A Longitudinal Twin Study of 1-Year Prevalence of Major Depression in Women

Kenneth S. Kendler, MD; Michael C. Neale, PhD; Ronald C. Kessler, PhD; Andrew C. Heath, DPhil; Lindon J. Eaves, PhD, DSc

**Objectives:** This study seeks to clarify the etiologic importance and temporal stability of the genetic and environmental risk factors for 1-year prevalence of major depression (1YP-MD) in women.

**Design:** One-year prevalence of major depression was personally assessed, using DSM-III-R criteria, at two time points a minimum of 1 year apart.

**Participants:** Both members of 938 adult female-female twin pairs ascertained from the population-based Virginia Twin Registry.

**Results:** The correlation in liability to 1YP-MD was much greater in monozygotic (MZ) than in dizygotic (DZ) twins at time 1 alone, time 2 alone, or at either time 1 or time 2. Model fitting suggested that the liability to 1YP-MD was due to additive genes and individual specific environment with a heritability of 41% to 46% and was not biased by violations of the equal environment assumption. Jointly analyzing both times of assessment using a longitudinal twin model suggested that, over a 1-year period, genetic effects on the liability to 1YP-MD were entirely stable, while environmental effects were entirely occasion specific.

**Conclusions:** These results suggest that (1) genetic factors play a moderate etiologic role in the 1YP-MD, (2) the temporal stability of the liability to major depression in adult women is largely or entirely genetic in origin, and (3) environmental factors play a significant role in the etiology of major depression, but their effects are generally transitory and do not result in enduring changes in the liability to illness.

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From the Departments of Psychiatry (Drs Kendler and Eaves) and Human Genetics (Drs Kendler, Neale, and Eaves), Medical College of Virginia/Virginia Commonwealth University, Richmond; the Institute for Social Research, University of Michigan, Ann Arbor (Dr Kessler); and the Department of Psychiatry, Washington University School of Medicine, St Louis, Mo (Dr Heath).

MAJOR DEPRESSION (MD) is a common and often disabling psychiatric condition,13 with affected individuals at increased risk for both psychosocial and medical problems.14 Many studies have found that MD is a familial disorder.7 Twin and adoption studies have, with conflicting results, attempted to clarify the degree to which the familial aggregation of MD8,15 is due to genetic vs familial-environmental factors. Of the three major adoption studies of depression, only one11 has found significant evidence for genetic effects, while the other two provided more support for the etiologic importance of environmental factors.12,13 Before 1990, there were 11 major twin studies of affective illness,7 all of which suffered from one or more of the following methodologic limitations: (1) unrepresentative samples, (2) small sample sizes that precluded rigorous statistical evaluation, (3) nonblind evaluation and diagnosis, (4) use of indirect diagnostic information, and (5) nonblind or potentially inaccurate zygositivity evaluation. Since 1990, three twin studies of MD have been published. Andrews et al14 blindly interviewed 446 twin pairs from a volunteer twin sample from Australia. Concordance rates for MD were low but somewhat greater in dizygotic (DZ) than in monozygotic (MZ) twins, suggesting no etiologic role for genetic factors in MD. McGuffin and colleagues15 studied 141 twin probands with DSM-III16 major affective disorder who were ascertained through a hospital-based registry. Personal interviews were available in 35% of the sample, with the re-
METHODS

The sample and our general approach to the analysis of population-based twin data have been outlined in detail elsewhere. In brief, this sample of white female same-sex twins was obtained from the population-based Virginia Twin Registry which was formed from a systematic review of birth records in the commonwealth of Virginia. Twins were eligible to participate if both members of the pair had previously responded to a mailed questionnaire. Of the 2352 individuals from 1176 twin pairs who met these criteria, we proceeded in personally interviewing—at what we will call time 1—2163 (92.0%) of them, including both members of 1033 pairs. Of the completed time 1 interviews, 89.3% were performed face to face, and 10.7% were done by telephone. Interviews were conducted by trained social workers who were “blinded” to the status of the co-twin. Zygosity was determined blindly by standard questions, photographs, and, when necessary, DNA.33

Attempts were made to recontact all 2163 originally interviewed twins a minimum of 1 year after their time 1 interview. We succeeded in completing time 2 personal interviews in 2001 (92.5%) of them, including both members of the 938 pairs, the zygosity assignment of which were 546 MZ twins, 390 DZ twins, and two pairs of unknown zygosity. Unlike the time 1 interview, nearly all of the time 2 interviews (98.6%) were completed by telephone. The average number of months (+SD) between the time 1 and time 2 interviews was 17.0±3.7. With the goal of increasing cooperation, where possible, the same interviewer completed the interview at both times. However, because of changes in personnel, this was not possible for a substantial proportion of the twins. Interviewers did not review time 1 interviews before the time 2 interviews. If they recalled information from the time 1 interview, they were instructed not to mention this during the time 2 interview, nor to let it bias their scoring of that interview. The time 2 interviews were also conducted blind to the knowledge of the psychopathologic status of the co-twin.

Both the time 1 and time 2 interviews inquired of all respondents whether, in the last year, they had experienced 20 individual psychiatric symptoms, including all of the DSM-III-R criteria for MD.25 If a respondent answered positively, further questions inquired whether the symptom was due solely to medication or physical illness. If two or more symptoms were endorsed, at the conclusion of the section, the respondent was asked which, if any, of the symptoms had occurred together. If these symptoms co-occurred, we then asked how many such episodes in the past year they had experienced, how long the longest had lasted, and the specific dates of the episodes. The diagnosis of MD was made by applying, by computer algorithm, all of the relevant DSM-III-R criteria for a MD episode. Any individual whose only episode of MD occurred between 1 month before and 3 months after the death of a parent, spouse, sibling, or child was assumed to have normal grief rather than MD.

Interrater reliability was assessed in 53 jointly conducted time 1 interviews where the reliability for MD occurring in the last year was perfect (Restimate±SE k=1.00±.06).30 To assess possible violations of the “equal environment assumption,” twins were asked at time 1 the frequency with which they saw or had contact with their co-twin, with responses ranging from every day to once a year or less.

PRESENTATION OF POPULATION-BASED TWIN DATA

As outlined previously,37 probandwise concordance is an appropriate summary statistic for twin studies when affected individuals have been ascertained through treatment facilities. However, when examining a general population twin sample, probandwise concordance is very inefficient because it ignores twins who are concordant for nonaffectation. In the interest of historic continuity, we present probandwise concordances, but our analyses focus on a more appropriate and efficient statistic: the tetrachoric correlation37 (or “correlation of liability”38). This correlation and its SE were calculated directly from 2×2 tables by the beta test version of PRELIS II.39 Genetic models were fit to these correlations with the use of asymptotic-weighted least squares by the program LISREL 8.50 These models postulated three sources of variance in liability to MD: (1) additive genetic effects (A), (2) shared family or “common” environment (C), and (3) individual-specific environment (E). No evidence for dominance genetic effects were found for any of the models presented below. The proportion of total variance in liability due to additive genetic effects and common and individual-specific environments are termed, respectively, A, C, and E. As a general-fit index for our models, we used Akaike’s information criterion (AIC),11 which reflects both the goodness of fit and parsimony of the model. The more negative the value of the AIC, the better is the overall fit of the model relative to the number of estimated parameters. Where appropriate, we also report a χ² difference test between a model and a submodel, where the df represents the number of parameters in the model that is fixed in the submodel.

A LONGITUDINAL TWIN MODEL

The assessment of twins at two points in time permits the fitting of a longitudinal twin model,32 as illustrated in Figure 1. This model is identical in structure to the bivariate twin model that has been outlined previously in this journal.41 While the bivariate twin model decomposes the sources of comorbidity between two disorders that are assessed at the same time, the longitudinal twin model decomposes the sources of temporal stability of one
disorder that is assessed at two points in time. The critical feature of the longitudinal twin model is the estimation of the correlations between the genetic, common environmental, and individual-specific environmental factors at the two time points, symbolized as $r_1, r_2,$ and $r_3$, respectively. If these correlations are estimated at unity, this indicates that the risk factors are entirely stable throughout the period of measurement. If, by contrast, they are estimated at 0, this indicates that the risk factors are entirelyoccasion specific in their effect, impacting on liability to illness only at a single time of measurement. Estimates between 0 and 1 indicate varying degrees of temporal stability of the risk factors.

The impact of an environmental risk factor for MD could be stable across the two periods of measurement in two ways. First, the event could have occurred before the first period of measurement but produced an enduring increase in liability to MD (e.g., early parental loss). Second, the environmental factor could perpetuate itself across the two periods of measurement (e.g., marital difficulties). Occasion-specific environmental risk factors must, by definition, have only a transient effect on the liability to MD that dissipates between the two times of measurement. Genetic effects will be stable across the two times of measurement if gene expression, and its physiologic sequelae, remain constant throughout that period. Occasion-specific genetic effects would require the expression of new genetic variation between the two periods of measurement.

By "tracing" the paths in the best-fitting longitudinal model, it is possible to determine the degree to which the observed temporal stability of the trait or disorder is due to stable genetic factors (path equals $a_1$, $r_1$, $a_2$, where the subscripts 1 and 2 refer to times 1 and 2 of measurement, respectively) (Figure 1), stable familial-environmental factors (path equals $c_1$, $r_1$, $c_2$), or stable individual-specific environmental factors (path equals $e_1$, $r_1$, $e_2$).

The information to fit the longitudinal model comes from a comparison between three sets of correlations: (I) between twins within one time of measurement, (II) within individuals across the two times of measurement, and (III) between twins across the two times of measurement. The logic of this model can best be illustrated by five examples. First, if all of the genetic and environmental risk factors for MD are occasion specific, then type I correlations could be substantial, but type II and type III correlations would be 0. That is, there should be no correlation in the liability to MD across time. Second, if environmental experiences unique to the individual are the only stable source of variation in liability, then type I and type II correlations can be substantial, but type III correlations will be 0. That is, the risk in a twin at time 1 will predict that twin's future risk for MD but will not predict the future risk for MD in her cotwin. Third, if genetic effects are the only stable source of variation in liability to MD, then type III correlations should be significant and be twice as great in MZ twins as in DZ twins. That is, knowledge of one twin's liability to MD at time 1 would allow you to predict the liability of twin 2 at time 2, but the prediction would be only half as good if the twins were DZ than if they were MZ. Fourth, if the only stable effects are those of the shared family environment, then the type II correlations should be significant and approximately equal in MZ and DZ twins. Finally, fifth, if genetic effects are the only stable source of variation in liability and there are no occasion-specific genetic effects, then not only should the type III correlations be twice as great in MZ and DZ twins, but (1) in both MZ and DZ twins, the type I and type III correlations should be equal; (2) in MZ twins, the type II and type III correlations should be equal; and (3) in DZ twins, the type II correlations should be twice as great as the type III correlations. That is, in both twin types, an individual who is assessed at time 1 will equally predict her cotwin's risk at time 1 or time 2, and in MZ twin pairs, an individual will predict her own risk for MD across time as well as she would predict her cotwin's risk. However, in DZ twin pairs, a twin will predict her own future depression twice as well as she would predict that in her cotwin. For further details with regard to the application of biometric genetic models to twin data, and specifically to longitudinal models, see Eaves et al.23

One of us (M.C.N.) has recently developed a model-based approach to assessing the equal environment assumption based on the computer program Mx.24 In addition to the standard sources of variance in liability (e.g., $a^2$, $c^2$, and $e^2$), this model incorporates a specified common environment ($c_{x}$), in this case indexed by the reported frequency of twin contact. We subdivided the twins into four groups based on their mean frequency of contact as reported at time 1. We then fixed the correlation of this specified common environment for these four groups, in order of increasing frequency of contact, at 0.00, 0.33, 0.66, and 1.00, respectively. Models were then fitted to the eight $2 \times 2$ contingency tables (four levels of contact times two zygosities) that cross-classified twins on the basis of the presence or absence of an episode of MD in the year prior to the time 2 interview. By fixing the value of $c_{x}$ to 0 and examining the deterioration of the model, it is possible to assess rigorously possible violations of the equal environment assumption. Furthermore, if there is a significant estimate of $c_{x}$, this model permits an estimation of additive genetic effects, correcting for the violation of the equal environment assumption.

The MZ twins in this sample were, on average, 1.4 years younger than the DZ twins which, because of the large sample size, was statistically significant.17 Because age was significantly related to the 1-year prevalence of MD in this sample, in presenting the prevalence and concordance rates for MD, we removed, by regression analysis, the effect of the small mean difference in age between the two zygosity groups.
more likely than others to recall previously acknowledged lifetime episodes of depression.

A second limitation of previous twin, family, and adoption studies of MD is that they have been cross-sectional in nature, focusing on a one-time determination of the presence or absence of lifetime episodes of illness. Substantial new insights into the nature of the genetic and environmental risk factors for psychiatric illnesses can be provided by designs that incorporate two or more times of measurement. In particular, little is known about the temporal stability of the risk factors for MD. Several putative environmental risk factors for MD, such as premature parental loss, poor parental-rearing behavior, and sexual abuse, have been hypothesized to have an enduring, and perhaps lifelong, effect on the liability to depression. By contrast, stressful life events appear to have a much more transient effect, producing an increased risk for MD for no more than 3 months. While genetic factors are commonly conceptualized as being temporally stable, in fact, gene expression may be quite variable throughout the life cycle, with certain genetic systems “switching” on and off. While the rate of such switching is probably highest during development (and also may increase during senescence), it cannot be assumed that genetic effects assessed at one age will necessarily be the same as those expressed at a later age.

GOALS OF THIS STUDY

In this report, we examine the 1-year prevalence of MD that was assessed at a personal interview at two time points that were approximately 17 months apart in 938 female twin pairs from the population-based Virginia Twin Registry. We wish to address the following two questions:

1. What is the role of genetic, familial-environmental, and individual-specific environmental risk factors in the etiology of MD as assessed during a 1-year period, and how does this compare with our previous estimates of the lifetime prevalence of MD in this sample?  
2. To what extent are the genetic and environmental effects on liability to depression stable over time vs specific to individual occasions of measurement?

RESULTS

Of the 2001 twins who completed both a time 1 and a time 2 interview, 193 (9.6%) of them at time 1 met DSM-III-R criteria for one or more episodes of MD in the last year. At the time 2 interview, the rate was exactly the same (9.6% [193/2001]). Of the 1808 twins who did not report an episode of MD in the year prior to their time 1 interview, 139 (7.7%) reported an episode of MD in the year prior to the time 2 interview. Of the 193 twins who reported an episode of MD in the year before their time 1 interview, 54 (28.0%) reported an episode of MD in the year before their time 2 interview. The correlation in liability for one or more episodes of MD in the last year between the time 1 and time 2 interviews was + .433 ± .051 (estimate ± SE).
correlation was higher in MZ twins than in DZ twins (+.48 ± .07 vs +.36 ± .08), but this difference was not statistically significant (z = 1.12, not significant [NS])

**POTENTIAL BIASES IN THE SAMPLE**

While 89.3% of the time 1 interviews were conducted face to face, 98.6% of the time 2 interviews were conducted by telephone. Consistent with previous research,

by using logistic regression controlling for age and zygosity, the rates of the 1-year prevalence of MD at the time 1 interview did not differ in those interviewed by telephone vs in person (χ² = 0.09, NS). Of the time 2 interviews, 1110 were conducted by the same interviewer who interviewed the twin at time 1, and 891 were conducted by another interviewer. We predicted, by logistic regression, the probability of having depression at time 2 as a function of being interviewed at time 2 by a “same or different” interviewer and found neither a main effect of the same or different interviewer (χ² = 0.10, df = 1, P = .75) nor an interaction between the prevalence of MD at time 1 and the same or different interviewer at time 2 (χ² = 0.01, df = 1, P = .94). The tetrachoric correlations of the 1-year prevalence of MD at times 1 and 2 were virtually the same in those twins who were interviewed at time 2 by the same or different individual who interviewed them at time 1 (+.414 ± .068 and +.419 ± .076 [estimate ± SE], respectively). In those with known zygosity, the number of months between the two assessments did not differ significantly as a function of zygosity (r = 0.54, df = 1, 948, P = .59).

There was variation in the number of months between the time 1 and time 2 assessments. However, in predicting the 1-year prevalence of MD at time 2 by logistic regression, there was no interaction between the 1-year prevalence of MD at time 1 and the duration of time between the two assessments (χ² = 0.00, df = 1, P = .95). Thus, the variation in time between the two assessments was not incorporated into further modeling. By controlling for the year of birth, there was a trend that fell short of statistical significance for the 1-year prevalence of MD to be higher in the DZ twins than in the MZ twins both at the time 1 (χ² = 3.16, df = 1, NS) and the time 2 (χ² = 0.88, df = 1, NS) assessments. Among twin pairs where both members participated at time 1, successful completion of an interview at time 2 was predicted by higher educational attainment (χ² = 16.72, df = 1, P < .001) but neither by zygosity (χ² = 1.90, P = .17) nor by a history of the 1-year prevalence of MD that was assessed at time 1 (χ² = 1.15, df = 1, P = .28).

**TWIN ANALYSIS OF THE 1-YEAR PREVALENCE OF MD AT TIME 1**

Probandwise concordance for 1-year prevalence of MD at time 1 was 27.0% in MZ twins and 17.6% in DZ twins, with the tetrachoric correlations equal to +.44 and +.12, respectively (Table 1). By fitting standard twin models to the tetrachoric correlations (Table 2), the simple AE model provides a reasonably good fit as well as the full (or ACE) model (χ² = 0.46). However, because of its greater parsimony, the AE model was preferable, suggesting that the liability to episodes of MD in the year prior to time 1 could be accounted for by additive genes and individual-specific environment with an estimated heritability of 41%. The fit of the CE model, which suggested that all the familial resemblance to liability to MD resulted from shared environmental factors, was poor and not substantially, but not significantly, worse than the full model (χ² difference test = 2.99, df = 1, P = .08).

**TWIN ANALYSIS OF THE 1-YEAR PREVALENCE OF MD AT TIME 2**

The probandwise concordance for the 1-year prevalence of MD at time 2 was 28.9% in MZ twins and 15.4% in DZ twins (Table 1), with the tetrachoric correlations equal to +.44 and +.12, respectively (Table 1). By fitting standard twin models to the tetrachoric correlations (Table 2), the simple AE model provides a reasonably good fit as well as the full (or ACE) model (χ² = 0.46). However, because of its greater parsimony, the AE model was preferable, suggesting that the liability to episodes of MD in the year prior to time 1 could be accounted for by additive genes and individual-specific environment with an estimated heritability of 41%. The fit of the CE model, which suggested that all the familial resemblance to liability to MD resulted from shared environmental factors, was poor and not substantially, but not significantly, worse than the full model (χ² difference test = 2.99, df = 1, P = .08).

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**Table 1. Population Prevalence, Probandwise Concordance, and Tetrachoric Correlation for 1- or 2-Year Prevalence of MD as Assessed at Time 1 or Time 2**

<table>
<thead>
<tr>
<th>Time</th>
<th>Zygosity</th>
<th>Population Prevalence</th>
<th>Probandwise Concordance</th>
<th>Correlation in Liability ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MZ</td>
<td>7.7</td>
<td>27.0</td>
<td>+.44 ± .10</td>
</tr>
<tr>
<td>1</td>
<td>DZ</td>
<td>11.2</td>
<td>17.6</td>
<td>+.47 ± .14</td>
</tr>
<tr>
<td>2</td>
<td>MZ</td>
<td>8.6</td>
<td>28.9</td>
<td>+.48 ± .10</td>
</tr>
<tr>
<td>2</td>
<td>DZ</td>
<td>11.2</td>
<td>15.4</td>
<td>+.49 ± .13</td>
</tr>
<tr>
<td>1 or 2</td>
<td>MZ</td>
<td>14.7</td>
<td>37.3</td>
<td>+.49 ± .08</td>
</tr>
<tr>
<td>1 or 2</td>
<td>DZ</td>
<td>19.1</td>
<td>23.9</td>
<td>+.49 ± .10</td>
</tr>
</tbody>
</table>

* MD indicates major depression; MZ, monozygotic; and DZ, dizygotic. Adjusted for the modest mean difference in age between MZ and DZ twins.

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**Table 2. Cross-sectional Twin Model Fitting to the Time 1 or Time 2 Data on 1- or 2-Year Prevalence of MD**

<table>
<thead>
<tr>
<th>Parameter Estimates of Best-Fitting Model</th>
<th>Fit of Models</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE (df = 0)</td>
<td>0.46</td>
</tr>
<tr>
<td>CE (df = 1)</td>
<td>3.45</td>
</tr>
<tr>
<td>AE (df = 1)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

* MD indicates major depression; A, additive genetic factors; C, common environmental factors; E, individual-specific environmental factors; a, proportion of variance in liability due to additive genetic factors; e, proportion of variance in liability due to individual-specific environmental factors; and AIC, Akaike's information criterion. Values of greater than zero are obtained for this model because all parameter estimates are constrained to be positive. 1-Best-fitting model by AIC.
ing +.48 and +.13, respectively. By fitting standard twin models to the tetrachoric correlations, the simple AE model fit as well as the full ACE model (χ²=0.59) (Table 2) and suggested that the liability to episodes of MD in the year prior to time 2 could be accounted for by additive genes and individual-specific environment with an estimated heritability of 45%. The fit of the CE model was substantially poorer and could almost be rejected against the full model by the rigorous χ² difference test (χ² =3.82, df=1, P=.05).

TWIN ANALYSIS OF THE 1-YEAR PREVALENCE OF MD AT TIME 1 AND/OR TIME 2

Examination of the prevalence of MD in the year prior to time 1 or time 2 permitted the assessment of episodes of MD over a 24-month period, with the duration of retrospective recall never exceeding 12 months. So defined, the probandwise concordance for the 2-year prevalence of MD was 37.3% in MZ twins and 23.9% in DZ twins (Table 1), and the tetrachoric correlations equaled +.49 and +.14, respectively. By fitting standard twin models to the tetrachoric correlations, again the simple AE model fit as well as the ACE model (χ²=0.91) (Table 2) and was preferred because of its greater simplicity. The AE model estimated the heritability of liability to MD at 46%. Unlike the results with the 1-year prevalence of MD, the fit of the CE model that examined the 2-year prevalence of MD could now be strongly rejected against the full model by the χ² difference test (χ² =6.38, df=1, P=.01).

EQUAL ENVIRONMENT ASSUMPTION

At time 1, MZ twins reported that they were in more frequent contact with one another than DZ twins. Part of the greater resemblance for MD in MZ twins vs DZ twins in the year prior to time 2 could, therefore, have resulted from a greater correlation in MZ twins for exposure to environmental risk factors. We prospectively tested this by determining whether twin resemblance at time 2 could be predicted by the frequency of contact of the twins at time 1. A full model, including additive genes (a²), specified common environment (c²), other common environment (c³), and individual-specific environment (e²) fit well (χ²=19.09, df=19, P=.451, AIC=-18.91) with the following parameter estimates: a²=0.424, c²=0.061, c³=0.000, and e²=0.515. However, setting c³ to 0 produced a trivial deterioration in fit and an improvement in the AIC (χ²=19.15, df=20, AIC=-20.85), with heritability estimated at 45%, which was nearly identical to that obtained by standard twin analysis.

TETRACHORIC CORRELATIONS BETWEEN TWINS AND ACROSS TIME

The tetrachoric correlation matrices for the liability to MD in twins 1 and 2 at times 1 and 2 in the MZ and DZ pairs are illustrated in Figure 2. Four features of these matrices are noteworthy. First, the correlations in liability to MD between twins 1 and 2 were quite similar at times 1 and 2 both in MZ twin pairs and in DZ twin pairs. Twin similarity for MD appeared to be fairly constant over time. Second, in both MZ and DZ twin pairs, the correlations between twins at the same time were quite similar to the correlations between twins across time. That is, twin 1's risk for the 1-year prevalence of MD that was assessed at time 1 about equally predicted her co-twin's risk for the year prior to time 1 or the year prior to time 2. Third, in MZ twins, the correlation between a twin at time 1 and herself at time 2 was very similar to the correlation between a twin at time 1 and her co-twin at time 2. That is, to predict MD in the year prior to the time 2 evaluation in MZ twins, one could equally assess the history of MD in the year prior to the time 1 evaluation in that twin or in her co-twin! Fourth, by contrast, for DZ twin pairs, the correlation between a twin at time 1 and herself at time 2 was approximately twice as great as the correlation between a twin at time 1 and her co-twin at time 2.

LONGITUDINAL TWIN MODELS

The full longitudinal model (model 1), as illustrated in Figure 1, fit the twin correlation matrices (as depicted in Figure 2) quite well (χ²=3.34, df=5, NS, AIC=-6.66) (Table 3). The parameter estimates that were obtained are depicted in Figure 3, top. The path from common

Figure 2. The observed tetrachoric correlations in monozygotic twins (MZ) (top) and dizygotic (DZ) twins (bottom) for 1-year prevalence of major depression as assessed at two points in time, approximately 17 months apart. Three kinds of tetrachoric correlations are depicted: (1) between twins within one time of measurement (eg, twin 1 at time 1 to twin 2 at time 1); (2) within individuals across the two times of measurement (eg, twin 1 at time 1 to twin 1 at time 2); and (3) between twins across the two times of measurement (eg, twin 1 at time 1 to twin 2 at time 2).
environment to MD was estimated at 0 for both times 1 and 2, leaving r, undefined. The estimated proportion of variance in liability to MD due to additive genetic factors and individual-specific environment was nearly the same at time 1 (0.425 and 0.575, respectively) and at time 2 (0.434 and 0.566, respectively). The individual-specific environmental correlation (r,.) between the 1-year prevalence of MD that was assessed at times 1 and 2 was estimated at very close to 0 (.003), while the genetic correlation (r,.) was estimated at nearly unity (.999).

In model 2, the two common environmental paths and their correlation were set to 0 with no deterioration in fit in the model and an improvement in the AIC (χ²=3.34, df=8, AIC=−12.66), suggesting no evidence for a significant familial-environmental contribution to liability to the 1-year prevalence of MD.

In model 3, r, was set to 0, resulting in an identical fit of the model and a further improvement in the AIC (χ²=3.34, df=9, AIC=−14.66). This sample provided no evidence for stable environmental risk factors for MD that persisted in their effect from time 1 to time 2.

In model 4, r, was set to unity. The fit of the model remained unchanged with another improvement in the AIC (χ²=3.34, df=10, AIC=−16.66), indicating that there was no evidence for occasion-specific genetic effects for liability to MD. In this sample, the results were consistent with a model in which all of the genetic risk factors for MD were stable over the period from occasion 1 to occasion 2 (a mean of 17 months).

Model 5 represented a further simplification of the model in which we constrained the two genetic paths (a, and a,2) and the two individual-specific environmental paths (e, and e,2) to be equal at times 1 and 2. This produced the best-fitting model (χ²=3.35, df=11, AIC=−18.65) and indicated that the relative importance of genetic and environmental risk factors for MD was stable over the two times of measurement.

We also tested three other submodels. First, we forced all of the environmental risk factors for MD to be stable across the two times of measurement, modifying model 2 to set r, to unity. This model failed badly (χ²=34.00, df=9, AIC=+16.00) and could be rejected against model 2 (χ² difference test=30.66, df=1, P=.000). Second, we forced all of the genetic effects of liability to MD to be occasion specific, modifying model 1 by setting r, to 0. This model also fit poorly (χ²=10.55, df=6, AIC=−1.45) and could be rejected against model 1 (χ²=7.21, df=1, P<.01). Third, we set all of the genetic paths to 0, forcing twin resemblance to be explained entirely by familial-environmental factors. This model fit much more poorly (χ²=10.82, df=8, AIC=−5.18) than the parallel model 2 in which all twin resemblance was due to genetic factors and all common environmental paths were set to 0 (χ²=3.34, df=8, AIC=−12.66).

The parameter estimates from the best-fitting model (model 5) are illustrated in Figure 3, bottom. At each time point, genetic factors accounted for 43.2% and environmental factors accounted for 56.8% of the variance in liability to MD. However, the genetic factors that influenced MD at the two time points were entirely stable. That is, the same genetic factors influenced liability to MD during the year prior to time 1 and the year prior to time 2. By contrast, the environmental factors that influenced MD during the two 1-year periods were entirely occasion specific. That is, the environmental risk factors that influenced the liability to MD in the year prior to time 1 were uncorrelated with the environmental factors that influenced liability in the year prior to time 2.

![Figure 3. Parameter estimates from the full longitudinal twin model (top) and the best-fitting submodel (model 5—see Table 3) (bottom) that are fitted to the correlations as illustrated in Figure 2 for 1-year prevalence of major depression assessed at two time points 17 months apart. A indicates additive genetic factors; C, familial or common environmental factors; and E, individual-specific environmental factors. The subscripts 1 and 2 refer to times 1 and 2, respectively. The depicted estimates of the path coefficients, which equal standardized regression coefficients, must be squared to equal the proportion of variance that is accounted for by the relevant independent variable.](image)

**COMMENT**

**THE ROLE OF GENETIC AND ENVIRONMENTAL FACTORS IN MD ASSESSED DURING A 1- OR 2-YEAR PERIOD**

The first goal of this report was to determine the role of genetic and environmental factors in the etiology of MD as assessed over relatively short time periods. We found that the liability to MD for 1 year prior to our time 1 interview, 1 year prior to our time 2 interview, or the 2 years prior to the two times of assessment could be best explained by additive genetic effects and individual-specific environment, with heritability estimates ranging from 40% to 45%. Consistent with our results for a life-
time prevalence of MD in this sample, we found no evidence that familial-environmental factors played a major role in the etiology of MD when assessed over short time periods. Rather, we found that genetic factors were responsible for a substantial, but not overwhelming, proportion of the liability to MD, while individual-specific environmental factors accounted for the remaining somewhat larger proportion of the variance in liability. Our results for MD, when assessed over a 1- or 2-year period, were very similar to those previously obtained in this sample for lifetime prevalence and broadly congruent with those found in one but not the other recent twin study of lifetime prevalence of MD. While our 1-year prevalence data at time 1 were not independent of our previously reported lifetime prevalence (having been assessed at the same interview), this criticism was not applicable to our time 2 data. What does it mean that the heritability of MD when assessed over a lifetime is the same, within sampling error, of that found over 1 or 2 years? Much of the variation in long-term recall of episodes of MD could be a function not of the actual occurrence of these episodes, but rather of characteristics that influence their recall and reporting. Furthermore, if such traits were heritable, the “heritability” of lifetime MD would in part be the heritability of “reporting bias.” Although such traits would also influence the 1-year prevalence rates of MD, they should play a lesser role when recall is over much shorter time periods. Therefore, if heritability of lifetime prevalence of MD were an artifact of heritable traits that influence recall and reporting, heritability should be higher for lifetime than for 1-year MD. This was not observed.

Any remaining interpretation of the heritability of MD when assessed over short vs long periods is a function of (1) the amount of “error” that accrues in the assessment of episodes of MD over varying periods and (2) the relationship between the number or frequency of episodes of MD and the liability to illness. In standard twin models, the individual-specific environment also includes the unreliability of measurement. Given a certain proportion of stable variation in liability due to genetic factors, the larger the error of measurement, the lower the heritability. Errors of recall may occur when assessing MD over long vs short time periods, thereby reducing the heritability of lifetime vs 1-year MD. However, when assessing MD over short time periods, individuals with a high liability to illness may not have an episode because of insufficient time or the absence of an environmental precipitant. This kind of error may reduce the heritability of 1-year vs lifetime MD.

Finally, the etiologic role of familial/genetic factors in MD may be positively related to the number of reported episodes. In assessing MD over a brief period of time, the probability of detection is directly related to the frequency of recurrence. Therefore, the shorter the time frame of ascertainment, the greater would be the ratio of recurrent to single-episode cases and the higher the observed heritability of illness.

Current information is lacking to predict the relative importance of these potential factors that influence the heritability of lifetime vs 1- or 2-year MD. It may be that they all play little role, or that several may be important but have counterbalancing effects. Only further research, and especially the frequent follow-up of a genetically informative cohort, will be able to address these questions definitively.

A LONGITUDINAL MODEL OF THE 1-YEAR PREVALENCE OF MD

The second goal of this article was to clarify the extent to which the genetic and environmental effects on liability to depression were stable over time vs specific to individual occasions of measurement. The results of fitting a longitudinal twin model to our results from MD assessed in the year prior to our time 1 and time 2 assessments clearly indicated that, when examined over time, genetic and environmental factors impact on the liability to MD in different ways. While all of the genetic factors that influence liability to MD were stable over time, all of the environmental risk factors for MD were transitory in their effect, dissipating over a 1-year period. These results are not compatible with previous etiologic models for MD that postulate that stressful experi-
ences, often acquired in childhood or adolescence, produce enduring and substantial effects on the liability to MD. Our results cannot exclude the plausible hypothesis that traumatic environmental events produce an impact on the liability to MD that endures to early adulthood, but disappears thereafter. However, when we perform a median split by age in our sample, there is still no evidence for enduring environmental risk factors for MD in the younger cohort (mean ± SD age, 25.0 ± 3.3 years). By contrast, our findings are consistent with a major etiologic role in depression for stressful life events, the impact of which on the liability to MD probably dissipates within 3 months.29,30

Our results indicate that over a short time period in a sample, mostly in early and middle adulthood, the genetic risk factors to MD are temporally stable. It remains quite possible, however, that when examined either over longer periods of time or at different life stages (e.g., adolescence), changing genetic risk factors for MD may be detected.

LIMITATIONS

These results should be interpreted in the context of seven potentially significant methodologic limitations. First, the sample is entirely female, and given gender differences in the prevalence and familial transmission of MD,2,3 similar results might not be found in a male sample.

Second, we did not examine the test-retest reliability of our assessment of MD that others have found to be far from perfect.22,23 Since individual-specific environment in twin models include both “true” environmental variation and error of measurement, it remains possible that, correcting for errors of measurement, the heritability of MD is substantially higher than that reported here.51

Third, the rates of the 1-year prevalence that we obtained for MD in our female twin sample was somewhat higher than those obtained in some but not all previous epidemiologic samples.1 Our interviewers were mental health professionals, and we systematically assessed, without “skip-outs,” all of the relevant depressive symptoms that were experienced during the last year. Interrater reliability was high, and we excluded, at the symptom level, items that were due to physical illness or medication.

Fourth, because this was an epidemiologic sample, the majority of individuals who met criteria for MD were more mildly ill than most cases that are seen in a psychiatric setting. It remains to be seen whether the etiologic role of genetic and environmental risk factors in MD, as assessed in an epidemiologic sample, is the same as that found in a clinical sample, which would contain a greater proportion of severely impaired individuals.

Fifth, the analyses of the 1-year prevalence of MD, assessed at times 1 and 2, were not statistically independent. A more statistically appropriate use of the two waves of data is their joint inclusion in the longitudinal model fitting.

Sixth, we did not formally test causal models in which episodes of MD directly predisposed to future episodes. The full disentanglement of the role of stable risk factors vs “phenotype-to-phenotype” transmission as causes of the temporal stability of episodes of MD would require more than two occasions of measurement.32-42 A model in which the observed stability of the 1-year prevalence of MD was due entirely to phenotype-to-phenotype transmission (e.g., one episode of MD directly predisposing to future recurrences), and that did not include error of measurement for the time 1 MD,32-42 fit the data very poorly ($\chi^2=17.13$, df=7, AIC=+3.13) and could be rejected against the full longitudinal model (model 1) ($\chi^2$ difference test=13.79, df=2, P=.001). Furthermore, if we add phenotype-to-phenotype transmission (e.g., an arrow directly from time 1 MD to time 2 MD) to our best-fitting model (model 5), the fit of the model remained essentially unchanged, the AIC deteriorated due to the estimation of an additional parameter ($\chi^2=3.34$, df=10, AIC=−16.66), and the path from time 1 MD directly to time 2 MD was estimated at nearly 0 (+.005). If we more correctly included errors of measurement for time 1 MD,32-42 the best-fitting phenotype-to-phenotype model fit, as well as our best-fitting model ($\chi^2=3.34$), required one more parameter (df=10) and therefore would have had a poorer AIC (−16.66). More importantly, the resulting model was qualitatively the same as those obtained by the best-fitting standard longitudinal model: the temporal stability of MD was due entirely to stable genetic factors (details available on request). Although a definitive resolution of this question will require additional follow-up periods, these results suggest that the findings of our main longitudinal twin analyses (Table 3) are not seriously biased because of their exclusion of a phenotype-to-phenotype path from time 1 MD directly to time 2 MD.

Finally, while based on a relatively large sample size, the statistical power of the modeling presented here is still modest. In our analyses of the 1-year prevalence of MD, the CE model could not be rejected by the rigorous $\chi^2$ difference test. In addition, our longitudinal model probably has little power to detect stable environmental risk factors that account for 5% or even 10% of the variance in liability to MD. Thus, our results with respect to stable environmental risk factors for MD might be more accurately summarized as “no evidence for stable environmental risk factors for MD that account for a substantial proportion of variance in liability to illness.” In a previous report from this sample, premature parental loss significantly predicted a lifetime history of MD.24 While early parental loss should be an enduring environmental risk factor for MD, it accounted for less than 2% of the population variance in liability to MD—far too small to be detected in our current analysis.

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