ORIGINAL ARTICLE

Heritability Estimates for Psychotic Disorders

The Maudsley Twin Psychosis Series

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Background: Previous twin studies have supported a genetic contribution to the major categories of psychotic disorders, but few of these have employed operational diagnostic criteria, and no such study has been based on a sample that included the full range of functional psychotic disorders.

Methods: A total of 224 twin probands (106 monozygotic, 118 dizygotic) with a same-sex co-twin and a lifetime history of psychosis was ascertained from the service-based Maudsley Twin Register in London, England. Research Diagnostic Criteria psychotic diagnoses were made on a lifetime-ever basis. Main-lifetime diagnoses of *DSM-III-R* and *International Statistical Classification of Diseases, 10th Revision* schizophrenia were also made. Probandwise concordance rates and correlations in liability were calculated, and biometrical model fitting applied.

Results: A substantial genetic contribution to variance in liability was confirmed for the major diagnostic categories except Research Diagnostic Criteria depressive psychosis and unspecified functional psychosis, where familial transmission was confirmed, but the relative contribution of genetic and common environmental factors was unclear. Heritability estimates for Research Diagnostic Criteria schizophrenia, schizoaffective disorder, mania, *DSM-III-R* schizophrenia, and *International Statistical Classification of Diseases, 10th Revision* schizophrenia were all between 82% and 85%. None of the estimates differed significantly from any other.

Conclusions: Heritability estimates for schizophrenia, schizoaffective disorder, and mania were substantial and similar. Population morbid risk estimates were inferred rather than directly measured, but the results were very similar to those from studies where morbid risks were directly estimated.

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TWIN STUDIES have made an important contribution to our understanding of genetic and environmental influences on functional psychotic disorders[1-3]; however, few of these have used operational diagnostic criteria, and to our knowledge, no study using such criteria has been based on a sample that covered the full range of functional psychoses.

Studies of schizophrenia using clinical diagnoses[1,2,4] have consistently suggested an important genetic component, with heritability estimates from 41% to 87%. Heritability estimates for commonly used operational definitions of schizophrenia have been toward the top end of this range, between 83% and 87%.[5-7] There have been fewer studies of bipolar disorder, but these also suggest an important genetic effect,[3,8,9] with a heritability of 79%[10] using *DSM-III-R*[11] criteria. Other psychotic diagnoses have been less studied, but concordance rates consistent with a genetic effect have been found for clinically defined schizoaffective disorder[12,13] and all functional psychoses combined.[14]

Gottesman and Shields[15] investigated twins registered at the Maudsley Hospital, London, England, between 1948 and 1964, with a clinical diagnosis of schizophrenia; their data have subsequently been reanalyzed applying operational diagnostic criteria.[5,6] Other studies of affective disorders[16,17] in Maudsley twins included psychotic disorders but did not analyze these specifically. Our study is based on twins registered at the Maudsley Hospital between 1948 and 1993 with any functional psychosis. We report probandwise concordance rates for operationally defined functional psychotic disorders, correlations in liability, and the application of biometrical model fitting to these disorders.

SUBJECTS AND METHODS

SUBJECTS

Probands were ascertained from the Maudsley Twin Register. They were defined as patients of multiple birth who had attended any facility of the Maudsley and Bethlem Royal Hospitals between 1948 and 1993 for clinical reasons unrelated to being a twin, who had a same-sex co-twin surviving to 15 years of age, and who had suffered psychotic symptoms (following the inclusion criteria of Sartorius et al[18]), or an episode of Research Diagnostic Criteria (RDC)[19] mania or hypomania without delusions or hallucinations, at some time in their lives. All episodes of mania and hypomania were included because these are traditionally regarded as functional psychoses in the United Kingdom. Probands whose psychotic symptoms occurred only during acute organic states were excluded, as were probands with a primary diagnosis of dementia; learning disability services were not screened for probands. The 114 twins studied by Gottesman and Shields[15] were included in the current sample. One hundred seven of these were followed up for an additional 25 years or until death, through information from hospital case notes and primary care physicians. Thirty-one of these twins were also further interviewed.

Pairs were counted probandwise. All doubly ascertained pairs were assessed by one of us (P.M.) blind to zygosity and clinical details other than those relating to registration, as a check that both twins in these pairs were independently ascertained. One of us (P.M.) also blindly assessed all probands where there was any suggestion that twin status, rather than clinical factors, might have been involved in their ascertainment, and excluded those where this was judged to be the case.

DIAGNOSTIC ASSESSMENT

Diagnoses were based on all available clinical information concerning each twin, including research interviews (Gottesman and Shields[15] cued-questions interview and/or Schedule for Affective Disorder and Schizophrenia–Lifetime version[20]), case notes, case summaries, and information from relatives and primary care physicians. Interviewed twins gave informed consent to be studied. The information on probands included a research interview in 163 cases (72.8%) and a detailed clinical description from the other sources in the remaining 61 (27.2%). All included probands were regarded as having a sufficiently comprehensive description of the psychopathology and other features of their clinical history to make valid lifetime-ever operational diagnoses. The information on co-twins included a research interview in 133 cases (59.4%), a detailed description in 61 cases (27.2%), and a statement that they had not suffered from a psychiatric disorder or a partial clinical description (where there was evidence of a psychiatric disorder, but also reason to believe that the clinical information was incomplete) in 30 cases (13.4%). The quality of clinical information for co-twins was significantly greater for RDC schizophrenia than mania ($\chi^2_2 = 8.20$, $P = .02$) and unspecified functional psychosis ($\chi^2_2 = 7.18$, $P = .03$), and for RDC schizoaffective disorder than mania ($\chi^2_2 = 6.50$, $P = .04$). Lower quality clinical information in co-twins may be associated with underestimation of genetic and common environmental effects and overestimation of individual specific environmental effects. Diagnoses of the individual members from each pair were made by separate clinical raters (A.G.C., N.J.D., P.V., and L.A.J.) in all cases where there was any suggestion of concordance for psychosis. Three raters were psychiatrists (A.G.C., N.J.D., and P.V) with at least 6 years' clinical experience and 1 was a psychologist (L.A.J.) with 3 years' clinical research experience in psychotic disorders. Research Diagnostic Criteria diagnoses were made on a lifetime-ever basis. Main-lifetime diagnoses of *DSM-III-R*[11] schizophrenia and *International Statistical Classification of Diseases, 10th Revision* (*ICD-10*)[21] schizophrenia were also made using a computer diagnostic program (OPCRIT [created by one of us, P.M.]).[22] It was not logistically possible to make consensus diagnoses among groups of raters. Diagnostic interrater reliability was performed on 30 cases. Mean κ coefficients (and percentage agreement) between raters were as follows: 0.64 (82.2%) for RDC schizophrenia; 0.58 (84.4%) for schizoaffective disorders of all types; 0.58 (87.8%) for schizoaffective disorder–manic; 0.46 (92.2%) for schizoaffective disorder–depressed; 0.65 (86.7%) for affective psychoses of all types (ie, mania, hypomania, or depressive psychosis); 0.68 (91.1%) for mania; 0.65 (94.4%) for depressive psychosis (ie, major depressive disorder with delusions or hallucinations); 0.40 (81.1 %) for unspecified functional psychosis; 0.73 (88.9%) for *DSM-III-R* schizophrenia; and 0.77 (88.9%) for *ICD-10* schizophrenia. Unreliability of clinical raters may cause underestimation of genetic and common environmental effects.

ZYGOSITY DETERMINATION

Zygosity determination was based on all available information, including analysis of genetic markers and resemblance from direct observation, photographs, resemblance questionnaires,[23] information from case notes, and statements by twins and their relatives. The 62 pairs investigated by Gottesman and Shields[15] had been classified by Shields, MD(Hon) blind to research diagnoses. Information from further follow-up of these twins was consistent

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RESULTS

SUBJECT CHARACTERISTICS

Initially, 276 probandwise pairs were considered for inclusion. Subsequently, 52 pairs were excluded for the following reasons: psychotic symptomatology in proband not confirmed (n = 17); inadequate clinical information (n = 15); inadequate zygosity information (n = 12); and twin status judged to be involved in registration (n = 8). This left 224 pairs, from which 28 probands (12.5%) were doubly ascertained. One triplet was included as 1 proband

with the original zygosities. Zygosities in the remainder of the sample were assessed by one of us (A.M.M.) who was blind to research diagnoses. In 95 pairs (42.4%) at least 13 blood group antigen markers had been analyzed. Agreement between zygosity assignment by genetic markers and by resemblance information in 62 pairs was 95.2%.

STATISTICAL ANALYSIS

Twin Method Issues

The equal environments assumption was supported by finding no significant positive correlation between degree of physical resemblance (n = 18, r = -0.20) or length of cohabitation (n = 21, r = -0.02) and concordance for psychosis in pairs determined to be monozygotic (MZ) by genetic marker data, where such information was also available. Measures of the degree of environmental sharing during and after cohabitation were not available.

Rates of psychotic illnesses in the twin sample could not be directly compared with general population rates because the twins did not all come from a specific area. Two previous studies[15,24] found no excess of twins among all Maudsley patients and no significant difference in the distribution of clinical diagnoses between twin probands with living co-twins and all Maudsley patients. With respect to RDC diagnoses, the case register for Camberwell, the local catchment area of the Maudsley Hospital, has been used to ascertain first-contact patients between 1965 and 1984 with nonaffective psychoses, mania, or hypomania.[25,26] Two twins (0.45%) from our present sample were among the 445 individuals from Camberwell who received an RDC diagnosis of psychosis. This was within the confidence interval (CI) for the estimate of 1.15% (95% CI, 0.16-2.14) same-sex twins with a co-twin surviving to 15 years of age (calculated from Maudsley Twin Register data).

The distribution of proband RDC diagnoses did not significantly differ according to zygosity ($\chi^2_4 = 0.48$, $P = .98$), suggesting no large difference in illness risk or ascertainment bias related to zygosity. There was also no suggestion of ascertainment bias for zygosity in years of high ascertainment or for age of first psychiatric contact; however, there was a nonsignificant trend toward a higher proportion of males among MZ pairs and females among dizygotic (DZ) pairs ($\chi^2_1 = 3.75$, $P = .053$). There were no significant differences in the distributions of sex, ethnicity, or proband RDC diagnoses in pairs excluded because of inadequate zygosity information compared with the included pairs.

Genetic Analyses

Probandwise concordance rates for MZ and DZ pairs were calculated for each diagnosis. Logistic regression was used to investigate the effects of possible confounding variables, treating presence or absence of the diagnosis in co-twins as the dependent variable, and zygosity and potential confounding variables as independent variables. The odds ratio for zygosity was compared with vs without the inclusion of sex, ethnicity, year of registration, age of co-twin at follow-up, level of co-twin clinical information, level of zygosity information, abuse of alcohol or other drugs within 1 year of onset of illness, and premorbid organic pathology as covariates. *Organic pathology* was defined as head injury with loss of consciousness, more than 3 seizures or a diagnosis of epilepsy, and other disorders with central nervous system involvement.

Population lifetime morbid risks for diagnoses were estimated following the approach of McGuffin et al,[5] based on data from the Camberwell Case Register and the twin series of Gottesman and Shields.[15] The lifetime morbid risk of clinical schizophrenia was estimated as 1.19%. The morbid risk for RDC schizophrenia was extrapolated as the proportion of probands in Gottesman and Shields'[15] series of twins with clinical schizophrenia who fulfilled criteria for RDC schizophrenia. Estimates for the other lifetime-ever and main-lifetime diagnoses were based on the relative frequencies of these diagnoses in the current sample. This assumes that the sample is a representative group of patients with treated psychotic illness. Calculation of the SEs for estimates also followed the approach of McGuffin et al[5] (more details of these calculations are available from us on request). In case of errors in the morbid risk estimates, analyses were also performed for RDC lifetime-ever schizophrenia and mania using widely spaced, higher and lower morbid risk estimates.

The Mx program[27] was used to calculate correlations in liability for each diagnosis. These are tetrachoric correlations based on a liability threshold model[28] that makes use of concordance rates and estimates of morbid risk. Mx was also used for biometrical model fitting. For each diagnosis, the following 5 models were fitted, differing in which parameters were assumed to contribute variance in liability: (1) individual specific environmental variance only (E model); (2) common and specific environmental variance (CE model); (3) additive genetic and specific environmental variance (AE model); (4) additive genetic and common and specific environmental variance (ACE model); and (5) additive genetic, genetic dominance, and specific environmental variance (ADE model). Nested models were compared using the χ^2 difference test. Where there was no significant difference, the best-fitting model was determined on grounds of parsimony, models with fewer parameters being preferred.

and 2 co-twins, and 1 pair came from triplets where the third member was not included because they were of the opposite sex. There were 106 MZ and 118 DZ pairs, and 120 male and 104 female pairs. One hundred ninety-seven pairs (87.9%) were white, 17 pairs (7.6%) were African Caribbean, 4 pairs (1.8%) were Asian, and 6 pairs (2.7%) were of other or mixed ethnicities. Mean age (all values are expressed as mean [SD]) at first psychiatric contact was 24.2 (8.5) years for RDC schizophrenia, 25.6 (9.7) years for schizoaffective disorder, and 28.0 (13.2) years for affective psychoses. Mean age of co-twins at last follow-up was 46.5 (15.4) years (reference range, 15-88

Table 1. Probandwise Concordance Rates for Operational Diagnoses

Diagnoses	Probandwise Concordance Rate, No. (%) [95% CI*]†	
	Monozygotic	Dizygotic
Research Diagnostic Criteria lifetime-ever		
Schizophrenia	20/49 (40.8) [26.9 to 54.7]	3/57 (5.3) [0.0 to 11.2]
Schizoaffective disorders, all	9/23 (39.1) [18.7 to 59.5]	1/22 (4.5) [0.0 to 13.4]
Manic	4/13 (30.8) [4.7 to 56.9]	0/10 (0.0)
Depressed	5/12 (41.7) [12.6 to 70.8]	0/13 (0.0)
Affective psychoses, all	15/40 (37.5) [22.3 to 52.7]	5/43 (11.6) [1.9 to 21.3]
Mania	8/22 (36.4) [15.8 to 57.0]	2/27 (7.4) [0.0 to 17.5]
Mania and hypomania	11/25 (44.0) [24.1 to 63.9]	3/33 (9.1) [0.0 to 19.1]
Depressive psychosis	2/20 (10.0) [0.0 to 23.5]	1/20 (5.0) [0.0 to 14.8]
Unspecified functional psychosis	5/33 (15.2) [2.8 to 27.6]	1/32 (3.1) [0.0 to 9.2]
OPCRIT‡ main-lifetime		
DSM-III-R schizophrenia	20/47 (42.6) [28.3 to 56.9]	0/50 (0.0)
ICD-10§ schizophrenia	21/50 (42.0) [28.2 to 55.8]	1/58 (1.7) [0.0 to 5.1]

*CI indicates confidence interval.
†Some twins qualified for more than 1 Research Diagnostic Criteria diagnosis on a lifetime-ever basis. One monozygotic and 1 dizygotic proband did not fulfill criteria for any Research Diagnostic Criteria psychotic diagnosis.
‡OPCRIT is a computer diagnostic program created by one of us (P.M.).
§ICD-10 *indicates* International Statistical Classification of Diseases, 10th Revision.

Table 2. Lifetime Morbid Risk Estimates and Correlations in Liability for Operational Diagnoses

Diagnoses	Percentage of Lifetime Morbid Risk (95% CI*)	Correlation in Liability (95% CI)	
		Monozygotic	Dizygotic
Research Diagnostic Criteria lifetime-ever			
Schizophrenia	0.82 (0.69 to 1.04)	0.83 (0.72 to 0.91)	0.31 (0.07 to 0.52)
Schizoaffective disorders, all	0.35 (0.25 to 0.51)	0.85 (0.70 to 0.94)	0.37 (–0.04 to 0.67)
Manic	0.18 (0.11 to 0.28)	0.82 (0.59 to 0.94)	–0.31 (–1.00 to 0.69)
Depressed	0.19 (0.12 to 0.30)	0.88 (0.69 to 0.97)	–0.52 (–1.00 to 0.64)
Affective psychoses, all	0.65 (0.50 to 0.87)	0.82 (0.69 to 0.90)	0.52 (0.30 to 0.69)
Mania	0.38 (0.27 to 0.55)	0.83 (0.66 to 0.93)	0.46 (0.15 to 0.69)
Mania and hypomania	0.45 (0.33 to 0.64)	0.86 (0.74 to 0.95)	0.49 (0.23 to 0.70)
Depressive psychosis	0.31 (0.22 to 0.46)	0.54 (0.22 to 0.77)	0.40 (0.00 to 0.70)
Unspecified functional psychosis	0.51 (0.38 to 0.71)	0.60 (0.38 to 0.77)	0.27 (–0.11 to 0.56)
OPCRIT† main-lifetime			
DSM-III-R schizophrenia	0.75 (0.61 to 0.99)	0.85 (0.74 to 0.92)	–0.65 (–1.00 to 0.26)
ICD-10‡ schizophrenia	0.84 (0.69 to 1.08)	0.84 (0.73 to 0.91)	0.11 (–0.23 to 0.38)

*CI indicates confidence interval.
†OPRIT is a computer diagnostic program created by one of us (P.M.).
‡ICD-10 *indicates* International Statistical Classification of Diseases, 10th Revision.

years), 64 (28.6%) being followed up beyond 55 years of age.

CONCORDANCE RATES

The probandwise concordance rates for each diagnosis are shown in **Table 1**. In each case the rate was higher for MZ than DZ twins and the difference was statistically significant for RDC schizophrenia, all schizoaffective disorders, all affective psychoses, mania plus hypomania, and *ICD-10* schizophrenia. There were no concordant DZ pairs with RDC schizoaffective disorder–manic or schizoaffective disorder–depressed, or with *DSM-III-R* schizophrenia. Only diagnoses where the DZ concordance was greater than 0 were entered into the logistic regression analysis. There was no significant difference in odds ratio for any diagnosis taking zygosity as the only independent variable vs controlling for potential confounding factors.

CORRELATIONS IN LIABILITY AND MODEL FITTING

The correlations in liability for RDC lifetime-ever diagnoses are shown in **Table 2**. For each diagnosis the correlation was greater for MZ than DZ pairs, and the difference was statistically significant for RDC schizophrenia, all schizoaffective disorders, schizoaffective disorder–depressed, all affective psychoses, mania plus hypomania, *DSM-III-R* schizophrenia, and *ICD-10* schizophrenia.

The results of biometrical model fitting are shown in **Table 3**. For RDC schizophrenia, the models of specific environmental factors explaining all of the vari-

Table 3. Biometrical Model Fitting for Operational Diagnoses*

Diagnoses	Fit of Model in χ^2					Parameter Estimates of Best-Fitting Model (95% CI)†			
	E (*df* = 2)	CF (*df* = 1)	AE (*df* = 1)	ACE (*df* = 0)	ADE (*df* = 0)	a^2	d^2	c^2	e^2
Research Diagnostic Criteria lifetime-ever									
Schizophrenia	132.72	21.12	0.80‡	0.80	0.00	0.82 (0.71 to 0.90)	. . .	. . .	0.18 (0.10 to 0.29)
Schizoaffective disorders, all	74.69	8.75	0.08‡	0.08	0.00	0.85 (0.70 to 0.94)	. . .	. . .	0.15 (0.06 to 0.30)
Manic	34.33	5.20	0.82‡	0.82	0.22	0.80 (0.57 to 0.94)	. . .	. . .	0.20 (0.06 to 0.43)
Depressed	46.66	8.72	1.29‡	1.29	0.32	0.87 (0.67 to 0.97)	. . .	. . .	0.13 (0.03 to 0.33)
Affective psychoses, all	119.25	7.83	0.97‡	0.00	0.97	0.83 (0.72 to 0.91)	. . .	. . .	0.17 (0.09 to 0.28)
Mania	70.54	6.49	0.13‡	0.00	0.13	0.84 (0.69 to 0.93)	. . .	. . .	0.16 (0.07 to 0.31)
Mania/hypomania	97.24	9.71	0.19‡	0.00	0.19	0.87 (0.75 to 0.95)	. . .	. . .	0.13 (0.05 to 0.25)
Depressive psychosis§	14.20	0.37	0.42	0.00	0.42				
Unspecified functional psychosis§	27.38	3.05	0.03	0.00	0.00				
OPCRIT‖ main-lifetime									
DSM-III-R schizophrenia	133.71	34.61	8.44	8.44	2.95‡	0.00 (0.00 to 0.64)	0.84 (0.19 to 0.92)	. . .	0.16 (0.08 to 0.26)
ICD-10 schizophrenia	133.63	31.05	4.92	4.92	0.47‡	0.00 (0.00 to 0.75)	0.83 (0.07 to 0.91)	. . .	0.16 (0.09 to 0.27)

CI indicates confidence interval; E, model with specific environmental variance in liability only; CE, model with common and specific environmental variance; AE, model with additive genetic and specific environmental variance; ACE, model with additive genetic and common and specific environmental variance; ADE, model with additive genetic, genetic dominance, and specific environmental variance; a^2, additive genetic variance in liability; d^2, genetic dominance variance in liability; c^2, common environmental variance in liability; e^2, specific environmental variance in liability; and ICD-10, International Statistical Classification of Diseases, 10th Revision.

†*Ellipses indicate that a parameter was not estimated in the best-fitting model.*

‡*Best-fitting model.*

§*The CE and AE models could not be distinguished as best fitting.*

‖*OPCRIT is a computer diagnostic program created by one of us (P.M.).*

ance in liability (E), and of common plus specific environmental variance (CE) could be rejected by the χ^2 difference test compared with the models of additive genetic, common environmental, and specific environmental variance (ACE) and additive genetic, genetic dominance, and specific environmental variance (ADE). The model of additive genetic and specific environmental variance (AE), however, could not be rejected when compared with the ACE and ADE models, and on the grounds of parsimony was the best-fitting model. Similar patterns of results occurred for all RDC schizoaffective disorders, schizoaffective disorder–manic, schizoaffective disorder–depressed, all affective psychoses, mania, and mania plus hypomania. In each case the AE model fitted best, with heritability estimates between 80% and 87%. For depressive psychosis, the model of specific environmental variance alone (E) could be rejected when compared with the other models. The CE and AE models could not be rejected when compared with the ACE and ADE models, and they were preferred on the grounds of parsimony; however, a single best-fitting model could not be specified, as it was not possible to distinguish between the CE and AE models. For unspecified functional psychosis, only the E model could be rejected, and the CE and AE models could not be distinguished. For *DSM-III-R* and *ICD-10* schizophrenia, the ADE model fitted best, being significantly better than the E, CE, and AE models. The ACE model did not fit significantly better than the AE model. In both cases, the genetic variance in liability was entirely attributed to dominance effects, but the parameter estimates had wide 95% CIs.

Model fitting for RDC schizophrenia and mania using morbid risk estimates of 0.1% and 1.5% produced similar patterns of results to the analyses based on the initial morbid risk estimates. In each case the AE model fitted best. For schizophrenia with a 0.1% morbid risk, $\chi^2 = 0.53$, additive genetic variance in liability (a^2) = 0.90 and with a 1.5% morbid risk, $\chi^2 = 1.88$, $a^2 = 0.79$. For mania with a 0.1% morbid risk, $\chi^2 = 1.14$, $a^2 = 0.88$ and with a 1.5% morbid risk, $\chi^2 = 0.17$, $a^2 = 0.76$.

COMMENT

CONCORDANCE RATES

The concordance rates in our study did not differ significantly from those in previous studies of operationally defined schizophrenia[5,6,29-31] and of schizoaffective disorder,[12,13] and mania.[8,9] The 0 concordance rates for RDC schizoaffective disorder–manic and schizoaffective disorder–depressed, and *DSM-III-R* schizophrenia were probably owing to most twins not being through the risk period for these disorders. An ascertainment bias against concordant DZ pairs cannot be excluded, but an opposite bias would have seemed more likely in our clinically ascertained sample. The number of concordant pairs would be expected to increase if twins were followed up for longer but, as this applies to both zygosities, the effect on model fitting is not predictable. The MZ concordance rate for RDC depressive psychosis (10%) was considerably lower than that for mania. To our knowledge, no previous twin study has specifically examined concordance for operationally defined depressive psychosis. The lack of significant change in odds ratios when potential confounding variables were controlled for suggests that these had no major effect on concordance ra-

tios. Small effects cannot be excluded because of the sample size or because of the relatively low frequency of nonwhite ethnicities (27 probands), abuse of alcohol or other drugs in the year prior to onset (26 probands), and premorbid organic pathology (16 probands).

MODEL FITTING

For RDC schizophrenia, all schizoaffective disorders, schizoaffective disorder–manic, schizoaffective disorder–depressed, all affective psychoses, mania, mania plus hypomania, *DSM-III-R* schizophrenia, and *ICD-10* schizophrenia models that did not include a genetic component were rejected, and heritability estimates were substantial and similar across diagnoses, ranging from 80% to 87%. None of these estimates differed significantly from any other.

The heritability estimates for schizophrenia were similar to those from previous analyses as part of our present sample: 83% for RDC schizophrenia[5] and 85% for *DSM-III* schizophrenia.[6] A similar result was also found when the data from the latter study[6] were combined with an independent study[29] of *DSM-III-R* schizophrenia (87%[7]). For *DSM-III-R* and *ICD-10* schizophrenia, parameter estimates for the best-fitting ADE model suggested that the heritability was entirely due to genetic dominance effects. This was unexpected since additive effects would usually be expected to form the larger genetic component.[32] The result could indicate the presence of epistasis that cannot be distinguished from dominance effects here, and that may occur in schizophrenia.[33] It could also be an artifact of low DZ concordance rates. Consistent with this, we performed further analyses for *DSM-III-R* and *ICD-10* schizophrenia, adding 1 concordant DZ pair, and we found that the heritability estimates for both diagnoses remained very similar, but the AE model became best fitting (for *DSM-III-R*, $\chi^2 = 3.53$, $a^2 = 0.83$; and for *ICD-10*, $\chi^2 = 2.42$, $a^2 = 0.82$). Overall, the results for schizophrenia are consistent with previous twin studies of operationally defined schizophrenia in suggesting heritabilities toward the top end of the range found for studies of clinical diagnoses.[2,4]

Heritability estimates for mania (84%) and mania plus hypomania (87%) were not significantly different from those found by Kendler et al[10] for *DSM-III-R* narrow (79%) and broad (73%) definitions of bipolar disorder. Kendler et al assumed higher morbid risks (1.6% and 2.8%) than in our current study. Interestingly, analysis assuming a morbid risk of 1.5% for mania resulted in a more similar heritability of 76%. For depressive psychosis and unspecified functional psychosis, only the model of no familial transmission could be rejected, so a genetic effect could not be confirmed. Although previous twin studies support a genetic contribution to major depression as a whole,[10,17,34] they have not specifically investigated operationally defined depressive psychosis. The status of unspecified functional psychosis is uncertain, since it is particularly heterogeneous.[35]

LIMITATIONS

Morbid risk estimates were extrapolated from local case register data for clinical schizophrenia, rather than based directly on population estimates; however, when analyses were performed for schizophrenia and mania using higher and lower morbid risks, the pattern of results from model fitting remained similar and the heritability estimates were still substantial. The results were also similar to those from studies of schizophrenia[4] and bipolar disorder[10] that were able to estimate population morbid risks directly.

Where the AE model was best fitting, it was preferred over ACE and ADE models only on grounds of parsimony, a process that must be treated with some caution in a sample of this size. It was therefore impossible to exclude the presence of any common environmental effects or genetic dominance. However, the AE models were further supported by fact that the estimates for common environmental variance (c^2) under the ACE model were 0 for RDC schizophrenia and schizoaffective disorders and low for mania (0.10). Additionally, heritability estimates may be overestimated (eg, in the presence of undetected dominance or epistasis) and underestimated (eg, with assortative mating, variability in the quality of clinical information, and imperfect reliability of clinical raters).

Extrapolation of results from our twin sample to more general populations should be done cautiously. Although most studies have not found an increased risk of psychotic illnesses in twins compared with the general population,[14,36-40] 2 studies have shown evidence for an elevated risk of schizophrenia in twins[41,42]; however, one[41] included probands who were subsequently thought to have organic psychoses,[1] and in the other[42] the risk was greater for twins from opposite-sex than same-sex pairs, with a trend toward a higher risk where 1 twin had died before the age of 15 years. Neither of these factors applied to our present study. Another issue regarding extrapolation of results is that our sample was probably somewhat selected for severity. It was derived from a service-based register rather than being population-based, although most people in the United Kingdom with psychotic illnesses have contact with psychiatric services.[43,44] It also included many referrals from other psychiatric services of patients who did not respond to treatment.

Our study has confirmed a substantial genetic contribution to variance in liability for operationally defined schizophrenia, schizoaffective disorder, and mania. This is an important prerequisite to further investigations of relevance to molecular genetic research. Estimating the number of loci involved and their relative effects would require other types of analysis,[33] and probably the inclusion of further classes of relatives. In future studies, we will report on the genetic relationships between diagnoses, and the effects of sex, age of onset, and symptom heterogeneity within and across diagnoses.

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