Heritability Estimates for Psychotic Disorders

The Maudsley Twin Psychosis Series

Alastair G. Cardno, MB, MRCPsych; E. Jane Marshall, MD, MRCPsych; Bina Coid, PhD; Alison M. Macdonald, PhD; Tracy R. Ribchester, BSc; Nadia J. Davies, MB, MRCPsych; Piero Venturi, MD; Lisa A. Jones, BSc; Shôn W. Lewis, MD, FRCPsych; Pak C. Sham, MB, MRCPsych; Irving I. Gottesman, PhD; Anne E. Farmer, MD, MRCPsych; Peter McGuffin, MB, PhD, FRCPsych; Adrianne M. Reveley, MB, MRCPsych; Robin M. Murray, MD, FRCPsych, DSc

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 psychotic diagnoses have been less studied, but concordance rates consistent with a genetic effect have been found for clinically defined schizoaffective disorder12,13 and all functional psychoses combined.14

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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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 al19), or an episode of Research Diagnostic Criteria (RDC)10 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 Shields15 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 Shields15 cued-questions interview and/or Schedule for Affective Disorder and Schizophrenia–Lifetime version20), 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 ($\chi^2 = 8.20$, $P = .02$) and unspecified functional psychosis ($\chi^2 = 7.18$, $P = .03$), and for RDC schizoaffective disorder than mania ($\chi^2 = 6.50$, $P = .04$). 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-R11 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.]).21 It was not logistically possible to make consensus diagnoses among groups of raters. Diagnostic intrarater reliability was performed on 30 cases. Mean $\kappa$ 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 Shields15 had been classified by Shields, MD(Hon) blind to research diagnoses. Information from further follow-up of these twins was consistent

Continued on next page
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 based on data from the Camberwell Case Register and the twin series of Gottesman and Shields. The lifetime morbid risk of clinical schizophrenia was estimated as 1.9%. The morbidity risk for RDC schizoaffective disorder was extrapolated as the proportion of probands in Gottesman and Shields’ series of twins with clinical schizoaffective disorder who fulfilled criteria for RDC schizoaffective disorder. Estimates for the other lifetime- 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 (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 morbidity risk estimates.

The Mx program was used to calculate correlations in liability for each diagnosis. These are tetrachoric correlations based on a liability threshold model 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 χ² difference test. Where there was no significant difference, the best-fitting model was determined on grounds of parsimony, models with fewer parameters being preferred.

The distribution of proband RDC diagnoses did not significantly differ according to zygosity (χ² = 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 (χ² = 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, age of registra- tion, 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, based on data from the Camberwell Case Register and the twin series of Gottesman and Shields. The lifetime morbid risk of clinical schizophrenia was estimated as 1.9%. The morbidity risk for RDC schizoaffective disorder was extrapolated as the proportion of probands in Gottesman and Shields’ series of twins with clinical schizoaffective disorder who fulfilled criteria for RDC schizoaffective disorder. Estimates for the other lifetime- 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 (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 morbidity risk estimates.

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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*

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>Fit of Model in χ²</th>
<th>Parameter Estimates of Best-Fitting Model (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E (df = 2)</td>
<td>CF (df = 1)</td>
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<td>----------------------------------</td>
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<td></td>
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<tr>
<td>Research Diagnostic Criteria</td>
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<tr>
<td>lifetime-eve</td>
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</tr>
<tr>
<td>Schizophrenia</td>
<td>132.72</td>
<td>21.12</td>
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<td>Schizoaffective disorders, all</td>
<td>74.69</td>
<td>8.75</td>
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<tr>
<td>Manic</td>
<td>34.33</td>
<td>5.20</td>
</tr>
<tr>
<td>Depressed</td>
<td>46.66</td>
<td>8.72</td>
</tr>
<tr>
<td>Affective psychoses, all</td>
<td>119.25</td>
<td>7.83</td>
</tr>
<tr>
<td>Mania</td>
<td>70.54</td>
<td>6.49</td>
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<tr>
<td>Mania/hypomania</td>
<td>97.24</td>
<td>9.71</td>
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<tr>
<td>Unspecified functional</td>
<td>27.38</td>
<td>3.05</td>
</tr>
<tr>
<td>OPCRIT†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSM-III-R schizophrenia</td>
<td>133.71</td>
<td>34.61</td>
</tr>
<tr>
<td>ICD-10 schizophrenia</td>
<td>133.63</td>
<td>31.05</td>
</tr>
</tbody>
</table>

* 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; a², additive genetic variance in liability; d², genetic dominance variance in liability; c², common environmental variance in liability; e², 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.).]

Comment

Concordance Rates

The concordance rates in our study did not differ significantly from those in previous studies of operationally defined schizophrenia and of schizoaffective disorder, and mania. 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-
The heritability estimates for both diagnoses remained very small, since it is particularly heterogeneous. Studies of clinical diagnoses consistently report heritabilities toward the top end of the range found for studies of schizophrenia. 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

The heritability estimates for schizophrenia were similar to those from previous analyses as part of our present sample: 83% for RDC schizophrenia6 and 85% for DSM-III schizophrenia. A similar result was also found when the data from the latter study6 were combined with an independent study29 of DSM-III-R schizophrenia (87%). 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.2 The result could indicate the presence of epistasis that cannot be distinguished from dominance effects here, and that may occur in schizophrenia. 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.4

Heritability estimates for mania (84%) and mania plus hypomania (87%) were not significantly different from those found by Kendler et al10 for DSM-III-R narrow (79%) and broad (73%) definitions of bipolar disorder. Kendler et al10 assumed higher morbid risks (1.6% and 2.8%) than in our current study. Interestingly, analysis of the same 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, 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 and bipolar disorder that were able to estimate population morbidity 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,2,36-38 2 studies have shown evidence for an elevated risk of schizophrenia in twins; however, one included probands who were subsequently thought to have organic psychoses, and in the other 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. 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 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, 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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