A Pilot Swedish Twin Study of Affective Illness, Including Hospital- and Population-Ascertainment Subsamples

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Objective: We sought to compare the probandwise concordance rate (PRC) for affective illness (AI) in monozygotic (MZ) and dizygotic (DZ) twins in samples ascertained through psychiatric hospitalization vs samples from the general population.

Methods: Twins were ascertained through psychiatric hospitalization for AI from the Swedish Psychiatric Twin Registry or as a matched sample from the population-based Swedish Twin Registry. Lifetime diagnoses were based on a mailed questionnaire containing, in self-report format, DSM-III-R criteria for mania and major depression. Returned questionnaires were obtained from 1484 individuals and both members of 486 pairs, of whom 154 were classified as MZ, 326 as DZ, and six of unknown zygosity.

Results: No evidence was found for violations of the equal environment assumption. Using either a narrow or broad diagnostic approach, the risk for AI in cotwins of proband twins was independent of the gender, polarity (ie, unipolar vs bipolar) and mode of ascertainment of the affected proband (ie, via hospitalization vs from the general population). Combining both subsamples, PRC for total AI using narrow diagnostic criteria was 48.2% in MZ and 23.4% in DZ twins. Using broad diagnostic criteria, the parallel figures were 69.7% and 34.9%. The risk for bipolar illness was substantially increased in the cotwins of probands with bipolar AI.

Conclusions: Genetic factors play a major role in the etiology of AI in Sweden, as assessed by self-report questionnaire. Heritable factors appear to be equally important in AI as ascertained in clinical and epidemiological samples.

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Twin studies of affective illness (AI) that find with considerable consistency higher concordance rates in monozygotic (MZ) than dizygotic (DZ) twins have, to date, used one of two different methods. Twelve major studies ascertained affected twins through psychiatric hospitalization.1,1 Two studies ascertained twins with AI through general population2 or volunteer twin registries.3 Since only a modest proportion of individuals in the population with AI ever seek specialist care and since few are psychiatrically hospitalized, these two methods may be examining quite different populations of cases with AI. Indeed, some researchers have argued that community and clinical cases of AI are qualitatively different, so that studying AI in the community provides little information about "real" clinical AI.5 In a review of the literature evaluating differences between clinical and community cases of major depression, Costello6 noted that few methodologically rigorous studies have addressed this crucial question, and in particular, little evidence is available to test the widely held hypothesis that clinical cases of major depression are more "biologic/genetic" and that community cases are more "environmental." As Costello noted, there are no studies "directly comparing the heritability of community and clinic cases of depression."7

In this article, we report results from the preliminary phase of a twin study of AI, including, for the first time ever in a twin study of psychiatric illness, twins hospitalized for AI as ascertained through the
SUBJECTS AND METHODS

SUBJECTS

Index (or hospitalized) twin probands were ascertained from the Swedish Psychiatric Twin Registry, which was formed by matching the "old" and "new" Swedish Twin Registries, covering the birth years from 1886 to 1967 to the Swedish "discharge" Psychiatric Registry for the years 1968 to 1983 and two "census" registries for the years 1979 and 1983. Matching was performed using the unique 10-digit identification number assigned to all individuals in Sweden. The old Swedish Twin Registry consists of more than 95% of same-sex twin pairs born from 1886 to 1925 where both members were alive in 1959 and responded to a questionnaire in 1960 and contains 10,943 pairs. The new Twin Registry, covering 1926 to 1967, is more than 99% complete in identifying all same-sex and opposite-sex twins born in Sweden and contains 54,890 pairs. Both the discharge and census psychiatric registries, which contain one or more recorded diagnoses in International Classification of Diseases, Eighth Revision, codes for each case, cover all mental hospitals in Sweden as well as all inpatient psychiatric departments of general hospitals. 

The match that created the Swedish Psychiatric Twin Registry identified 5691 twins hospitalized for psychiatric disorder. Using International Classification of Diseases, Eighth Revision, codes, we defined bipolar illness (BPI) as 296.1, 296.3, and 298.1 and unipolar illness (UPI) as no BPI diagnosis and a diagnosis of any other 296 code or 298.0 or 300.4. We subdivided unipolar cases into two forms: neurotic (code 300.4) and non-neurotic (nonbipolar 296 and 298.0 codes). Subjects were excluded from the study if (1) they had a recorded diagnosis of schizophrenia; (2) they were dead at last registry update; or (3) their cotwin was stillborn or not locatable at the time of the registry compilation. This match yielded 2017 twin probands with BPI or UPI, of whom 1222 were female and 224 had BPI. The morbidity risks for hospitalization for AI can be estimated using the new Twin Registry (details available on request) and are, for BPI and UPI, 0.32% and 2.96%, respectively, well within the range reported in other epidemiologic samples.

Control twin probands were obtained from the Swedish Twin Registries, initially using one-for-one matching to index twins with AI based on (1) date of birth within the same year and same quarter of the year and (2) gender composition of twin pair. In addition, twins were matched for county of residence or birth in the older and younger cohorts, respectively. Control twins were selected independent of any history of psychiatric treatment.

Our initial sample of more than 4000 index and control probands and their cotwins was too large for our limited financial resources. We reduced the total number of index twin probands to 1002 by including only 500 twin probands whose only AI diagnosis was neurotic depression. Of the 1002 matched control twins, we randomly selected 800. The final sample of 1802 ascertained pairs consisted of 1731 unique pairs, of whom 1661 were singly ascertained, 69 doubly ascertained, and one triply ascertained. Results in this report are based on probandwise ascertainment correction. Records indicated that 57 cotwins of index probands and 44 cotwins of control probands were dead at the time of attempted contact.

QUESTIONNAIRE AND ZYGOSITY DETERMINATION

Contact with the twins was limited to a mailed questionnaire that contained expanded versions of the sections of the Structured Clinical Interview for DSM-III-R (SCID) for mania and major depression adapted to a self-report format (details available on request). Accuracy of translation into Swedish was assessed by a back-translation into English. The questionnaire contained three possible responses to all symptom criteria: yes, maybe-somewhat, and no. Because of the uncertainty of the proper criterion threshold in self-report measures, throughout these analyses we

RESULTS

SUBJECT CHARACTERISTICS

Completed questionnaires were received from a total of 1484 independently ascertained individuals, including both members of 486 pairs. The mean age (±SD) was 53.0±13.1 years, and 68% of the sample was female. Of the complete pairs, 154 were MZ twins; 326, DZ twins; and six, of unknown zygosity. The index sample consisted of 721 individuals and both members of 217 pairs (57 were MZ twins; 157, DZ twins; and three, of unknown zygosity). The control sample included 763 individuals with 269 pairs (97 were MZ twins; 169, DZ twins; and three, of unknown zygosity).

LIFETIME PREVALENCE FOR AI

The lifetime prevalences for narrowly and broadly defined UPI, BPI, and total AI in the general population sample of control twins and cotwins are seen in Table 1. Using narrow diagnostic criteria, the prevalence of BPI is similar in females (1.7%) and males (1.3%) (X^2 = 0.22, df = 1, P was not significant [NS]), while the prevalence of UPI is greater in
used two different approaches: narrow diagnostic criteria, counting only yes answers as positive responses, and broad diagnostic criteria, where both yes and maybe-somewhat answers were counted as positive. The DSM-III-R criteria were applied to the questionnaire responses by computer algorithm. The questionnaire also contained items to assess similarity of the twins' child and adult environments.16,17

Questionnaires were mailed to the 3503 living proband twins and co-twins with at least one reminder letter sent to nonrespondents and telephone follow-up to a small subsample. There were 1484 responses obtained from independently ascertained twins for an overall response rate of 42.4%. The response rate was lowest in index probands (35.8%), intermediate in index co-twins (38.4%), and highest in control proband twins and co-twins (49.0%).

The questionnaire included an extensive series of zygosity questions used previously in the Virginia and Swedish Twin Registries. When tested against blood typing, shorter lists of similar items are usually greater than 95% accurate in diagnosing zygosity.18 In a large sample of Virginia twins, zygosity was assigned based on a “blind” review of these items, photographs, and, when uncertain, DNA.2 We developed a Fisher’s linear discriminant function based on common items in the Virginia and Swedish samples.19 When applied to all same-sex twin pairs from our Swedish sample, very good separation into two groups was obtained20 (available on request). Six twin pairs with uncertain zygosity were excluded from the twin analyses.

STATISTICAL ANALYSIS

To test the equal environment assumption, we examined whether, by logistic regression, controlling for zygosity and age, childhood, or adult environmental similarity predicts twin similarity for AI.21 Since AI has an age-dependent onset, we used the Cox proportional hazards model, as operationalized in the PHGLM procedure in SAS,22 to explore factors that influence the risk of illness in co-twins. Some correction, however, is required for assuming independence of the observations from the doubly counted twin pairs. If T is the total number of observations, N the number of doubly counted twin pairs, and P the number of parameters in our model, we multiplied the SEs obtained by \( \frac{1}{\sqrt{T - P(T - N - P)}} \). Although approximate, this correction is likely to be conservative.22 All significant values reported herein are based on our corrected SEs.

POTENTIAL COOPERATION EFFECTS

Twins hospitalized for AI returned their questionnaires at a lower rate than the matched general population sample. To be included in the twin analyses, both members of the twin pair had to return questionnaires. Such an ascertainment pattern will produce reductions in both the observed prevalence rate and the probandwise concordance rate (PRC).23 The reduction in the observed PRC will depend on the true population PRC. Since we have a direct estimate of the cooperation effect, it is possible to correct our results for this effect and to determine whether our original results were substantially biased by the cooperation effect, using a model previously outlined.21

DIAGNOSTIC HIERARCHIES

Because UPI cannot be diagnosed given a history of mania, individuals with manic episodes are not, by definition, vulnerable to UPI.24 Therefore, two alternative approaches could be taken toward the presentation of PRC for UPI. The denominator for the calculation of PRC for UPI could be either all co-twins of proband twins or only all co-twins without BMI. While the latter is probably correct,25 family and twin studies of AI traditionally take the former approach, which, in the interest of continuity, we also adopted. However, this approach results in an underestimation of the true PRC for UPI, which is greater the higher the PRC is for BMI.24 The application of structural equation model fitting to these data will be reported elsewhere.

females than in males (16.8% vs 7.9%, \( x^2=12.56, df=1, P=.000 \)). The lifetime prevalence of narrowly defined AI in the entire sample is 14.8%. A similar overall pattern of results is seen with broadly defined AI, but rates of illness are approximately twice that seen with the narrow definition.

RELATIONSHIP BETWEEN SELF-REPORT AND HOSPITAL DIAGNOSES

Table 2 depicts the relationship in index probands between hospital discharge diagnoses from the psychiatric registry and narrow or broad DSM-III-R diagnoses based on the self-report questionnaire. Two major trends in these results are noteworthy. First, using narrow or broad criteria for BPI, rates of BPI are highest in those individuals with a bipolar discharge diagnosis, intermediate in those diagnosed as having nonneurotic depression, and lowest in those with a hospital diagnosis of neurotic depression. Second, the proportion of probands who failed to meet criteria for AI is lowest in those individuals with a bipolar discharge diagnosis, intermediate in those diagnosed as having nonneurotic depression, and highest in those with a diagnosis of neurotic depression. Dichotomizing the discharge diagnoses into bipolar and unipolar categories and examining only those twins with a DSM-III-R diagnosis of AI by self-report questionnaire, the chance-corrected agreement25 between the hospital and DSM-III-R diagnosis is highly significant using both narrow (\( \kappa=0.43 \pm 0.08, P=.00 \)) and broad (\( \kappa=0.39 \pm 0.07, P=.00 \)) diagnostic criteria.
Table 1. Life Table Prevalence of Bipolar and Unipolar Affective Illness (AI) in Control Twins by Gender and by Narrow vs Broad Criteria

<table>
<thead>
<tr>
<th>Breadth of Diagnostic Criteria and Gender</th>
<th>Lifetime Prevalence†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unipolar, n (%)</td>
</tr>
<tr>
<td>Narrow</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>24 (7.9)</td>
</tr>
<tr>
<td>F</td>
<td>77 (16.8)</td>
</tr>
<tr>
<td>Both</td>
<td>101 (13.2)</td>
</tr>
<tr>
<td>Broad</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>57 (18.8)</td>
</tr>
<tr>
<td>F</td>
<td>155 (33.8)</td>
</tr>
<tr>
<td>Both</td>
<td>212 (27.8)</td>
</tr>
</tbody>
</table>

*DSM-III-R criteria.
†Total number of males equals 304; females, 458; and both, 763.

Table 2. Concordance Between Hospital Diagnosis and Self-Report DSM-III-R Diagnoses in Index Proband Twins

<table>
<thead>
<tr>
<th>Diagnostic Breadth and DSM-III-R Diagnosis</th>
<th>Hospital Diagnosis</th>
<th>Bipolar, (n=58) (%)</th>
<th>Nonneurotic Depression, (n=104) (%)</th>
<th>Neurotic Depression, (n=186) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narrow</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar</td>
<td>25 (43.1)</td>
<td>14 (13.5)</td>
<td>14 (7.5)</td>
<td></td>
</tr>
<tr>
<td>Unipolar</td>
<td>13 (22.4)</td>
<td>50 (48.1)</td>
<td>69 (47.9)</td>
<td></td>
</tr>
<tr>
<td>Unaffected</td>
<td>20 (34.5)</td>
<td>40 (38.5)</td>
<td>83 (44.6)</td>
<td></td>
</tr>
<tr>
<td>Bread</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar</td>
<td>30 (51.7)</td>
<td>17 (16.4)</td>
<td>23 (12.4)</td>
<td></td>
</tr>
<tr>
<td>Unipolar</td>
<td>16 (27.6)</td>
<td>62 (59.0)</td>
<td>116 (63.4)</td>
<td></td>
</tr>
<tr>
<td>Unaffected</td>
<td>12 (20.7)</td>
<td>25 (24.0)</td>
<td>45 (24.2)</td>
<td></td>
</tr>
</tbody>
</table>

Testing for Biases

By logistic regression, controlling for age, gender, and mode of ascertainment, no relationship was found between zygosity and risk for either narrowly defined ($\chi^2=1.58$, P=NS) or broadly defined ($\chi^2=2.01$, P=NS) total AI. With the same control variables, twin similarity for narrowly or broadly defined total AI was unrelated to measures of either childhood environmental similarity ($\chi^2=2.94$, df=1, P=0.09 and $\chi^2=0.04$, df=1, P=0.85, respectively) or current environmental similarity in adulthood ($\chi^2=0.04$, df=1, P=0.84 and $\chi^2=0.12$, df=1, P=0.73, respectively).

Probandwise Concordance in Index and Control Subjects

Restricting probands to those meeting narrow diagnostic criteria for AI, diagnostic information was available on 116 cotwins of hospitalized (or index) probands and on 68 cotwins of probands ascertained through the general population (control probands). Applying broad diagnostic criteria for AI to probands, information was available on 159 cotwins of index probands and on 145 cotwins of control probands.

Table 3 presents the probandwise concordance in MZ and DZ twins for both narrowly and broadly defined total AI separately in the index and control samples. In the index sample, the PRC for AI was substantially greater in MZ than in DZ twins using both the narrow (45.5% vs 19.3%) and the broad (76.6% vs 33.0%) diagnostic criteria. In the control sample, a similar pattern of PRC was seen using both the narrow (MZ twins, 52.2%; DZ twins, 31.1%) and the broad (MZ twins, 61.9%; DZ twins, 36.9%) diagnostic criteria.

The PRC by polarity is seen for both index and control cotwins in Table 4. Two trends are noteworthy. First, in index twin pairs, the rates of BPI are notably higher in MZ cotwins of bipolar probands than in either DZ cotwins of BPI probands or MZ cotwins of UPJ probands. Second, lifetime prevalence for total AI, across both samples, differs little in cotwins of BPI vs UPJ probands. While in MZ index twins using the narrow diagnostic criteria, total AI is substantially higher in cotwins of BPI vs UPJ probands, this trend disappears when broad diagnostic criteria are used and is not seen at all in DZ cotwins of index twins.

Proportional Hazards Regression

Using the Cox proportional hazards model, we examined (df=1 for all) the impact on risk for total AI in the cotwin of (1) gender of the proband twin; (2) gender of the cotwin; (3) polarity of the proband (unipolar vs bipolar); (4) mode of ascertainment of the proband (via hospitalization vs from the general population); and (5) zygosity of the twin pair. Using narrow diagnostic criteria, proband gender ($\chi^2=1.0$, P=NS), polarity of proband ($\chi^2=0.25$, P=NS), and mode of proband ascertainment...
Table 4. Probandwise Concordance in the Index and Control Samples as a Function of Polarity and Narrow vs Broad Diagnostic Criteria

| Proband Diagnosis | Index vs Control | Diagnostic Criteria | MZ Twins | | | DZ Twins | | |
|-------------------|------------------|---------------------|----------|----------|----------|----------|----------|
|                   |                  |                     | Total No. | BPI, n (%) | UPI, n (%) | AI, n (%) | Total No. | BPI, n (%) | UPI, n (%) | AI, n (%) |
| BPI               | I                | N                   | 10       | 5 (50.0)  | 2 (20.0)  | 7 (70.0)  | 19       | 1 (5.3)  | 1 (5.3)  | 2 (10.5) |
| BPI               | I                | B                   | 12       | 5 (41.7)  | 4 (33.3)  | 9 (75.0)  | 27       | 1 (3.7)  | 7 (25.9) | 8 (28.6) |
| UPI               | I                | N                   | 23       | 0         | 8 (34.8)  | 8 (34.8)  | 64       | 1 (1.6)  | 13 (20.3) | 14 (21.9) |
| UPI               | I                | B                   | 35       | 3 (8.6)   | 24 (68.6) | 27 (77.1) | 85       | 2 (2.4)  | 27 (31.8) | 11 (34.1) |
| BPI               | C                | N                   | 3        | 0         | 1 (33.3)  | 1 (33.3)  | 3        | 0         | 1 (33.3) | 1 (33.3) |
| BPI               | C                | B                   | 3        | 0         | 1 (100.0) | 1 (100.0) | 3        | 0         | 1 (37.5) | 1 (37.5) |
| UPI               | C                | N                   | 20       | 1 (5.0)   | 10 (50.0) | 11 (55.0) | 42       | 1 (2.4)  | 12 (28.6) | 13 (31.0) |
| UPI               | C                | B                   | 39       | 3 (7.7)   | 20 (51.3) | 23 (59.0) | 95       | 3 (3.2)  | 32 (33.7) | 35 (36.8) |
| BPI               | I+C              | N                   | 13       | 5 (38.5)  | 3 (23.1)  | 8 (61.5)  | 22       | 1 (4.5)  | 2 (9.1)  | 3 (13.6) |
| BPI               | I+C              | B                   | 15       | 5 (33.3)  | 7 (46.7)  | 12 (80.0) | 35       | 1 (2.9)  | 10 (28.6) | 11 (31.4) |
| UPI               | I+C              | N                   | 43       | 1 (2.3)   | 18 (41.9) | 19 (44.2) | 106      | 2 (1.9)  | 25 (23.6) | 27 (25.5) |
| UPI               | I+C              | B                   | 74       | 6 (8.1)   | 44 (59.5) | 50 (67.6) | 180      | 5 (2.8)  | 59 (32.6) | 64 (35.6) |

* n indicates narrow; B, broad; BPI, bipolar illness; UPI, unipolar illness; AI, affective illness; MZ, monozygotic; DZ, dizygotic; I, index sample; and C, control sample.

(χ²=1.62, P=NS) did not predict the risk of AI in the cotwin. However, risk of AI in the cotwin was significantly predicted by both cotwin gender (females higher: χ²=5.60, P=.02) and cotwin zygosities (MZ cotwins higher: χ²=10.45, P=.001).

Using broad diagnostic criteria, the effects of proband gender (χ²=2.27, P=NS), polarity of proband (χ²=2.03, P=NS), and mode of ascertainment of proband (χ²=0.00, P=NS) remained nonsignificant. The effect of cotwin gender was significant at a trend level (χ²=2.67, P=.10), while the effect of zygosities was even more significant (χ²=28.62, P=.00). These analyses were repeated predicting the risk for only BPI in cotwins. Using narrow diagnostic criteria, proband gender (χ²=0.08, P=NS), cotwin gender (χ²=0.0, P=NS), and mode of ascertainment of proband (χ²=0.05, P=NS) were significant predictors. Zygosity of the pair predicted at the trend level (χ²=2.90, P=.09) and polarity of proband twin (χ²=9.03, P=.003) were highly significant. Using broad diagnostic criteria, gender of proband (χ²=0.32, P=NS), gender of cotwin (χ²=0.27, P=NS), and mode of ascertainment (χ²=0.36, P=NS) remained nonsignificant. By contrast, both zygosity of the pair (χ²=9.38, P=.002) and polarity of the proband (χ²=4.46, P=.03) significantly predicted the risk of BPI in the cotwin.

PROBANDWISE CONCORDANCE IN COMBINED SUBJECTS

The Cox proportional hazards analyses suggested that the index and control twin samples could be combined to

Table 5. Probandwise Concordance for Total Affective Illness in the Combined Index and Control Sample Divided by Zygosity and Gender

<table>
<thead>
<tr>
<th>Zyosity</th>
<th>Diagnostic Criteria</th>
<th>Total No.</th>
<th>Affected, n (%)</th>
<th>Total No.</th>
<th>Affected, n (%)</th>
<th>Total No.</th>
<th>Affected, n (%)</th>
<th>Total No.</th>
<th>Affected, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MZ</td>
<td>N</td>
<td>11</td>
<td>4 (36.4)</td>
<td>45</td>
<td>23 (51.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MZ</td>
<td>B</td>
<td>20</td>
<td>12 (60.0)</td>
<td>69</td>
<td>50 (72.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DZ</td>
<td>N</td>
<td>12</td>
<td>2 (16.7)</td>
<td>56</td>
<td>15 (26.9)</td>
<td>25</td>
<td>9 (36.0)</td>
<td>35</td>
<td>4 (11.4)</td>
</tr>
<tr>
<td>DZ</td>
<td>B</td>
<td>20</td>
<td>5 (25.0)</td>
<td>97</td>
<td>33 (34.0)</td>
<td>44</td>
<td>20 (45.6)</td>
<td>54</td>
<td>17 (31.5)</td>
</tr>
</tbody>
</table>

* For male-female and female-male twins, the gender of the proband is listed first, followed by the gender of the cotwin. MZ indicates monozygotic; DZ, dizygotic; N, narrow; and B, broad.
provide the most accurate estimate of the PRC for AI in our sample. These results are seen for total AI in Table 3 and by polarity in Table 4. For narrowly defined total AI, the best estimate of PRC is 48.2% ± 6.7% in MZ and 23.4% ± 3.7% in DZ twins. The parallel percentages for broadly defined AI are 69.7% ± 4.9% and 34.9% ± 3.2%, respectively.

With the combined sample, the numbers of twins are sufficient to meaningfully examine the impact of gender on concordance rates for total AI. As seen in Table 5, PRC in both MZ and DZ twins is consistently greater in female-female than in male-male pairs. In the DZ opposite-sex pairs, the rates of total AI in the male and female cotwins are similar to those found in the same-sex pairs.

EXAMINATION OF POTENTIAL COOPERATION BIAS

The response rate to the mailed questionnaire was 37% higher in control twins sampled at random from the population than in twins hospitalized for AI. While several factors might explain this finding, it is reasonable to assume that individuals with AI are less likely to return questionnaires. If this is the case, the impact of this bias on population prevalence and PRC for AI can be estimated. For narrowly defined total AI, the true population prevalence, DZ PRC, and MZ PRC can be estimated at 20.3%, 30.0%, and 56.0%, respectively. For broadly defined total AI, the parallel figures are 39.6%, 42.3%, and 75.9%, respectively.

COMMENT

GENETIC AND ENVIRONMENTAL INFLUENCES IN AI

As reported by previous studies of twins hospitalized for AI, concordance rates for AI in this sample were substantially higher in MZ than in DZ twins. As no evidence was found for violations of the equal environment assumption, these results strongly argue for the operation of genetic factors in the etiology of AI. In particular, these results are not consistent with the results from two adoption studies or one recent population-based twin study that suggested little or no genetic influence on risk for AI.

Results from our index sample can be usefully compared with those reported by Bertelsen et al since both studies ascertained twin probands through a Scandinavian psychiatric twin registry and both used narrow and broad diagnostic criteria (although the criteria were conceptualized differently in the two studies). With narrow criteria, Bertelsen et al found a PRC rate for total AI of 67% (46/69) in MZ twins and 20% (11/54) in DZ twins. With their broad criteria, the parallel figures were 87% (60/69) and 37% (20/54). Despite marked differences in method of diagnostic assessment (unstructured, "non-blind" personal interviews vs structured self-report questionnaire), with the exception of a lower MZ concordance using the narrow diagnostic criteria in the current sample, the PRC figures are similar in the two studies.

UPI AND BPI

The etiologic relationship between UPI and BPI remains one of central interest to affective disorder research. A recent review of the published family studies of UPI and BPI concluded that the "findings regarding the relationship of unipolar and bipolar disorders were ambiguous." The small number of BPI probands in our sample made it impossible to reach any definitive conclusion regarding the BPI/UPI relationship. However, our results are inconsistent with an independent transmission model of BPI and UPI since the nonbipolar MZ cotwins of BPI probands are at increased risk for UPI. The results are also inconsistent with an environmental model (in which BPI and UPI are the same familial disorder but are differentiated by nonfamilial environmental factors) since BPI in the proband twin is a strong predictor of BPI in the cotwin.

HOSPITAL- VS COMMUNITY-ASCERTAINED CASES OF AI

Clinical and epidemiologic researchers have disputed the relationship between cases of AI seen in treatment settings and those seen in the community. In particular, some have argued that community cases are more environmental and less genetic or biologic than cases seen in treatment settings. This hypothesis, which may be widely held, has not, to our knowledge, been previously subject to empirical test since no previous twin study of AI has included both hospitalized and epidemiologic subsamples.

In our study, we found no evidence that the risk of illness in cotwins of proband twins meeting diagnostic criteria for AI differed if the proband twin had been ascertained through psychiatric hospitalization or from the general population. These results suggest that genetic and environmental factors play similar etiologic roles in AI as it occurs in hospitalized samples and in the community. The factors that influence whether an individual affected with AI will be hospitalized appear, in our sample, to be uncorrelated with the familial liability to illness. These results are broadly consistent with two previous findings. First, Weissman and his colleagues found that the risk for AI in first-degree relatives of "severe" hospitalized cases of AI was no greater than that seen in relatives of "mild" cases of major depression seen in an outpatient setting. Second, unpublished analyses from the Virginia population-based sample of female twins, the heritability of major depression, defined by DSM-III-R, did not significantly
change when the definition was revised to require treatment seeking (K.S.K., unpublished data, September 1990). If confirmed, these results have broad implications for research strategies for AI. In particular, they suggest that research into the genetic risk factors for AI can be carried out equally well in treated and community samples.

NARROWLY AND BROADLY DEFINED AI

A major uncertainty in the use of self-report information to derive DSM-III-R diagnoses was the threshold at which to consider an individual criterion "present." We therefore included in the questionnaire and in our current analyses two possible thresholds. Varying the threshold had a large impact on case definition. Affective illness defined by the broad criteria was twice as common both in the general population and in the cotwins of affected twins as was AI defined by the narrow criteria. These results do not, however, suggest that either the narrow or broad definition of AI is clearly more valid.

LIMITATIONS

The most important methodological limitation of this study is that the psychiatric diagnoses were solely based on self-report questionnaires. Eight arguments can be made that this mode of evaluation, although unconventional, provides a valid assessment of the twins' lifetime vulnerability to AI. First, the face validity of the questionnaires is high because the questions were directly adapted from the Structured Clinical Interview for DSM-III-R to cover all DSM-III-R criteria for major depression and mania. Second, in this study, diagnoses derived from our questionnaires agreed with hospital diagnoses at far above chance levels. Third, the pattern of lifetime prevalences of UPI and BPI in men and women produced by this questionnaire in our epidemiologic twin sample (Table 1) is similar to that reported with more standard assessment techniques. Fourth, our results in twin pairs provide further support for the validity of the assessment technique. Not only are our overall concordance rates in MZ and DZ twins similar to earlier studies but, in addition, there are several patterns in our results (eg, an effect of gender in cotwin but not in proband, a significant increase risk for BPI in cotwins of BPI proband twins) that would be difficult to explain by error or biased reporting. Fifth, other researchers have examined the validity of a self-report instrument—the Inventory to Diagnose Depression—to diagnose current major depression by DSM-III criteria. Concordance between the Interview to Diagnose Depression and a structured psychiatric interview was generally high. Major depression diagnosed by the Interview to Diagnose Depression was two to three times more common in relatives of patients with major depression than in relatives of controls. Sixth, in the Virginia Twin Registry, a joint analysis of a lifetime history of major depression assessed both by self-report questionnaire and by personal interview indicated that the former reflected the underlying liability to major depression slightly more strongly than did the latter (results available on request). Seventh, previous survey research suggests that the validity of data obtained by self-report mailed questionnaire favorably compares with that obtained at interview and may even be superior for sensitive information. Last, by applying a computer algorithm directly to the informant responses, subjective bias on the part of investigators was eliminated. Since only 2.7% of the complete twin pairs lived together and only 10.7% of them filled out their questionnaires on the same day, collusion in completion of the questionnaires was probably uncommon. However, it cannot be ruled out that substantially different results might have been obtained had the diagnoses been based on structured psychiatric interviews and/or hospital records. In particular, the absence of hospital records may have resulted in an underdiagnosis of BPI because compared with depressive episodes, manic episodes may be more often forgotten.

This study has three other potentially significant methodologic limitations. First, zygosity diagnoses were also solely based on self-report measures, the error rate of which has usually been estimated to be in the range of 5% to 10%. We suspect that in this study, the error rate is toward the lower end of this figure because we validated our diagnoses against a large, well-characterized database and excluded uncertain pairs. Agreement in self-report blood type, when available in both members of a pair, was strongly associated with our zygosity diagnosis. The similarity of our results in same-sex DZ twins (where zygosity errors may occur) and opposite-sex DZ pairs (who can be confidently diagnosed as DZ) further suggests that large effects of biased zygosity diagnosis are unlikely.

Second, due to the unscreened nature of the sample and the modest resources of the study (which precluded a rigorous follow-up of nonrespondents), the response rate to the questionnaire was relatively low. Furthermore, the pattern of nonresponse was not random but was greatest in index probands. We showed that such a cooperation bias was unlikely to produce a substantial bias in the results obtained. However, it cannot be ruled out that other biases were present in the response pattern that could have substantially influenced the observed results.

Third, a lifetime history of AI was assessed in this study at a single point in time so that we are unable to distinguish factors that influence the actual occurrence of AI from factors that influence its recall or reporting. Furthermore, the reliability of single cross-sectional assessments for AI is far from perfect. Discordance for AI in some twin pairs therefore may be due to the unreliability of reporting rather than differences in environmental experiences or, in DZ twins only, differences in genetic vulnerability.
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