The Genetic Epidemiology of Schizophrenia in a Finnish Twin Cohort

A Population-Based Modeling Study

Tyrone D. Cannon, PhD; Jaakko Kaprio, MD, PhD; Jouko Lönnqvist, MD; Matti Huttunen, MD; Markku Koskenvuo, MD

Background: The magnitude of heritability of schizophrenia remains controversial, due in part to limitations of estimates derived from index twin pairs exclusively. We applied structural equation modeling in a total population of twins to determine the significance and magnitudes of the genetic and environmental contributions to schizophrenia.

Methods: All monozygotic (1180 male and 1315 female pairs) and same-sex dizygotic (2765 male and 2613 female pairs) twins born from 1940 to 1957 in Finland were screened for nonorganic psychotic disorder diagnoses as recorded on an inpatient or outpatient basis or from an eligibility review for a disability pension.

Results: The lifetime prevalence of schizophrenia was 2.0%, with a marginally higher prevalence in men (2.2%) than women (1.8%). Model fitting indicated that 83% of the variance in liability was due to additive genetic factors, and the remaining 17% was due to unique environmental factors. Sex-limitation modeling revealed no evidence of sex-specific genetic effects and no sex difference in the magnitude of heritability. A multiple threshold model incorporating affective and other psychoses as a phenotype intermediate between schizophrenia and no diagnosis was rejected.

Conclusions: In a population-based twin study of schizophrenia, heritability was estimated at 83%, with the remaining variance in liability attributed to environmental factors not shared in common among co-twins. Despite the notable limitation of using diagnoses ascertained through treatment contacts, the heritability estimate in this study is almost identical to those reported in recent studies of index pairs using standardized applications of DSM-III or later criteria.

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That genetic factors are involved in the etiology of schizophrenia is no longer a matter of controversy.\(^1\) Less certain is the nature and extent of the genetic contribution to liability. Previous twin studies have reported estimates of broad heritability ranging from 0.41 to 0.87.\(^2-5\) In all but one\(^5\) of these studies, heritability estimates were calculated using information from exclusively index twin pairs (ie, one or both co-twins affected), by either subtracting from one the ratio of the probandwise concordance rates in dizygotic (DZ) and monozygotic (MZ) pairs or multiplying by 2 the difference between the correlations in liability\(^7\) in MZ and DZ pairs using a literature-derived estimate of the population base rate. Estimates using the first approach are limited in that concordance rates are proportions that do not derive their meaning from a genetic liability model and ignore critical information on pairs concordant for nonaffection.\(^2\) Estimates using the second approach are limited in that the population base rate is assumed to be known without error, resulting in an underestimation of confidence intervals,\(^8\) and assumed to be representative of the base rate in twins, the truth of which can only be determined empirically. A limitation of both approaches is that there is no direct statistical test of whether additive and dominance genetic effects contribute to liability.

Another unresolved issue is whether the genetic and environmental contributions to schizophrenia differ by sex. Several studies have detected a higher prevalence of schizophrenia in men than women, particularly those that ascertained probands through treatment sources.\(^9\) If the sex difference in prevalence is not an artifact of method of ascertainment,\(^10\) it is possible that the higher prevalence in men reflects a sex difference in the genetic and environmental influences on liability. Previous twin stud-
SUBJECTS AND METHODS

SUBJECTS

The formation of the twin cohort has been described in detail elsewhere. Briefly, it was compiled in 1974 by searching the Finnish National Population Register for pairs of like-sexed individuals with the same surname and the same date and place of birth. Pairs born after 1957 or in which one or both co-twins had died or emigrated by 1967 were excluded. The overall cohort consists of 17,000 pairs. Because information on psychiatric outcome was limited to individuals born after 1939, it was necessary to exclude pairs born before 1940, leaving a total of 9,362 pairs from 18 consecutive birth years (1940-1957).

ZYGOSITY CLASSIFICATION

A zygosity questionnaire was sent by mail in 1975, with a 90% response rate. The decision rules for zygosity classification have been described in detail elsewhere. Briefly, pairs were classified into 3 groups (MZ, DZ, and unclassified [UZ]) based on both co-twins’ responses to the 2 most discriminatory items from the questionnaire (ie, “Were you and your twin partner during childhood as like as ‘two peas in a pod’ or were you of ordinary family likeness?” and “Were you and your twin partner so similar in appearance at school age that people had difficulty telling you apart?”). If co-twins gave conflicting answers to the zygosity questionnaire, if one or both co-twins failed to respond, or if the address was missing (eg, emigrants or residents of long-term care facilities), the pair was classified as UZ. To test the validity of this classification, a random sample of 164 pairs was chosen for blood marker phenotyping of the A,A,BO, MN, Rh (CDEce), Ss, Fy, Hp, Gc, Gm, AK, PGM, AcP, and GPT systems, with 104 agreeing to participate. The blood marker phenotyping and questionnaire-based classifications of zygosity agreed in almost all of the difference accounted for by the overrepresentation of men among UZ pairs. The mean (±SD) year of birth was 1949±5 in all zygosity groups.

ASCERTAINMENT OF PSYCHIATRIC MORBIDITY

All Finnish citizens have free access to inpatient and outpatient health care and are entitled to a state-funded pension in the case of work disability, for which psychiatric disorders are a major indication. All such contacts are recorded in 1 of 3 national computerized databases: Hospital Discharge Register, Pension Register, and Free Medicine Register. The Hospital Discharge Register indexes admission and discharge dates and primary diagnoses for inpatient stays at public and private facilities. The Pension Register indexes beginning and ending dates and primary diagnoses justifying disability pensions. The Free Medicine Register indexes primary diagnoses for state-subsidized outpatient medications. Eligibility for a pension or medication subsidy must be documented by the treating physician and checked by another independent physician specialized for this purpose. For each register, computerized information is available beginning in 1968.

These 3 registers were searched for the social security numbers of the 19,124 cohort members for entries between 1969 and 1991. Entries in 1992 and beyond had not been integrated into the computer databases at the time of our searches. Information was obtained for records in which the primary diagnosis was in the range of 295 to 299, according to the Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death, edition 8 (ICD-8), numbering scheme, corresponding to schizophrenia, affective psychosis, paranoid psychosis, reactive psychosis, and unspecified psychosis, respectively.

This diagnostic information spans 24 years. Before 1987, the ICD-8 descriptions were used as a basis for diagnosis, after which all psychiatric diagnoses in Finland used DSM-III-R criteria. While this change could differentially affect the classification of individuals with health contacts before and after 1987, for all of the diagnostic categories previously listed, the ICD-8 descriptions correspond well to the DSM-III-R criteria. In particular, the DSM-III-R and ICD-8 concepts of schizophrenia emphasize persistent disturbances in reality testing (eg, hallucinations and delusions).

PRIMARY DIAGNOSES

Each case was assigned a set of psychotic disorder diagnoses according to each of the 3 diagnostic sources and overall. Because it was possible for the same individual to have different diagnoses at different admissions in the Hospital Discharge Register, we operationally defined the hospital diagnosis as the one that occurred most frequently in the admission history; the diagnosis at the most recent admission was given primacy for ties. Each case also received an overall summary diagnosis (ie, collapsed across sources) using the following hierarchy: (1) schizophrenia, (2) affective psychosis, (3) paranoid psychosis, (4) reactive psychosis, and (5) unspecified psychosis.

AGREEMENT BETWEEN ASCERTAINMENT SOURCES

Simple percentage agreement statistics and κ coefficients were calculated for each diagnosis under each combination of the ascertainment sources. These figures are based on only those cases with a diagnosis in all sources relevant to a particular combination. Paranoid, reactive, and unspecified...
psychoses were collapsed into a single “other psychosis” category because their low base rates produce prohibitively low \( \kappa \) coefficients when considered separately. Simple percentage agreement was excellent (85.9%-95.8%) for all diagnostic categories and combinations of ascertainment sources. \( \kappa \) Coefficients were moderate to excellent for schizophrenia (0.65-0.67) and affective psychosis (0.62-0.74) and low to moderate for other psychoses (0.46-0.58).

ASCERTAINMENT OF OPPOSITE-SEX PAIRS

To determine whether the same or a different set of genes or shared environmental experiences influence liability to schizophrenia in men and women, it was necessary to obtain diagnostic information on opposite-sex DZ pairs.14 When the original twin cohort was formed, opposite-sex DZ pairs were excluded. However, when the morbidity data on the same-sex twins were obtained, we also ascertained the total population of individuals born from 1940 to 1957 in Finland with a schizophrenia diagnosis in at least 1 of the 3 sources. After merging this database with the National Population Register to ascertain first-degree relatives, we identified the total cohort of opposite-sex twin pairs in which one or both co-twins were listed in a health care database with a diagnosis of schizophrenia. This cohort consists of 163 pairs, including 71 discordant pairs in which the affected co-twin is a female, 82 discordant pairs in which the affected co-twin is male, and 10 concordant pairs. What is missing from this approach is the overall sample size of opposite-sex DZ pairs. Because the base rates of same- vs opposite-sex status in DZ twins are equivalent,24 we used the sample size of same-sex DZ pairs as an estimate.

STATISTICAL ANALYSES

We first conducted a series of analyses to test for potential biases in attrition, cohabitation, and age at first treatment contact. At the time of the diagnostic ascertainment, the youngest cohort members were aged 35 years. Almost 90% of the patients with schizophrenia had their first treatment contact before the age of 35 years. Thus, attrition was defined as the percentage of patients who had died or emigrated (without reimmigrating) before the age of 35 years. Logistic regression was used to test for possible differences in attrition according to sex and zygosity group. These analyses were conducted separately for index and control twins, and another analysis compared attrition between index and control twins. Logistic regression was also used to examine whether duration of cohabitation (as reported by twins on questionnaires given in 1975 and 198119) prior to the age at initial treatment contact for schizophrenia (of the twin treated first in the case of concordant pairs) predicted concordance for schizophrenia diagnosis after controlling for zygosity and sex. This analysis provided a test of the equal environment assumption. The age at first treatment contact for schizophrenia was compared by zygosity and sex using an analysis of variance, and intraclass correlations were computed within the concordant pairs of each zygosity.

The lifetime prevalences of schizophrenia and the different possible groupings of schizophrenia with the other psychotic disorder categories were compared by sex, zygosity, and birth year using \( \chi^2 \) tests. To permit direct comparison with prior studies, we also report probandwise concordance rates. However, all modeling analyses used tetrachoric correlations (ie, correlations in liability\(^2\)), which were estimated using a computer program (PRELIS 2, Scientific Software International Inc, Chicago, Ill).23 from the \( 2 \times 2 \) contingency tables classifying affection status in the first and second twin in each pair, where affection status was schizophrenia and all combinations of schizophrenia with the other categories. In addition, a \( 3 \times 3 \) contingency table was used to test the viability of a multiple threshold model in which liability is distributed on a continuum, with affective and other psychotic disorders representing a phenotype intermediate between schizophrenia and no diagnosis.

Another computer program (Mx, Medical College of Virginia, Richmond)26 was used to fit genetic models to these correlations by the method of asymptotic weighted least squares. In these models, there are \( 4 \) possible contributors to variance in liability: additive genetic effects (A), dominance genetic effects (D), environmental effects shared in common among co-twins (C), and individual-specific environmental effects (E), with the respective proportions of variance accounted for reflected in the estimated parameters \( a^2, d^2, c^2 \), and \( e^2 \). Model fitting began with the most parsimonious model hypothesizing no correlation in liability among co-twins’ (E) and proceeded to higher-order models in which 1 or 2 of the other factors were allowed to influence the correlation in liability. There are \( 4 \) observed statistics for each model: (1) a \( \chi^2 \) goodness-of-fit statistic; (2) the degrees of freedom; (3) a \( P \) value; and (4) the Akaike information criterion (AIC).27 which indexes the fit of the model and its parsimony. Better-fitting models produce more nonsignificant \( P \) values and lower values of the AIC. The fits of nested models were compared using the \( \chi^2 \) difference test; in this case, a significant value of \( \chi^2 \) indicates improvement in model fit. In situations in which the \( \chi^2 \) difference test cannot unambiguously segregate the relative fits of 2 models, the preferred model is one that produces the smallest AIC. We also tested a set of nested sex-limitation models after incorporating the estimated correlation in liability to schizophrenia in opposite-sex DZ pairs (ie, 0.418±0.080). In this case, the order of model fitting proceeded from least to most parsimonious. The fit of each model was assessed as previously described, and the relative fits of pairs of models were compared using \( \chi^2 \) difference tests and the AIC.

Because there were no differences between the results using diagnoses from each of the 3 ascertainment sources or uncorrected for hierarchy, we only report results using the hierarchical summary diagnoses.

When diagnostic information is available on a total population of twins, structural equation modeling can be used to determine the significance and magnitude of the additive and dominance genetic and shared and unique environmental contributions to liability to a disorder or group of putatively related disorders and to determine whether these contributions differ by sex.13,14 This approach has recently made important contributions to the genetic epidemiology of depression and anxiety disorders in women from the Virginia Twin Registry.15-18 In this study, we take a similar approach to schizophrenia and other psychotic disorders in the total population of twins born from 1940 to 1957 in Finland.
RESULTS

TESTS OF BIAS
Table 1 shows the death and emigration rates in index and control twins. There were no effects of sex, zygosity, or the interaction of sex by zygosity on attrition due to either of these sources in index twins. Among control twins, the only significant differences pertained to a higher mortality rate in men and a higher emigration rate in UZ twins, with no differences between MZ and DZ twins. Overall attrition did not differ significantly between index (8.9%) and control (7.6%) twins (χ²=1.8, df=1, P=.19). Information on cohabitation was reported by one or both co-twins in 80% and 78% of the index pairs in 1975 and 1981, respectively. After controlling for zygosity and sex, there was no relationship between duration of cohabitation prior to onset of schizophrenia and concordance for schizophrenia in 1975 (χ²=0.1, df=1, P=.87) or in 1981 (χ²=0.0, df=1, P=.92). The mean (±SD) ages at first treatment contact for schizophrenia among MZ, DZ, and UZ twins were 28.0±7.4, 26.7±3.8, and 28.6±7.4 years, respectively. The corresponding values for male and female twins were 27.2±6.5 and 28.0±6.9 years, respectively. There were no differences in age at first treatment contact according to sex (F=1.3; df=1.355; P=.26) or the interaction of sex by zygosity (F=1.1; df=2.355; P=.34). The age at first treatment contact did differ by zygosity group (F=3.1; df=2.355; P=.05). Unclassified probands were older at first treatment contact than DZ probands (t=2.5, df=278, P=.01) but not MZ probands (t=0.8, df=173, P=.42), with no difference between MZ and DZ probands (t=1.5, df=268, P=.14). The intraclass correlations for age at first treatment contact were 0.76, 0.26, and 0.47 for concordant MZ, DZ, and UZ pairs, respectively.

PREVALENCE
Table 2 shows the lifetime prevalence of schizophrenia and the combinations of schizophrenia with the other psychotic disorder categories by sex and zygosity. Schizophrenia was somewhat more prevalent in men than women (χ²=2.7, df=1, P=.09), but there were no sex differences when schizophrenia was collapsed with the other psychosis categories overall (P>.50 for all) or within each zygosity group (P>.25 for all). Unclassified twins had significantly higher prevalences of all diagnostic permutations compared with MZ and DZ twins (P<.001 for all), with no differences between MZ and DZ twins (P>.62 for all). There was not an effect of birth year on prevalence of schizophrenia (χ²=10.9, df=17, P=.86).

CORRELATIONS IN LIABILITY
Table 2 also shows the probandwise concordance rates and tetrachoric correlations in liability. Within each sex and overall, the correlation in liability to schizophrenia among MZ pairs is substantially higher than that among DZ pairs. However, the MZ/DZ ratio of these correlations is markedly higher in females (18.23) than in males (1.73), a difference due entirely to the lower liability correlation among female compared with male DZ pairs.

For all combinations involving schizophrenia and either or both of the other psychosis subtypes, the correlations in liability among MZ twins are marginally to significantly lower than those obtained for schizophrenia alone, while the liability correlations among DZ twins are approximately the same across the different phenotype definitions. The multiple threshold model for these phenotypes failed in the overall cohort (χ²=11.4, df=3, P=.01), in men (χ²=7.4, df=3, P=.05), and in MZ pairs (χ²=17.1, df=3, P=.001) and bordered on failure in women (χ²=6.3, df=3, P=.10), but was not rejected in DZ pairs (χ²=0.9, df=3, P=.81). Given this pattern, the modeling analyses were performed using schizophrenia diagnoses exclusively.

STRUCTURAL EQUATION MODELING
Table 3 shows goodness-of-fit statistics and parameter estimates for the best-fitting genetic models by sex and overall. In men, the model specifying no familial resemblance for schizophrenia provides an extremely poor fit to the data (P<.001). Adding a term specifying that all of the familial resemblance for schizophrenia is due to common environmental effects (CE) produces a significant improvement in fit (χ²=172.22, df=1, P<.001), but the model fits the data poorly (P<.001). When the term for common environmental effects is replaced by the term for additive genetic effects (AE), there is significant improvement in fit compared with the model specifying no familial resemblance for schizophrenia (χ²=181.30, df=1, P<.001) and the model fits the data well (P=.51), with no room for significant improvement by less parsimonious models (ACE [a model in which additive genetic and common and unique environmental effects influence liability] or ADE [a model in which additive and dominance genetic and unique environmental effects influence liability]). The additive genetic effects model is also the best-fitting model in men according to the AIC. Under this model, 83% of the variance in liability to schizophrenia in men is due to additive genetic effects and the remaining 17% is due to unique environmental effects.

In women, the model specifying no familial resemblance for schizophrenia diagnosis (E) is also rejected (P<.001). Adding a term for common environmental effects (CE) produces a significant improvement in fit (χ²=205.80, df=1, P<.001), but the model fits the data poorly (P<.001). Replacing the term for common environmental effects with the term for additive genetic effects (AE) results in a significant improvement in fit compared with the model specifying no familial resemblance for schizophrenia (χ²=221.07, df=1, P<.001), but this model also fits poorly (P=.03). When the term for common environmental effects is added (ACE), the fit is not significantly better than in the more parsimonious model without this term (χ²=18.00, df=2, P=1.00). When the term for dominance genetic effects is incorporated (ADE), there is a significant improvement in fit compared with the additive genetic effects model (χ²=3.87, df=1, P<.05); this is the best-fitting model according to the AIC. Under the ADE model, 85% of the variance in liability to schizophrenia in women is due to dominance genetic effects and the remaining 15% is due to unique environmental effects. The results collapsed across sex paralleled those observed for men.
SEX LIMITATION

The results of the sex-limitation analyses are shown in Table 4. Model 1 is fully saturated, with parameters for additive and dominance genetic effects and unique environmental effects that are common to both sexes (the magnitudes of which are free to vary between sexes), plus a sex-specific additive genetic effect that loads only on the male phenotype. The significance of model fit is impossible to determine because there are no degrees of freedom, but a poor fit is suggested by the negligible value of the sex-specific genetic parameter. Model 2 fixes the sex-specific genetic effect to zero and does not result in a significant reduction in fit compared with model 1 but fits the data poorly ($P = .04$), in part because the parameter estimate for dominance genetic effects in men is negligible. Model 3 fixes this parameter to zero and becomes statistically acceptable ($P = .10$). Model 4 fixes the dominance genetic effect in women to zero, does not produce a significant reduction in fit compared with model 3 ($\chi^2 = 0.73$, $df = 1$, $P = .60$), and results in a more negative value of the AIC. Thus, the dominance genetic effect is not significant in either men or women.

To determine whether there are significant differences in the magnitude of the parameter estimates for additive genetic and unique environmental effects according to sex, we used logistic regression. The results are shown in Table 2. The logistic regression coefficients for zygosity, sex, and the interaction between zygosity and sex are presented in the table. The significance levels are indicated by asterisks: $*P < .001$, $**P < .01$, and $***P < .05$.

### Table 1. Attrition Due to Death and Emigration in Index and Control Twins

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. in Each Group*</th>
<th>Deceased</th>
<th>Emigrated</th>
<th>Overall</th>
<th>No. in Each Group*</th>
<th>Deceased</th>
<th>Emigrated</th>
<th>Overall</th>
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<tr>
<td>M</td>
<td>70</td>
<td>1 (1.4)</td>
<td>3 (4.3)</td>
<td>4 (5.7)</td>
<td>2290</td>
<td>32 (1.4)</td>
<td>97 (4.2)</td>
<td>129 (5.6)</td>
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<td>1 (1.6)</td>
<td>1 (1.6)</td>
<td>2 (3.1)</td>
<td>2566</td>
<td>12 (0.5)</td>
<td>103 (4.0)</td>
<td>115 (4.5)</td>
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<td>M</td>
<td>192</td>
<td>16 (8.3)</td>
<td>10 (5.2)</td>
<td>26 (13.0)</td>
<td>5338</td>
<td>87 (1.6)</td>
<td>219 (4.1)</td>
<td>306 (5.7)</td>
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<td>12 (6.8)</td>
<td>15 (8.5)</td>
<td>5044</td>
<td>22 (0.4)</td>
<td>242 (4.8)</td>
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<tr>
<td>M</td>
<td>96</td>
<td>4 (4.2)</td>
<td>6 (6.2)</td>
<td>10 (10.4)</td>
<td>1904</td>
<td>37 (1.9)</td>
<td>307 (16.1)</td>
<td>344 (18.0)</td>
</tr>
<tr>
<td>F</td>
<td>66</td>
<td>1 (1.5)</td>
<td>4 (6.1)</td>
<td>5 (7.6)</td>
<td>1312</td>
<td>9 (0.7)</td>
<td>237 (18.1)</td>
<td>246 (18.7)</td>
</tr>
</tbody>
</table>

Logistic Regression Effects ($\chi^2$)

- Zygosity: $0.2$, $0.4$, $0.1$; $53.8^{*}$, $34.8^{*}$
- Sex: $0.1$, $0.3$, $0.7$; $9.6^{***}$
- Zygosity by sex: $0.1$, $0.3$, $0.4$; $0.4^{**}$

* Ellipses indicate data not applicable.
†$P < .001$.
‡$P < .01$.

### Table 2. Prevalences, Probandwise Concordance Rates, and Tetrachoric Correlations in Liability for Schizophrenia and for Schizophrenia Grouped With Affective Psychosis and Other Psychotic Disorders*

<table>
<thead>
<tr>
<th>Diagnostic Group</th>
<th>Overall Prevalence</th>
<th>MZ</th>
<th>DZ</th>
<th>UZ</th>
<th>Probandwise Concordance</th>
<th>MZ</th>
<th>DZ</th>
<th>UZ</th>
<th>Tetrachoric Correlation (±SE)</th>
<th>MZ</th>
<th>DZ</th>
<th>UZ</th>
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<tr>
<td>M</td>
<td>2.15</td>
<td>1.95</td>
<td>1.92</td>
<td>3.05</td>
<td>0.44±0.15</td>
<td>0.23</td>
<td>0.47±0.09</td>
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<td>F</td>
<td>1.82</td>
<td>1.56</td>
<td>1.70</td>
<td>2.76</td>
<td>0.49±0.02</td>
<td>0.26</td>
<td>0.86±0.06</td>
<td>0.61±0.12</td>
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<td>Overall</td>
<td>1.99</td>
<td>1.74</td>
<td>1.81</td>
<td>2.93</td>
<td>0.46±0.09</td>
<td>0.24</td>
<td>0.84±0.04</td>
<td>0.57±0.08</td>
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<tr>
<td>M</td>
<td>2.81</td>
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<td>2.41</td>
<td>4.00</td>
<td>0.37±0.15</td>
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<td>0.74±0.07</td>
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<td>F</td>
<td>2.65</td>
<td>2.47</td>
<td>2.55</td>
<td>3.41</td>
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<td>0.77±0.07</td>
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<tr>
<td>Overall</td>
<td>2.74</td>
<td>2.61</td>
<td>2.47</td>
<td>3.76</td>
<td>0.39±0.10</td>
<td>0.27</td>
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<td>Schizophrenia and other psychoses</td>
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<tr>
<td>M</td>
<td>2.68</td>
<td>2.29</td>
<td>2.39</td>
<td>3.95</td>
<td>0.37±0.14</td>
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<td>F</td>
<td>2.56</td>
<td>2.28</td>
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<td>3.63</td>
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<tr>
<td>Overall</td>
<td>2.62</td>
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<td>2.40</td>
<td>3.82</td>
<td>0.37±0.11</td>
<td>0.30</td>
<td>0.75±0.05</td>
<td>0.61±0.07</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia, affective psychosis, and other psychoses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>3.34</td>
<td>3.09</td>
<td>2.88</td>
<td>4.90</td>
<td>0.33±0.14</td>
<td>0.31</td>
<td>0.68±0.08</td>
<td>0.59±0.08</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>3.39</td>
<td>3.19</td>
<td>3.25</td>
<td>4.28</td>
<td>0.38±0.08</td>
<td>0.37</td>
<td>0.73±0.06</td>
<td>0.69±0.09</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>3.36</td>
<td>3.15</td>
<td>3.36</td>
<td>4.65</td>
<td>0.36±0.11</td>
<td>0.33</td>
<td>0.71±0.05</td>
<td>0.64±0.06</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

* MZ indicates monozygotic twins; DZ, dizygotic twins; and UZ, unclassified twins. Prevalences are lifetime prevalences based on treatment contact by the time the youngest cohort members were 35 years old.
Table 4. Results of Sex-Limitation Model Fitting for Schizophrenia*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
<th>Model 5</th>
<th>Model 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>$a^2$</td>
<td>0.56</td>
<td>0.56</td>
<td>0.63</td>
<td>0.84</td>
<td>0.83</td>
<td>0.83</td>
</tr>
<tr>
<td>$d^2$</td>
<td>0.29</td>
<td>0.29</td>
<td>0.22</td>
<td>0.00</td>
<td>0.43</td>
<td>0.83</td>
</tr>
<tr>
<td>$e^2$</td>
<td>0.15</td>
<td>0.15</td>
<td>0.15</td>
<td>0.16</td>
<td>0.17</td>
<td>0.17</td>
</tr>
<tr>
<td>$k^2$</td>
<td>0.00†</td>
<td>.03</td>
<td>0.03</td>
<td>.03</td>
<td>.03</td>
<td>.03</td>
</tr>
<tr>
<td>$p^2$</td>
<td>0.15†</td>
<td>0.16†</td>
<td>0.16†</td>
<td>0.17†</td>
<td>0.17†</td>
<td>0.17†</td>
</tr>
<tr>
<td>$f^2$</td>
<td>0.00†</td>
<td>.00</td>
<td>.00</td>
<td>.00</td>
<td>.00</td>
<td>.00</td>
</tr>
</tbody>
</table>

*Parameters $a^2$, $d^2$, and $e^2$ indicate additive genetic, dominance genetic, and unique environmental effects, respectively; parameters with the subscript $m$, those that load on the male phenotype; parameters with the subscript $f$, those that load on the female phenotype; parameter $a^2_m$, the sex-specific additive genetic effect that loads only on the male phenotype; parameter $k^2$, the scalar multiplier that, when multiplied by the parameter estimates for additive genetic and unique environmental effects obtained for females, yields the corresponding parameter estimates for males; AIC, Akaike information criterion; and ellipses, data not available.
†Goodness-of-fit statistics and parameter estimates are identical to those shown under model 1 when the sex-specific dominance genetic effect ($d^2_f$) is modeled instead of the sex-specific additive genetic effect ($a^2_f$). It is impossible to estimate both of these parameters in the same model.
‡In this approach, there are 7 observed statistics (correlations in liability in monozygotic pairs, correlation in liability in dizygotic pairs, and variance in liability); as the 3-factor models require estimation of 7 parameters, this model has no degrees of freedom. Nonzero values for $\chi^2$ are possible for these models because all of the parameter estimates are constrained to be positive.

Thus, there are no sex-specific genetic effects and no difference in magnitude of heritability according to sex.

**COMMENT**

**HEREDITY**

Modeling analyses determined that 83% of the variance in liability to schizophrenia is attributable to additive genetic effects. Previous estimates of broad heritability have ranged from 0.41 to 0.87.2,3 Varying sample sizes and ascertainment methods no doubt accounts for a large share of this variability.2,3 Another source is the relatively large amount of error associated with estimates derived exclusively from index twins. The primary advantage of the present approach is the inclusion of pairs concordant for nonaffect, permitting unambiguous use of the correlation in liability. Another advantage is the use of statistical procedures that assessed competing models directly, demonstrating that only additive genetic effects are likely to influence liability.

At the same time, it is remarkable that the degree of heritability detected in this study is almost identical to estimates from recent studies of index pairs from England4 and Norway5 that employed standardized applications of DSM-III or later criteria. Given that the genetic contribution to this disorder is thus likely to be 80% to 86%, further efforts to locate predisposing genes seem warranted.

**ENVIRONMENT**

Individual-specific environmental effects (or error or both) accounted for the remaining 17% of the variance in liability. Consistent with adoption studies,29,30 there was no effect of environmental experiences shared in common among co-twins. Parent-child interactions and other factors expected to be similar among children in the same family are thus unlikely to contribute substantially to the etiology of schizophrenia. It remains to be determined what types of environments are contributory and whether their influences interact with or are independent of genetic predisposition.

Obstetric complications have been linked to an increased risk for schizophrenia.31,32 In twin births, such factors commonly affect both co-twins, but one co-twin
may be affected uniquely or with greater severity.\textsuperscript{35,34} Consistent with this pattern, some obstetric complications seem to be more common in the affected co-twins from MZ pairs discordant for schizophrenia.\textsuperscript{35-40} Because chronic hypoxia and other obstetric complications are more likely to be shared by MZ than DZ co-twins,\textsuperscript{39} it is possible that these factors also account for some of the variance in liability attributed to genetic effects. A modeling study of genetic and obstetric influences in a twin population is needed to resolve this issue.

**SEX DIFFERENCES**

Consistent with some but not all prior reports,\textsuperscript{9,10} a treatment-ascertained diagnosis of schizophrenia was somewhat more likely in men than women. Previous twin studies are in conflict as to whether such a difference could reflect sex-limitation effects.\textsuperscript{11} In this study, the correlations in liability among female and male MZ twins were equivalent, but there was a smaller liability correlation among female than male DZ twins. This pattern does not reflect a bias against ascertainment of zygosity in women, as there were more unclassified male pairs and as liability correlations did not differ significantly between male and female UZ pairs. Another unlikely possibility is that more women with schizophrenia were misclassified as having affective or other psychoses. In this case, the effect of including affective and other psychoses in the phenotype definition should have been to increase the liability correlations among MZ and DZ pairs in women, which was not observed. The low liability correlation in DZ females might thus be a chance effect. Indeed, exclusively dominance genetic effects, while statistically possible, are quite rare in complex traits. This interpretation is also supported by the fact that in the sex-limitation analyses, a dominance genetic effect was rejected in both sexes and there was no evidence of sex-specific genetic effects and no sex difference in the magnitude of additive genetic effects. Similar findings have recently been obtained for nuclear families from Ireland.\textsuperscript{41}

**OTHER PSYCHOSES**

This study assessed genetic associations between schizophrenia and putatively related phenotypes using the correlation in liability rather than the less genetically meaningful MZ/DZ concordance ratio.\textsuperscript{12} The model in which affective and other psychoses represent an intermediate threshold on a liability continuum shared with schizophrenia failed. This pattern argues against the multiple threshold model for these phenotypes, although it cannot speak to phenotypes not assessed in this study, such as schizotypal personality disorder.

**LIMITATIONS**

The foremost limitation of this study pertains to whether the clinical diagnoses were reliable and valid. A preliminary indication of reliability is provided by the high rate of diagnostic agreement (86%-96%) between the 3 treatment sources. A preliminary indication of validity is provided by a study in which hospital diagnoses of schizophrenia agreed with an interviewer’s independently assigned Present State Examination\textsuperscript{42} diagnoses in 85% of 297 randomly selected psychotic inpatients from Helsinki (κ=0.69).\textsuperscript{43,44} We have found 92% agreement (κ=0.84) between register diagnoses of schizophrenia and an interviewer’s DSM-III-R diagnoses in 72 randomly selected probands and 43 of their siblings born in Helsinki from 1950 to 1958. While more appropriate estimates would be obtained on a random national sample, we are not aware of any such study in Finland. However, if register diagnoses from outside Helsinki are less reliable or less comparable with narrower definitions of schizophrenia, one would expect great geographic variability in prevalence estimates. Apart from small genetic isolates, no such differences have been observed in large random population samples in Finland, whether diagnoses were ascertained via treatment sources or by direct structured interviews.\textsuperscript{45,46}

Still, because the prevalence of schizophrenia in this cohort is higher than that observed in interview-based studies conducted elsewhere,\textsuperscript{1} the register diagnoses probably reflect a broader definition than that of the DSM-III-R. It seems unlikely that substantial numbers of patients with affective, reactive, and paranoid psychoses were included because the multiple threshold model with these phenotypes failed. We can only speculate that patients with severe schizotypal personality disorder and atypical psychosis might have been included. In any case, diagnostic error is unlikely to have been higher in DZ than MZ pairs, and whatever is included in the register definition would seem to be related to schizophrenia. If the register definition encompassed phenotypes unrelated to schizophrenia, the effect should be an underestimation rather than an overestimation of heritability.

The diagnostic information in this study spanned 24 years, did not depend on patients’ self-reports, and ascertained cases with any inpatient or outpatient treatment contacts or disability pensions. More than 90% of psychotic individuals in Finland come into contact with health care providers (those who care for psychiatric patients) in one or more of these ways.\textsuperscript{45,46} It is possible, therefore, that our methods allowed for a more complete ascertainment of schizophrenia than is possible in interview-based population studies. In addition, schizophrenia even by narrow definitions may be more prevalent in Finland than in some other countries. In a 16-year longitudinal study of a random national population sample of 1000 Finnish adults, Present State Examination diagnoses of psychoses had a 3.5% lifetime prevalence (our figure was 3.4%).\textsuperscript{45} Unfortunately, this study did not provide lifetime prevalence figures for schizophrenia separately, but prevalence at the initial assessment was 1.5%. In the Mini-Finland Health Survey,\textsuperscript{46} for which 8000 adults aged 30 years or older who were sampled randomly from 40 geographic areas throughout the country were interviewed, there was a 1.3% prevalence of schizophrenia as determined by nonblind integration of Present State Examination and hospital diagnoses.

Another potential bias is that individuals from the first birth year in this study were 28 years old by the time diagnostic information was first available. Mitigating against this concern is the absence of a birth year effect on prevalence in this cohort and the tendency for patients with earlier onsets to continue to require treatment later in life.
We were unable to classify zygosity in 18% of the pairs. The unclassified group had a higher percentage of men, a higher prevalence of schizophrenia, and a greater proportion of individuals who had emigrated. However, we could detect no biasing effect of the UZ pairs on the heritability analyses because the observed correlation in liability to schizophrenia in the UZ group did not deviate from the expected value given the proportions that are expected to be DZ and MZ. The ratio of like-sexed DZ/MZ pairs in the Finnish population during the 1940s and 1950s was slightly greater than 2:1. Thus, the UZ group should contain 997 DZ pairs (59%) and 692 MZ pairs (41%). The expected correlation in liability is obtained by multiplying the observed liability correlations in the classified MZ and DZ pairs by the corresponding proportions of UZ pairs expected to be MZ and DZ and summing the products. These calculations produce an expected correlation of 0.58 (the observed correlation was 0.57±0.08). Also arguing against a classification bias is the fact that the DZ/MZ twin ratio in the classified group was expected (and observed) to be 2:1.

The heritability estimates in this study are, of course, limited to twins; future work will need to address whether similar estimates are obtained with other kinships. In addition, because Finland represents an isolated gene pool,7 studies using comparable approaches in other countries are needed to establish the generalizability of these findings. An initial indication of generalizability is provided by the correspondence between our estimate and those from recent studies of index twins from England and Norway,10 although comparable heritabilities do not necessarily imply that the same set of genes contributes to liability across gene pools.

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Corresponding author: Tyrone D. Cannon, PhD, Department of Psychology, University of Pennsylvania, 3815 Walnut St, Philadelphia, PA 19104 (e-mail: cannon@cattell.psych.upenn.edu).

REFERENCES