A Population-Based Twin Study of Lifetime Major Depression in Men and Women

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Background: Women report higher rates of major depression (MD) than men. Although genetic factors play an important etiologic role in MD, we are uncertain whether genetic factors are of equal importance in men and women, and whether the same genetic factors predispose men and women to MD.

Methods: We obtained, by telephone interview, a lifetime history of MD, defined by the DSM-III-R, from 3790 complete male-male, female-female, and male-female twin pairs, identified through a population-based registry. Results were analyzed using probandwise concordance, odds ratios, and biometrical twin modeling.

Results: The odds ratios (plus tetrachoric correlations) for lifetime MD were as follows: (1) male-male monozygotic, 3.29 (+0.37); (2) male-male dizygotic, 1.86 (+0.20); (3) female-female monozygotic, 3.02 (+0.39); (4) female-female dizygotic, 1.59 (+0.18); and (5) male-female dizygotic, 1.39 (+0.11). In the best-fitting twin model, the heritability of liability to MD was the same in men and women and equal to 39%, while the remaining 61% of the variance in liability was due to individual-specific environment. We rejected, with only modest confidence, the hypothesis that the genetic risk factors for MD were the same in men and women. The best-fitting model estimated the genetic correlation in the liability to MD in the 2 sexes to be +0.57. While we found no evidence to suggest a violation of the equal environment assumption, MD was less common in women from opposite-sex vs same-sex twin pairs.

Conclusions: Major depression is equally heritable in men and women, and most genetic risk factors influence liability to MD similarly in the 2 sexes. However, genes may exist that act differently on the risk for MD in men vs women.

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In 1992, we reported lifetime diagnoses of major depression (MD) in personally interviewed members of a group of 1033 female-female (FF) twin pairs identified through the population-based Virginia Twin Registry.1 We have since conducted a parallel study of male-male (MM) and male-female (MF) twin pairs from this registry and reinterviewed the original FF twins.

In this article, we examine monozygotic (MZ) and dizygotic (DZ) MM pairs to estimate the etiologic role of genetic and environmental risk factors for MD in men. We also analyze results from the MM, FF, and MF pairs together so as to (1) determine whether genetic and environmental risk factors are of similar importance in the etiology of MD in men and women and (2) assess whether the genetic risk factors for MD in men are the same as the genetic risk factors for MD in women.

RESULTS

MM TWIN PAIRS

The prevalence of lifetime MD as defined by the DSM-III-R14 was slightly higher in members of complete MM DZ pairs (17.0%), than in members of complete MZ pairs (14.9%), but this difference was not significant ($\chi^2 = 1.97, P = .16$). In these twin pairs, when controlling for zygosity, resemblance for a diagnosis of lifetime MD was predicted neither by measures of the resemblance of the twin pair's childhood environment ($\chi^2 = 0.28, P = .59$) nor by the frequency of their current contact in adulthood ($\chi^2 = 1.27, P = .26$). We also found no significant relationship between the lifetime history of MD in 1 twin and whether his co-twin agreed to be interviewed ($\chi^2 = 3.20, P = .07$).

The 2 × 2 contingency tables for MD in the MM twin pairs are given in Table 1.
SUBJECTS AND METHODS

SUBJECTS

The twins in this article derive from 2 interrelated projects using the population-based Virginia Twin Registry, formed from a systematic review of all birth certificates in the Commonwealth of Virginia, which now constitutes part of the Mid-Atlantic Twin Registry. The details of the samples in these 2 projects are outlined in the Figure. This article reports results from the third interview wave with the sample of FF twins (FF3) and the first interview wave with the sample of MM and MF twins (MM/MF). While the FF sample began with twins who had previously responded to registry contact and our first assessment was by mailed questionnaire (FFQ), the MM/MF sample began with raw registry files and the first wave of contact was by telephone interview (Figure). In FF3, we assessed both members of 834 pairs, 506 of whom were MZ, 345 of whom were DZ, and 3 of whom had unknown zyosity. The mean (SD) age of the participating twins in FF3 was 34.6 (7.5) years and ranged from 22 to 59. From the MM/MF sample, we interviewed both members of 851 MM MZ pairs, 647 MM DZ twins, and 1404 opposite-sex MF DZ pairs. In addition, this sample contained a group of 10 triplet sets in which we were able to interview only 2 members of each set; a group of 14 triplet sets in which we interviewed all 3 members of each set; and 1 set of quadruplets, all of whom we interviewed. From these higher-order multiple births, we formed a total of 58 additional twin pairs: 3 FF MZ, 3 FF DZ, 13 MM MZ, 12 MM DZ, and 27 MF DZ. We reran the major analyses presented in this article, excluding members of high-order multiple births, and the results were essentially unchanged. At the time of interview, subjects in MM/MF ranged in age from 18 to 60 years, with a mean of 35.1 (9.2).

The OR for a lifetime diagnosis of MD was significantly greater in MZ twins (OR = 3.29) than in DZ twins (OR = 1.86) (Breslow-Day test = 2.98, P = .04) (Table 2). The tetrachoric correlation for the liability to lifetime MD was estimated at +0.37 in MZ and +0.20 in DZ twins (Table 2).

We performed model fitting to these data, assuming a single threshold for MZ and DZ twins. The full ACE model fit well (\(\chi^2 = 2.86, P = .41, \text{AIC} = -3.13\)). The CE model, which postulates that twin resemblance for MD could be explained entirely by familial-environmental factors, fit more poorly (\(\chi^2 = 5.84, \text{AIC} = -2.16\)) and could, compared with the ACE model, nearly be rejected by the \(\chi^2\) difference test (\(\chi^2 = 2.98, P = .08\)). However, the AE model, which assumes that twin resemblance for MD entirely is due to genetic factors, fit as well as the ACE model \(\chi^2 = 2.87, \text{AIC} = -5.13\) and was preferable by AIC because of its greater parsimony. Based on the best-fitting AE model, the heritability of liability to MD in male twins was estimated at 38% (95% confidence intervals [CIs], 25%-50%). The remaining 62% of the variance in liability was due to individual specific environmental factors.

As outlined previously, in the FF sample, zyosity was initially determined by a blind review of 2 experienced twin researchers (K.S.K. and Ms Phyllis Winter) that used standard questions and photographs. Blood samples were obtained from both members of 119 pairs of uncertain zyosity and analyzed using 8 restriction fragment length polymorphism makers. More recently, we have performed polymerase chain reaction zyosity tests on an additional 269 twin pairs, oversampling those where our prior zyosity assignment was questionable. On the basis of these tests (where the mean number [SD] of markers tested per pair was 17.5 [8.4]), zyosity was changed for 12 pairs (4.5% of those tested). In the MM/MF sample, zyosity was initially determined by an algorithm based on standard questions, validated against the zyosity diagnoses in the FF sample. Application of the algorithm to this male sample was validated by analysis of polymerase chain reaction polymorphisms (mean [SD] of 11.5 [11.9] markers per pair) in a random sample of 196 twin pairs. The algorithm classified 186 pairs correctly, an error rate of 5.1%.

MEASURES

Lifetime MD was assessed, with high reliability between raters (mean ± SD, \(\kappa = 0.96 ± 0.04\)), by a structured psychiatric interview based on the Structured Clinical Interview for DSM-III-R.4 However, we assessed last-year history for MD and a lifetime history for MD prior to the last year in 2 separate sections. Interviewers were carefully trained and supervised and had at least a master’s degree in a mental health–related field or a bachelor’s degree in such a field and 2 years of clinical experience. Senior staff reviewed each interview for completeness and consistency. Data were double-entered to minimize errors. Members of a twin pair were interviewed by different interviewers who were blind to clinical information about the co-twin.

FF TWIN PAIRS

Controlling for age, the prevalence of lifetime DSM-III-R MD was nonsignificantly higher in members of complete DZ pairs (35.5%) than in members of the complete MZ pairs (31.2%) (\(\chi^2 = 2.53, P = .11\)). In these FF pairs, when controlling for zyosity, resemblance for a diagnosis of lifetime MD was predicted neither by measures of the resemblance of the childhood environment of the twin pairs (\(\chi^2 = 0.30, P = .59\)) nor by the frequency of their current contact in adulthood (\(\chi^2 = 0.20, P = .66\)). No relationship was found between the lifetime history of MD in 1 twin and whether the co-twin was successfully interviewed (\(\chi^2 = 0.38, P = .54\)).

Table 1 also gives the contingency tables for MD for FF (and MF) pairs. The OR for a lifetime diagnosis of MD was significantly greater in MZ twins (OR = 3.02) than in DZ twins (OR = 1.59) (Breslow-Day test (\(\chi^2 = 4.32, P = .02\)), while the tetrachoric correlation was estimated at +0.39 in MZ and +0.18 in DZ twins (Table 2).

We performed model fitting to these data, assuming a single threshold in MZ and DZ twins. The full ACE
STATISTICAL ANALYSIS

We present information about twin resemblance in several ways. Probandspecific concordance is the proportion of affected co-twins of affected twins. The odds ratio (OR) is the ratio of the risk of being affected among co-twins of affected twins and the risk of being affected among co-twins of unaffected twins. The difference in ORs between MZ and DZ twins is assessed by a 1-tailed Breslow-Day test,5 given our directional hypothesis of greater MZ resemblance.

We use a liability-threshold model to estimate the genetic and environmental contributions to twin resemblance. For categorical characteristics like MD, the estimates are for the similarity between twins in liability to develop the disorder.6 Liability is assumed to be continuous and normally distributed in the population, with individuals who exceed a theoretical threshold expressing the disorder. We also present the tetrachoric correlation, defined as the correlation in members of twin pairs for the liability to MDD.

When the basic twin model is used, individual differences in liability are assumed to arise from 3 sources: additive genes (A), common or familial environment (C), and individual-specific environment (E) (see references 8 and 9 for more detailed descriptions). In addition, by comparing estimates for A, C, and E in MM and FF pairs, we can examine whether the relative importance of genetic or environmental risk factors for MD differs in men and women. Furthermore, by analyzing all 5 twin zygosity groups, we can address an additional question: to what extent do the same genetic and/or environmental factors influence MD in men and women? Twin models can also contain nonadditive genetic effects (dominance or epistasis). However, in no case did the addition of such a parameter provide a better fit than that presented here. The twin models employed also assume independence and additivity of the latent variables, absence of assortative mating, equality of shared environmental effects for MZ and DZ twins, and no age effects.

Models were fit with maximum likelihood estimation using the Mx structural modeling program.10 Model fit is evaluated using the principle of parsimony. Models with fewer parameters are considered preferable if they do not provide a substantially worse fit. We operationalize parsimony by using the Akaike information criterion (AIC) statistic (which has been recently validated), calculated as the model $\chi^2 - 2$ times the degrees of freedom (df). We then present parameter estimates from the best-fitting model, where $a^2$ and $c^2$ equal the proportion of variance in liability due to additive genetic effects and individual specific environment, respectively. The parameter $r_g$ is the correlation of the additive genetic effects in men and women. If $r_g = 0$ or 1, then the genetic factors that influence MD in men and women are, respectively, entirely unrelated or identical.

Given that the risk to MD is correlated in twin pairs, twin studies provide a method of testing for the possible effect of differential cooperation. If noncooperation is positively correlated with the risk for MD, then the rates of MD should be higher in twins whose co-twin refused to participate in the study.

The equal environment assumption requires that MZ and DZ twin pairs be similar in their shared environments that are of etiologic relevance for the trait being studied. If the environments of DZ twin pairs were less similar than those of MZ twin pairs, this would lead to an underestimation of shared environment and a proportional overestimation of genetic influence. We examine this possibility in 2 ways: by examining standard measures of the environmental similarity of twins in childhood13 and by examining the frequency of contact between the twins in adulthood. Using logistic regression and controlling for zyosity, we examined whether the mean level of childhood or adult environmental similarity reported by the twin pair interacted with the diagnosis of MD in 1 twin in predicting the risk for MD in the co-twin.

MF TWIN PAIRS

The prevalence of lifetime MD as defined by the DSM-III-R in male members of MF DZ twin pairs (17.8%) was not significantly different from that seen in male members of MM DZ pairs (17.1%) ($\chi^2 = 0.72, P = .40$). However, controlling for age, the lifetime prevalence of MD was significantly lower in the female members of the MF DZ twin pairs (26.9%) than in female members of FF DZ twin pairs (35.8%) ($\chi^2 = 16.63, P = .001$). In the MF pairs, controlling for the effects of sex, similarity for lifetime MD was not predicted by resemblance of the childhood environment of the twin pairs ($\chi^2 = 0.99, P = .76$) or by the frequency of their contact in adulthood ($\chi^2 = 0.03, P = .85$). Similarly, the cooperation status of 1 twin was unrelated to the risk for MD in the co-twin ($\chi^2 = 1.80, P = .18$). Both the OR (1.39) and the tetrachoric correlation (+0.11) for lifetime MD were lower in the opposite-sex than same-sex DZ twin pairs.

MODEL FITTING TO MM, FF, AND MF TWIN PAIRS

Our model fitting assumed 3 thresholds: all men, female members of MF DZ pairs, and all other women. Model 1 separately estimated A, C, and E in men and women and allowed the correlation between the sexes for the effects of additive genetic factors to be estimated (Table 3). For model identification, in model 1 only, we assumed that the sexes were perfectly correlated for the effect of common environmental factors influencing the liability to MD. This model fit well ($\chi^2 = 11.20, P = .13$). In model 2, we set all the pa-
In addition, the classic twin study of affective illness by Silberg et al.13 estimated the heritability of MD to be the same in men and women. The findings in this report, both studies estimated heritability of 36%. Neither study found evidence that familial-environmental factors contributed to MD in men. The heritability of liability to lifetime MD, defined by DSM-III-R criteria, was estimated at 42%. This is reassuringly close to the 39% estimated here using our third wave of personal interviews, mostly conducted by telephone.

Table 1. Raw Contingency Tables for Major Depression in the 5 Twin Gender-Zygosity Groups*

<table>
<thead>
<tr>
<th>Zygosity</th>
<th>Sex</th>
<th>Lifetime Prevalence</th>
<th>Probandwise Concordance</th>
<th>Odds Ratio (OR)</th>
<th>Tetrachoric Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM</td>
<td>Male</td>
<td>14.9</td>
<td>31.1</td>
<td>3.29</td>
<td>+0.37</td>
</tr>
<tr>
<td>MM</td>
<td>Female</td>
<td>17.1</td>
<td>25.1</td>
<td>1.86</td>
<td>+0.20</td>
</tr>
<tr>
<td>DZ</td>
<td>Male</td>
<td>30.7</td>
<td>47.6</td>
<td>3.02</td>
<td>+0.39</td>
</tr>
<tr>
<td>DZ</td>
<td>Female</td>
<td>35.8</td>
<td>42.6</td>
<td>1.59</td>
<td>+0.18</td>
</tr>
<tr>
<td>DZ</td>
<td>Male</td>
<td>17.8</td>
<td>21.5</td>
<td>1.39</td>
<td>+0.11</td>
</tr>
<tr>
<td>DZ</td>
<td>Female</td>
<td>26.9</td>
<td>32.5</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*M2 indicates monozygotic; DZ, dizygotic; MM, opposite-sex twin pairs with the female as proband and the male as co-twin; and MF, opposite-sex twin pairs with the male as proband and the female as co-twin.

Table 3. Model Fitting for Lifetime Major Depression in Male-Female, Female-Female, and Male-Female Twin Pairs*

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Fit Indexes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
</tr>
<tr>
<td>1</td>
<td>A, C, E</td>
</tr>
<tr>
<td>2</td>
<td>A, E</td>
</tr>
<tr>
<td>3</td>
<td>A, E</td>
</tr>
<tr>
<td>4</td>
<td>A, E</td>
</tr>
<tr>
<td>5</td>
<td>A, E</td>
</tr>
</tbody>
</table>

*F indicates free to be estimated; $t_1$, correlation between the sexes for additive genetic (A) factors; $t_2$, correlation between the sexes for common environmental (C) factors; df, degrees of freedom; AIC, Akaike information criterion; E, individual specific environmental effects.

30%-47%) in both men and women. The remaining 61% of the variance in liability was attributed to individual-specific environment. The genetic correlation ($r_g$) between men and women was estimated at +0.57.

**HERITABILITY OF MD IN MEN AND WOMEN**

We are aware of one general population twin study of lifetime MD in men. In 3372 twin pairs from the Vietnam Era Twin Registry, Lyons et al.13 reported results that were similar to those found in our sample: tetrachoric correlations in MZ and DZ pairs of +0.37 and +0.13 and an estimated heritability of 36%. Neither study found evidence that familial-environmental factors contributed to MD in men.

In our previous report on lifetime MD in the FF twin sample, based on our first wave of interviews done face-to-face, heritability of liability to lifetime MD, defined by DSM-III-R, was estimated at 42%. This is reassuringly close to the 39% estimated here using our third wave of personal interviews, mostly conducted by telephone.

Two prior twin studies10,11 included MM and FF twin pairs and examined whether genetic risk factors were of equal importance in MD in men and women. In accord with the findings in this report, both studies estimated the heritability of MD to be the same in men and women. In addition, the classic twin study of affective illness by Bertelsen et al.13 reported no significant differences in con-
cords in men and women. In the single relevant adoption study of MD that we could find, Cadoret et al.\textsuperscript{29} report that both male and female adoptees had a similar 2.1-fold increased risk for MD associated with a history of affective disorders in biological relatives. The available evidence suggests that genetic factors are of similar etiologic importance for MD in men and women.

**GENETIC RISK FACTORS FOR MD IN MEN AND WOMEN: SAME OR DIFFERENT GENES?**

To examine the similarity of genetic risk factors for MD in men and women requires the comparison of resemblance in same-sex and opposite-sex relatives. Most but not all family studies that have examined this question find lower resemblance for lifetime MD in opposite-sex vs same-sex sibling or parent-offspring pairs.\textsuperscript{21,22} One prior twin study of MD has examined opposite-sex DZ pairs.\textsuperscript{17} Sample size was moderate and diagnoses were obtained by self-report questionnaire. The best-fitting model estimated the genetic risk factors for MD to be the same in the both sexes.\textsuperscript{18}

In this study, the preferred model estimated the genetic risk factors for MD in men and women to be positively, but not perfectly, correlated. This model provided a moderately better fit to the data than 2 alternative models that assumed either that (1) men and women shared all of their genes for MD or (2) men and women shared none of their genes for MD.

Given that the most parsimonious interpretation of all available data is that men and women share some, but not all, of their genes for MD, what might be the source of these differences in genetic risk factors? Three hypotheses are noteworthy. First, although such a pattern might be due to susceptibility genes for MD located on the X chromosome, the pattern of correlations in liability observed for sibling and parent-offspring pairs does not fit that predicted for an X-linked trait.\textsuperscript{24} Second, the developmental pathways toward MD may differ in men and women. In men, externalizing disorders such as antisocial personality, alcoholism, and other drug abuse, all of which are heritable,\textsuperscript{25-28} increase the risk of developing MD.\textsuperscript{29,30} In women, anxiety disorders, which are also heritable,\textsuperscript{31-33} may be particularly important as a precursor to MD.\textsuperscript{34} Third, exposure to gonadal hormones differs in men and women. Some portion of the genetic risk factors for MD in women might reflect the sensitivity to the depressogenic effect of menstrual and/or pregnancy-related hormonal changes,\textsuperscript{35-36} mediated, for example, by variation in the estrogen receptor.\textsuperscript{37} Such genetic risk factors, while expressed in women, would be largely dormant in men. In accord with this hypothesis, we recently found that genetic risk factors for premenstrual symptoms accounted for ~17% of the genetic risk factors for lifetime MD in female twins.\textsuperscript{38}

**LIMITATIONS**

The results of this study should be interpreted in the context of 8 potential methodologic limitations. First, despite our large sample and the considerably lower degree of resemblance for lifetime MD in opposite-sex vs same-sex DZ twin pairs, our study provides only suggestive evidence for sex-specific risk factors for MD. Very large samples are needed to reliably detect sex-specific familial transmission for a dichotomous trait such as MD.\textsuperscript{39} If this study is correct, and the genetic correlation between sexes in the liability to MD is ~0.6, this effect would be detectable in only the larger of family studies, and would not likely be observed in the previous twin study\textsuperscript{17} with one eighth the sample size. Replication of the results is required before sex-specific transmission of the liability to MD should be considered established.

Second, diagnostic assessments in this sample were completed largely by telephone. However, both we\textsuperscript{1} and others\textsuperscript{40-42} have found little difference in assessment of psychiatric disorders by telephone vs face-to-face. Furthermore, very similar heritability estimates for lifetime MD in FF twins were obtained from telephone vs face-to-face interviews.\textsuperscript{3}

Third, because of its low prevalence\textsuperscript{43} and low reliability in general population samples,\textsuperscript{44} mania was not assessed in our first interview of MM and MF twin pairs. Therefore, we cannot, in these analyses, distinguish persons with MD from those with bipolar illness. However, in our FF twins, removing cases who met criteria for bipolar illness produced very small effects on prevalence and heritability of MD.\textsuperscript{45}

Fourth, our estimates of lifetime prevalence for MD were substantially greater than those reported in the National Comorbidity Survey,\textsuperscript{46} although similar to or lower than those reported in other population-based studies.\textsuperscript{46,47} In our interview, the history of MD is assessed separately for the last-year and lifetime prior to last-year MD. While the National Comorbidity Survey used lay interviewers and a highly structured psychiatric interview, a procedure that may underestimate the population rates of MD,\textsuperscript{48} we employed experienced clinicians who worked with a semistructured interview. As done in the National Comorbidity Survey, we used several methods to encourage “effortful responding.” Our sample was somewhat younger than that assessed in the National Comorbidity Survey, which may also contribute to prevalence differences.\textsuperscript{49}

Fifth, female members of opposite-sex DZ twin pairs had a lower risk for MD than other female twins. It is unclear whether such differences are real or methodologic, resulting from differences in the prior history of the sample (the same-sex female twins having been interviewed twice before) or measurement (the lifetime MD section in the same-sex, but not opposite sex, pairs contained items assessing melancholia). Regardless, because we sampled twins independently of their psychiatric status, and therefore have “built in” control groups, such differences in prevalence do not invalidate our results when incorporated into our analyses.

Sixth, a lifetime history of MD was assessed at one point in time, an approach that confounds effects of individual-specific environment and measurement error. In our FF twin pairs, we found that heritability of liability to MD increased substantially when removing the effect of errors of recall.\textsuperscript{50}

Seventh, the sample was entirely white; therefore, the results cannot be extrapolated to other ethnic groups.
Eighth, because our twin analyses ignored the age structure of our sample, we performed 2 additional analyses. Using a Cox proportional hazards model, controlling for age, we found that the hazard rate for MD was significantly greater in the co-twins of MZ vs DZ twins ($\chi^2=18.95, P<.0001$, RR = 1.47) and the female co-twins of female vs male DZ twins ($\chi^2=5.07, P = .02, RR = 1.41$), while the difference in the hazard rate for the male co-twins of male vs female DZ twins did not differ significantly ($\chi^2=0.62, P = .43, RR = 1.15$). We also performed a median split on the sample and separately fit models to the younger and older subsets, finding similar estimates for heritability (36.6 and 38.2%, respectively) and for the genetic correlation across sexes ($+0.71$ and $+0.57$, respectively). When we set these 2 parameters to be equal across the 2 age cohorts, the model fit of the model hardly changed ($\chi^2=0.1, P = .95$).

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