown a higher concordance for the disease in monozygotic than in dizygotic twins, indicating the importance of a genetic contribution to the liability to this disorder (1). Probandwise concordance rates have varied from 0.33 to 0.75 for monozygotic twins and from zero to 0.13 for dizygotic twins. Disparities in diagnostic criteria, ascertainment method, or sample compilation among studies can explain this large variability. The few representative studies distinguishing bipolar I disorder from unipolar depressive disorder have all had some methodological limitations (2–4). The role of environmental risk factors, such as labor and delivery complications at birth, has been controversial (5, 6).

Previous twin studies are briefly characterized in Table 1. In the Danish study (2), no structured interview schedule was used, and the diagnoses were made according to Kraepelin's concept, which is less definitive than that in current diagnostic systems. In the Swedish study (3), diagnoses were based on self-assessment through a mailed questionnaire, to which the overall response rate was low. Cardno et al. (4) concentrated on the full range of nonorganic psychoses, and they did not actually diagnose bipolar I disorder but, instead, assessed the lifetime occurrence of affective psychosis, manic type, according to the Research Diagnostic Criteria (7). In another study of the same subjects (8), they used the DSM-IV criteria but combined patients with bipolar I and bipolar II disorder. They reported concordances of 0.40 for monozygotic twins and 0.05 for dizygotic twins and a heritability estimate of 0.85.

Our study involved a representative nationwide twin sample with bipolar disorder diagnosed by using a structured method with face-to-face interviews. Here we report the concordance rates, correlations in liability, and estimates of heritability from biometrical model fitting. Heritability is the proportion of variation of a feature in the population that is accounted for by genetic factors (9). A correlation in liability refers to the extent to which the liability (a whole combination of external and internal circumstances that makes one more or less likely to develop the disease) of a twin predicts the liability of a co-twin (10). We also investigated possible environmental factors, such as prenatal, obstetric, and early childhood complications, that might explain discordance between the twins.

Method

Subjects

Figure 1 shows the compilation of the study sample. Since 1968, Finland's National Hospital Discharge Register has covered all public and private hospitals in this northern European country of approximately 5 million inhabitants. For each stay, the hospital identification code, admission and discharge dates, primary diagnosis, and up to three subsidiary diagnoses are recorded. Before 1987 the diagnoses were coded according to ICD-8, and for 1987–

TABLE 1. Previous Twin Studies of Bipolar Disorder

Study	Subjects		Diagnostic Criteria	Assessment Method	Concordance of Twins	
	Pool	Study Group			Monozygotic	Dizygotic
Bertelsen et al. (2)	Danish Psychiatric Twin Registry same-sex twins born from 1870 to 1910	43 twin pairs having at least one bipolar proband with manic symptoms	Kraepelinian criteria for manic-depressive disorder	Personal semistructured interview	0.80	0.13
Kendler et al. (3)	Swedish Psychiatric Twin Registry and Swedish Twin Registry same-sex twins born from 1886 to 1967	35 twin pairs having at least one proband with narrowly defined bipolar disorder	DSM-III-R for bipolar disorder	Mailed questionnaire	0.38	0.04
Cardno et al. (4)	Maudsley Twin Register	49 twin pairs having at least one proband with lifetime diagnosis of affective psychosis, manic type	Research Diagnostic Criteria for affective psychosis, manic type	Personal structured interview (Schedule for Affective Disorders and Schizophrenia)	0.36	0.07

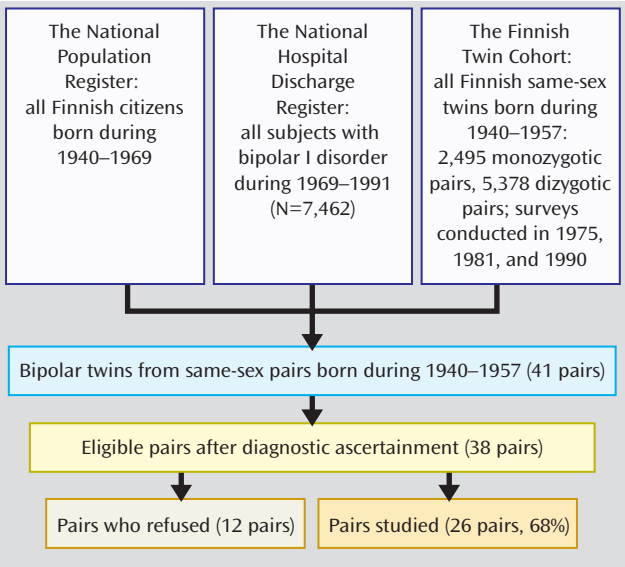
1991 they were coded according to DSM-III-R. From the register we identified all patients with at least one diagnosis of bipolar disorder (ICD-8 code 296.10 or 296.30 or DSM-III-R code 296.4, 296.5, or 296.6). In Finland, the majority of people with a psychotic disorder are hospitalized (11), and the accuracy of the schizophrenia and bipolar disorder diagnoses is over 90% (12, 13).

The National Population Register was computerized in 1968. It records the place of birth, residence, marital status, census data, and first-degree relatives of each Finnish citizen. The register was used to identify parents and siblings of patients born between 1940 and 1969 who had a first bipolar episode before the age of 31 years. The family data allowed us to identify all twins diagnosed with bipolar disorder. We then checked with the Finnish Twin Cohort to locate any additional twins. The older part of the Finnish Twin Cohort, which was used at this stage, comprises all same-sex Finnish twin pairs born before 1958 of which both co-twins were alive in 1967 (14). The Finnish Twin Cohort Study has surveyed the entire older cohort three times, and the lifetime occurrence of any specified mental disorders was asked about on each occasion. The overall response rate was 89% in the 1975 survey, 84% in 1981, and 77% in 1990.

To get information about possible environmental risk factors, we collected records on the study subjects from maternity and child welfare clinics and from obstetric hospitals.

The present study was approved by the Ministry of Social Affairs and Health and the Ethics Committee of the National Public Health Institute. After complete description of the study to the subjects, written informed consent was obtained.

FIGURE 1. Compilation of Twin Sample for Finnish Study of Bipolar Disorder[a]



[a] Bipolar I disorder was diagnosed according to ICD-8 (296.10 or 296.30) before 1987 and according to DSM-III-R (296.4, 296.5, or 296.6) from 1987 onward.

Diagnostic Assessment

After identifying bipolar probands (N=42) from the National Hospital Discharge Register and the twin cohort surveys (14), we requested all available medical records. A specialist (T.P.) and a trainee (T.K.) in psychiatry assessed the primary diagnosis on the basis of these records, blind to each other and using the DSM-IV criteria. The diagnoses were discussed, and when needed, the opinion of a senior psychiatrist (J.L.) was obtained for consensus. No disagreements remained after this procedure. Only patients with bipolar I disorder (N=38) or the bipolar type of schizoaffective disorder (N=1) were regarded as eligible probands. The latter diagnosis was accepted because there is increasing evidence that it shares a genetic background with bipolar I disorder (15).

Each proband was mailed an invitation to participate in the study through the treating clinician. The co-twin was asked to participate through the index subject; only if the proband was deceased was the invitation sent to the co-twin. The second step was to confirm the diagnosis of the probands and to assess any mental disorders of the co-twins by using the Structured Clinical Interview for DSM-IV Disorders (SCID) (16). Interviews were performed by one investigator (T.K.) and tape-recorded whenever the subject gave permission (85% of the subjects). Another author (T.P.) rediagnosed all pairs in which both twins had any psychiatric symptoms, while blind to the diagnostic statement of the interviewer. Field workers in a schizophrenia twin study (17) interviewed one pair, but two of us (T.K. and T.P.) formed the consensus diagnoses. In six cases the SCID information was completed with help from clinicians and family members because the proband or co-twin was deceased.

The final number of studied pairs comprised all those who participated in the SCID (24 pairs) or in the twin cohort surveys in 1975 and 1981 (two pairs). One pair contained two probands; thus, there were 27 probands from 26 twin pairs. Personal interviews were conducted with 22 of the 27 probands and 24 of the 25 co-twins. All of the co-twins diagnosed with psychiatric disorders were personally interviewed.

Five (19%) of the probands were deceased. In three cases the cause was suicide (11%), in one case it was cardiomyopathy with alcoholic withdrawal symptoms and acute mania, and in one case the reason remained unknown. A dizygotic co-twin, who had no psychiatric treatment or symptoms according to registers and relatives, had committed suicide (4%). For the final diagnosis all available information was used, and in cases of death we reviewed the death certificate and forensic examination records. For two pairs

the diagnosis was based solely on medical records and information from the twin cohort survey. The interviews were carried out between 1997 and 2000. The mean follow-up time after the first register diagnosis was 19.8 years (SD=9.0, range=0.5–37.6). The diagnostic procedure is described in more detail elsewhere (13).

Zygosity Determination

The interviewers were blind to zygosity. Zygosity determination was performed only after final diagnostic ascertainment, and it was based on genetic marker analysis in 16 cases of 21 pairs in which both twins were alive and in two cases of five pairs in which either or both twins were deceased. In these cases we received permission from the Ministry of Social Affairs and Health to obtain autopsy tissue samples preserved in pathology departments of local central hospitals. Ten highly polymorphic microsatellite markers (D3S1358, vWA, FGA, AMEL, THO1, TPOX, CSF1PO, D5S818, D13S317, D7S820) used in routine paternity testing procedures at the National Public Health Institute were analyzed. Microsatellites were assayed by automated sequencer. They were scored without knowledge of relationships. For the remaining pairs, zygosity was assessed with questionnaires on resemblance and confusability during childhood (18) and childhood photographs whenever available. The zygosity determination by questionnaire was verified with blood markers previously, and there was 100% agreement between the two classifications (18). In our sample, the zygosity of 15 pairs was assessed by using both questionnaires and genetic markers, with 100% agreement between the two methods.

Data Analysis

To verify the representativeness of the sample, we calculated the annual incidence of first admission for bipolar I disorder derived from this sample. We chose the follow-up period to start in 1976 (as the first Twin Cohort Survey was undertaken in 1975) and end in 1991. The morbid risk estimate for bipolar I disorder was calculated by dividing the ascertained cases of bipolar I disorder by the number of individuals at the beginning of the follow-up.

To determine whether the twins who participated in the study differed from those who refused, we compared clinical and demographic characteristics of these two groups using Fisher's exact test (for sex, occurrence of alcohol abuse or dependence, treatment setting, and death), the chi-square test (for marital status), Student's t test (for age at onset), and the Mann-Whitney rank sum test (for education, number of psychiatric hospitalizations, number of days spent in psychiatric hospitals). All tests were two-tailed. The baseline information was acquired from the Finnish Twin Cohort Surveys and the National Hospital Discharge Register and analyzed as it pertained to the sample in 1991. The follow-up information was obtained from the treating providers and the twins during the contact procedure or was acquired from the National Population Register.

The twin method is predicated on the equal-environment assumption that monozygotic and dizygotic twins share the same environment relevant to the disorder under study (19). We were able to assess the environmental similarity and psychiatric resemblance by using the length of cohabitation and frequency of contact as environmental variables. The information was derived from the Finnish Twin Cohort surveys, and the analysis of difference was made by using the two-tailed Mann-Whitney rank sum test.

The probandwise concordance rates for monozygotic and dizygotic pairs were calculated for narrow and broad diagnostic classifications of the co-twins. The narrowest diagnostic category included only bipolar I disorder, the intermediate category included bipolar I disorder and schizoaffective disorder, bipolar type, and the broad category included the preceding plus bipolar II disorder, bipolar disorder not otherwise specified, cyclothymia, and recurrent major depressive disorder. The occurrence of schizophrenia was also evaluated. We examined possible effects of confounding variables by using Fisher's exact test. The diagnostic status of the co-twin was tested against the type of diagnostic ascertainment, type of zygosity determination (genetic marker analysis or questionnaire evaluation), sex, education (academic or nonacademic), diagnosis of alcohol abuse or dependence based on the SCID (16), and premorbid organic pathology. Organic pathology was defined as head injury with loss of consciousness, at least one seizure, epilepsy, or other disorder with central nervous system involvement. The effect of age was analyzed by using the Mann-Whitney rank sum test. All tests were two-tailed.

Correlations in liability were calculated for bipolar I disorder according to the method described by Falconer (10). The Mx program (20) was used for biometrical model fitting to provide estimates of the genetic and environmental components of variance in the underlying liability to disease. The model-fitting procedures and assessment of model fit employed standard methods (20). Full two-by-two contingency tables with actual numbers of concordant and discordant twin pairs, including unaffected pairs, were used for model fitting. Significance levels for differences in pairwise concordance rates between monozygotic and dizygotic twins were calculated by using the Monte Carlo simulation method (21) (N=10,000,000 simulations) and Fisher's exact test. We used a one-tailed test, because prior studies indicate that the concordance rate for monozygotic pairs is higher than the rate for dizygotic pairs. The Results section contains appropriate test statistics related to the analysis of environmental risk factors in the twins with bipolar I disorder and the co-twins.

Results

Subject Characteristics

Of the 27 probands, 25 had bipolar I disorder and two had schizoaffective disorder, bipolar type, as assessed with the SCID (16). Seven of the 26 pairs were monozygotic, and 19 were dizygotic, a distribution that accords with the overall numbers of 2,495 confirmed monozygotic and 5,378 confirmed dizygotic twin pairs (χ^2=0.27, df=1, p=0.60). The mean age of the twins at the end of follow-up was 48 years (SD=5, range=37–57).

Incidence

The number of new cases of bipolar I disorder during the follow-up was 22, and the number of person-years derived from the Finnish Twin Cohort was 290,028. The overall annual incidence of bipolar I disorder per 100,000 population was 7.6, with a 95% confidence interval (CI) of 4.4 to 10.8. The rate was 6.9 for women (95% CI=2.6 to 11.2) and 8.3 for men (95% CI=3.6 to 13.0). Using the same registers, we also estimated the incidence of bipolar I disorder in the whole Finnish population. During the follow-up period of 1970–1991, the annual incidence in the 1954–1959 birth cohort was 5.8 (95% CI=5.4 to 6.3).

The number of bipolar I patients ascertained from medical records was 38, while the number of all twins at the beginning of the follow-up was 19,124. This yielded the cumulative incidence (morbid risk) of 0.2%.

TABLE 2. Characteristics of Same-Sex Twins With Bipolar Disorder or Schizoaffective Disorder, Bipolar Type, Born During 1940–1957 Who Did or Did Not Participate in a Nationwide Study in Finland

Characteristic	Participants (N=27)[a]		Nonparticipants (N=12)		Difference		
Baseline information from Finnish Twin Cohort Study and National Hospital Discharge Register							
	Mean	SD	Mean	SD	%	95% CI	p
Age at onset (years)	28	9	27	7	1	–5 to 7	0.74
	Median	95% CI	Median	95% CI	%	95% CI	p
Education (years)[b]	4	3 to 5	4	2 to 6	0	–2 to 1	0.98
Psychiatric hospitalizations	4	2 to 6	6	1 to 12	–1	–5 to 2	0.62
Days spent in psychiatric hospitals	220	130 to 365	245	58 to 520	–14	–191 to 136	0.82
	N	%	N	%	%	95% CI	p
Men	17	63	6	50	13	–21 to 47	0.50
Married	15	56	6	50	6	–28 to 40	0.75
Diagnosis of alcohol abuse or dependence	5	19	3	25	7	–35 to 22	0.68
Follow-up information from contacts with patients and treating providers and from National Population Register							
No treatment	9	41	2	25	16	–20 to 52	0.67
Current inpatient	4	18	1	13	6	–22 to 34	0.99
Deceased	5	19	4	33	–14	–45 to 16	0.42

[a] One twin pair included two probands.
[b] Based on 8-degree scale from the Finnish Twin Cohort Study (14).

Testing for Biases

No significant differences were observed between the participants and nonparticipants (Table 2). The mean length of cohabitation was 3 years longer (z=–2.57, p=0.01) among the monozygotic than the dizygotic twins, and the frequency of contacts in adulthood was higher (z=–2.95, p=0.003). However, no association was found between affection status and either the length of cohabitation (N=38, p=0.66) or the degree of environmental sharing (N=50, p=0.17). None of the possible confounding factors (type of diagnostic ascertainment, type of zygosity determination, sex, education, diagnosis of alcohol abuse or dependence, premorbid organic pathology, or age) showed a significant association (all p>0.18) with the status of the co-twin.

Concordance and Correlations in Liability

The probandwise concordance rates for different diagnostic classifications related to bipolar disorder are shown in Table 3. The concordance for bipolar I disorder was 0.43 for monozygotic twins and 0.06 for dizygotic twins. When we included patients with schizoaffective disorder, manic type, the rates were 0.50 and 0.05, respectively. The concordance for the broad affective disorder spectrum was 0.75 for monozygotic twins and 0.11 for dizygotic twins. No cases of schizophrenia occurred in this sample. The correlations in liability for bipolar I disorder were 0.85 (95% CI=0.28 to 0.98) for monozygotic twins and 0.41 (95% CI=0.00 to 0.73) for dizygotic twins. Although the concordance rates and correlations in liability for bipolar I disorder were greater for monozygotic twins than for dizygotic twins, the differences were not significant.

We recalculated the concordance rates by using the pairs for which zygosity was based on genetic marker analysis (18 of 26 pairs). The probandwise concordance rates for bipolar I disorder were 0.33 (two of six) for monozygotic twins and 0.08 (one of 13) for dizygotic twins, and the concordance rates for bipolar I disorder plus schizoaffective disorder, bipolar type, were 0.43 (three of seven pairs) and 0.07 (one of 14), respectively. The rates did not differ from the rates derived from the whole sample (Fisher's exact test).

We also calculated pairwise concordance rates for the same diagnostic categories. The pairwise concordance for bipolar I disorder was 0.33 for monozygotic twins and 0.06 for dizygotic twins (p=0.15). When we included patients with schizoaffective disorder, manic type, the rates were 0.43 and 0.05, respectively (p=0.05, Fisher's exact test), and the concordance for the broad affective spectrum was 0.71 for monozygotic twins and 0.10 for dizygotic twins (p=0.006, Fisher's exact test).

Model Fitting

Table 4 shows the results of biometrical model fitting for bipolar I disorder. The model with only specific environmental factors explaining the variance in liability (E) was rejected by the chi-square test. The model with common and specific environmental components explaining the variance (CE) could not be rejected, but it fitted clearly worse than the models involving genetic effects (ACE and AE). On the grounds of parsimony, the model of genetic and specific environmental factors (AE) was the best-fitting model, with a heritability estimate of 0.93. However, it should be noted that in the full model (ACE), the confi-

TABLE 3. Probandwise Concordance Among 26 Same-Sex Twin Pairs Containing a Proband With Bipolar Disorder or Schizoaffective Disorder, Bipolar Type, for Narrow and Broad Diagnostic Classifications of Co-Twins

Diagnostic Classification of Co-Twin	Proband Diagnosis	Co-Twin Diagnosis	Probandwise Concordance							
			Monozygotic Twin Pairs				Dizygotic Twin Pairs			
			Total Number	Concordant Pairs			Total Number	Concordant Pairs		
				Number	%	95% CI		Number	%	95% CI
Narrow definition of bipolar disorder	Bipolar I disorder	Bipolar I disorder	7	3	42.9	9.9 to 81.6	18	1	5.6	0.1 to 27.3
Intermediate definition of bipolar disorder	Bipolar I disorder or schizoaffective disorder, bipolar type	Bipolar I disorder or schizoaffective disorder, bipolar type	8	4	50.0	15.7 to 84.3	19	1	5.3	0.1 to 26.0
Broad affective disorder spectrum	Bipolar I disorder or schizoaffective disorder, bipolar type	Bipolar I disorder; schizoaffective disorder, bipolar type; bipolar II disorder; bipolar disorder not otherwise specified; cyclothymia; or major depressive disorder, recurrent	8	6	75.0	34.9 to 96.8	19	2	10.5	1.3 to 33.1
Schizophrenia	Bipolar I disorder or schizoaffective disorder, bipolar type	Schizophrenia	8	0	0.0		19	0	0.0	

dence limits for both genetic and environmental factors included zero.

Environmental Risk Factors

Reports from maternity clinics were available for 80.8% of the mothers. There were no significant differences between the concordant and discordant pairs in physical or mental problems during pregnancy or delivery (Fisher's exact test). Birth clinic information was available for 96.2% of the twins. There were no significant differences in reported postnatal complications between the probands with bipolar I disorder and the co-twins ($F=0.04$, $df=1, 28$, $p=0.85$). The mean heights were 47.3 cm and 47.4 cm ($F=0.14$, $df=1, 20$, $p=0.71$), and the mean weights were 2503 g and 2698 g ($F=2.60$, $df=1, 26$, $p=0.12$), respectively. Reports from child welfare clinics were available for 67.3% of the study subjects. The bipolar probands and healthy co-twins did not differ from each other in the occurrence of childhood infections ($F=0.44$, $df=1, 23$, $p=0.51$) or reported physical or behavioral complications ($F=1.56$, $df=1, 22$, $p=0.24$).

Discussion

To our knowledge, this is the first study that has evaluated the concordance rates and heritability for bipolar I disorder in a representative and well-defined twin sample with modern diagnostic assessment through personal interviews. Our concordance rates are almost identical to those of two studies (3, 4) employing standardized diagnostic systems, suggesting a considerable between-population stability of the genetic contribution to the liability for bipolar disorder. Although there are limitations from the genetic viewpoint in the use of concordance rates (22), they offer a simple way to compare results in different studies, provided that the prevalence of disease does not differ between them. The Danish study (2) produced higher concordance rates for both monozygotic and dizygotic twins. The semistructured diagnostic method used could partly explain the higher concordance, although the longer follow-up period could also be a factor.

The inclusion of schizoaffective disorder, bipolar type (two pairs), did not change the concordance rate much from the rate for pure bipolar I disorder. This similarity accords with the assumption that schizoaffective disorder, bipolar type, and bipolar I disorder have a common genetic background (15, 23). The phenotype might more precisely be a manic behavior (a manic polarity of the affective continuum). The findings of Cardno et al. (4) support the hypothesis of an affective status (especially a manic state) as the key heritable trait. Their reported concordance rates for the lifetime occurrence of mania were close to our rates for bipolar I disorder. In our study there were no cases of schizophrenia among the co-twins, a finding that somewhat strengthens the concept that schizophrenia and bipolar I disorder are distinct disorders.

When evaluating the concordance rates for different definitions of the disorder, we found, like Bertelsen et al. (2), that they were higher for the broad affective spectrum, especially in monozygotic twins. It is possible that monozygotic co-twins with bipolar II disorder or unipolar disorder, who were included in this category, could have a genotype for bipolar I disorder but only a partial phenotype that will later develop into the full disorder. Although the nature of the relationship between bipolar I disorder and bipolar II disorder is controversial, follow-up studies indi-

TABLE 4. Estimates From Biometrical Model Fitting of Genetic and Environmental Components of Variance in Liability to Illness Among 26 Same-Sex Twin Pairs That Contained a Proband With Bipolar Disorder or Schizoaffective Disorder, Bipolar Type

					Estimate of Contribution to Variance in Liability to Illness					
		Fit of Model		Akaike's Information Criterion	a^2 (genetic factors)		b^2 (common environmental factors)		e^2 (specific environmental factors)	
Model	Type of Factors	χ^2	df		Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
ACE	Genetic, common environmental, specific environmental	0.07	2	–3.93	0.67	0.00 to 0.99	0.25	0.00 to 0.82	0.08	0.01 to 0.36
AE	Genetic, specific environmental	0.46	3	–5.54	0.93	0.69 to 1.00	—[a]		0.07	0.00 to 0.31
CE	Common environmental, specific environmental	3.25	3	–2.75	—[a]		0.75	0.50 to 0.89	0.25	0.11 to 0.50
E	Specific environmental	27.92	4	19.92	—[a]		—[a]		1.00	

[a] Parameter was constrained to zero in the model.

cate that 4%–7% of patients with bipolar II disorder develop full mania in 3 to 10 years (24, 25). Of patients with unipolar disorder, 12%–41% eventually develop mania or hypomania (26, 27). The genetic relationship between bipolar I disorder and unipolar disorder has received special interest over the past three decades. The literature offers three models of transmission of bipolar I disorder and unipolar disorder (28): 1) a model in which they are nearly independent (29), 2) a multiple-threshold model in which bipolar I disorder represents a more severe form of the same familial condition (8, 28, 30), and 3) a model that does not subtype bipolar I disorder and unipolar disorder according to familiality but treats them as differentiated mainly by nonfamilial factors (31). Our results are in agreement with both the second and third models.

The correlations in liability to bipolar I disorder were much greater for monozygotic than dizygotic twins, indicating the importance of the genetic contribution. As expected, they closely resembled the findings of Kendler et al. (28) (0.80 for monozygotic, 0.28 for dizygotic) and Cardno et al. (4) (0.82 for monozygotic, –0.31 for dizygotic), despite the relatively small sample sizes of all three studies. We were unable to conclusively reject the model with no genetic component, but it fitted clearly worse than the models with both genetic and environmental components. The best-fitting model, the AE model (with the variance explained by common environmental factors constrained to zero), gave a heritability estimate of 0.93 for bipolar I disorder, while the ACE model produced a heritability of 0.67. Both Kendler et al. (28) and Cardno et al. (4) reported that the AE model was the best fitting, with heritability estimates of 0.79 and 0.84, respectively. They assumed higher morbid risks (1.6% and 1.5%, respectively) than we did, but Cardno et al. (4) also applied a 0.1% morbid risk estimate for mania, which then produced a heritability estimate of 0.88. Our estimate agrees with that. We were unable to differentiate between the proportions of additive and dominance genetic effects, and the modeling results must in any case be interpreted with caution.

The sample size of our study was relatively small, which limited the power to reject inappropriate models. The failure to find a statistically significant difference in concordance for bipolar I disorder between monozygotic and dizygotic twins is probably due to a lack of power. Indeed, the addition of two pairs (probands having schizoaffective disorder, bipolar type) gave a p value of 0.05. Six of the twins were deceased, but five of them were probands, and we were able to get carefully collected information about their medical history. Three of them had committed suicide. That is 11% of the study population, a proportion that is well in accordance with suicide rates among bipolar patients in other studies (32). A dizygotic co-twin had also committed suicide, although he had no previous psychiatric history according to records and interviews with relatives. Thus, it seems unlikely that he had had bipolar I disorder.

Although the sample was small, it represented the total population, being derived from the National Population Register and the Finnish Twin Cohort. The probands were screened by using data from the twin cohort surveys and the National Hospital Discharge Register for the follow-up period of 1969 to 1991. The annual incidence of bipolar I disorder in the sample was in accordance with rates in previous studies (33, 34). We were able to check the annual incidence in the Finnish 1954–1959 birth cohort during the follow-up period 1970–1991 and found it to be well in accordance with the incidence in our twin population.

The heritability estimate may be biased if there is substantial assortative mating for the disease. Another assumption underlying the model fitting is the multifactorial threshold model, which presupposes many common genes with modest effect sizes in the population (35). However, most of the evidence to date supports this assumption (36). It is noteworthy that twins classified concordant for nonaffection (according to the National Hospital Discharge Register and the Finnish Twin Cohort surveys) were not interviewed. The number of discordant pairs may thus have been underestimated and caused overestimation of familiality. However, there is no reason to believe that the underestimation would differ by zygosity, and the incidence of disease corresponded to expectation. Likewise, our period of primary ascertainment was

not the twin's lifetime but the several decades for which register information was available, yet all twins were interviewed for lifetime history. Again, this effect would be unlikely to depend on zygosity. Thus, our estimate of familiality may be somewhat biased upward.

Environmental factors, including measurement error, accounted for 7%–33% of the variance in liability. In addition to chance and errors, these could involve obstetric complications (5), infections during pregnancy or early childhood (37), and early losses (38). Our study did not give support to the hypothesis that complications during pregnancy, at birth, or postnatally or early childhood infections could explain vulnerability to bipolar I disorder. Preschool physical or behavioral complications were not more common among the probands than among the co-twins.

We believe that this is the first twin study of bipolar disorder involving a representative nationwide twin sample in which bipolar I disorder was diagnosed by using structured face-to-face interviews and long-term follow-up data. Our results confirm previous findings that the heritability for bipolar I disorder is high. However, in the future we need greater insight into the most heritable traits or components of bipolar I disorder and the specific environmental factors that could either increase the risk of its development or prevent it.

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