Alcoholism and Major Depression in Women
A Twin Study of the Causes of Comorbidity

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

Background: Although major depression (MD) and alcoholism co-occur in clinical and epidemiologic samples of women more often than expected by chance, the magnitude and causes of this comorbidity are uncertain.

Methods: Personal interviews were conducted with 2163 female twins from a population-based twin registry. Bivariate twin analysis was performed using two definitions of MD and three definitions of alcoholism of varying diagnostic breadth.

Results: Odds ratios ranged from 2.7 to 6.0 and were consistently higher using narrower diagnostic criteria for either disorder. Twin analyses found (1) no evidence for familial environmental factors for either MD or alcoholism; (2) significant genetic correlations, ranging from +.4 to +.6, between MD and alcoholism, which were higher using narrower criteria for alcoholism; (3) significant individual-specific environmental correlations, ranging from +.2 to +.4, for all but one of the diagnostic combinations, which were higher using narrower criteria for MD.

Conclusions: Comorbidity between MD and alcoholism in women is substantial and appears to result largely from genetic factors that influence the risk to both disorders, but common environmental risk factors also contribute. However, genetic factors exist that influence the liability to MD without influencing the risk for alcoholism and vice versa. Narrowing the diagnostic criteria for MD or alcoholism increases comorbidity, but for different reasons narrow diagnostic criteria for MD increase the environmental sources of comorbidity while narrow diagnostic criteria for alcoholism increase the genetic sources of comorbidity.

(Arch Gen Psychiatry. 1993;50:690-698)

Indivduals presenting for treatment of alcoholism have high rates of depressive symptoms and of current and lifetime major depression (MD). In epidemiologic samples, individuals with a lifetime diagnosis of alcoholism consistently have an increased risk of a history of MD, with relative risks ranging from 1.5 to 4.5.

In this article, we examine the causes of the comorbidity between MD and alcoholism in women. We seek, from a genetic epidemiologic perspective, to understand the relative importance of three different sources of this comorbidity: (1) genetic factors that increase the vulnerability to both alcoholism and MD, (2) familial environmental factors, such as inconsistent and harsh parental discipline, that predispose to both disorders, and (3) individual-specific environmental factors (that are not shared with close family members), such as most stressful life events of adulthood, that increase the risk of both MD and alcoholism.

Family studies can disentangle the effects of individual-specific environmental risk factors on comorbidity from those of genes or family environment. This is because individual-specific environmental risk factors contribute to comorbidity within individuals but should not increase the risk of alcoholism in the relatives of probands with MD or vice versa. (This tendency of one disorder to be increased in the relatives of the probands with another disorder is termed coaggregation.) There have been

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SUBJECTS AND METHODS

As outlined in detail previously, as part of a longitudinal study of the genetic and environmental risk factors for common psychiatric disorders in women, 2163 female twins from the population-based Virginia Twin Register were personally interviewed, including both members of 1033 pairs. The mean (± SD) age of the sample at personal interview was 30.1 ± 7.6 years. During the personal interview phase of the project, conducted by interviewers with master's degrees in social work or at least 2 years of clinical experience, the refusal rate was 8%. All individuals were interviewed "blind" to the psychopathologic status of their cotwin. Zygosity was determined by an algorithm based on questionnaire responses, photographs, and, where these sources were ambiguous, DNA polymorphisms and yielded 590 monozygotic (MZ) pairs, 440 dizygotic (DZ) pairs, and three pairs of unknown zygosity.

Lifetime psychopathology was assessed with an adapted section from the Structured Clinical Interview for DSM-III-R based on DSM-III-R criteria. For MD, we report results with the use of two criteria sets: DSM-III-R, made by one of us (K.S.K.) on blind review of the interview protocols, and the modification of the Research Diagnostic Criteria proposed by Mazure and Gershon, here termed the Gershon criteria, as operationalized by computer algorithm. The latter set was chosen because it is the narrowest of those previously examined in this sample that has a heritability compatible with the broader definitions. We will sometimes refer to the DSM-III-R criteria for MD as broad and the Gershon criteria as narrow. The diagnosis of MD was not made when, on specific probing, it was judged that the depressive symptoms were solely the result of alcohol consumption or withdrawal.

Because of uncertainty about the "correct" threshold for the diagnosis of alcoholism, we propose in this report three "levels" of alcoholism: (1) alcoholism with dependence/tolerance, which meets DSM-III-R criteria for alcohol dependence and endorses items reflecting tolerance and/or dependence; (2) alcoholism without dependence/tolerance, which meets DSM-III-R criteria for alcohol dependence but endorses none of the items relating to tolerance or dependence; and (3) problem drinking, in which the subject admits to having had, or to being considered by others as having, a significant "drinking problem" not isolated to single incidents, but does not meet DSM-III-R criteria for alcohol dependence. We then created three definitions of "alcoholism": (1) narrow, only alcoholism with dependence/tolerance; (2) intermediate, alcoholism with or without dependence/tolerance (which corresponds to the DSM-III-R definition of alcohol dependence); and (3) broad, alcoholism with or without dependence/tolerance or problem drinking. Interrater reliability as measured among 53 randomly chosen cases assessed by two interviewers was high for our measures of both MD and alcoholism.

The rationale and methods of bivariate twin analysis have been outlined previously. In brief, as illustrated in Figure 1, the major goal of bivariate twin analysis is to decompose the covariance between two disorders, in this case MD and alcoholism, into that due to genes, common environment (those environmental experiences shared by members of a twin pair that therefore tend to make twins similar), and individual-specific environment (those environmental experiences not shared by members of a twin pair that therefore tend to make them dissimilar). More specifically, bivariate analysis subdivides a phenotypic liability correlation between two disorders into three parts: (1) that due to the same additive genes predisposing to both disorders (the additive genetic correlation, or rA), (2) that due to the same common or familial environmental factors predisposing to both disorders (the common environmental correlation, or rC), and (3) that due to the same individual-specific environmental risk factors predisposing to both disorders (the individual-specific environmental correlation, or rE).

Analyses are conducted by means of tetrachoric correlation matrices that contain three kinds of correlations: withinvariable cross-twin, within-twin cross-variable, and cross-twin cross-variable. The general pattern of the causes of comorbidity can usually be intuited from the pattern of these correlations in MZ and DZ twins. For example, if additive genetic factors play an important role in comorbidity, then the cross-twin cross-variable correlations should be approximately twice as great in MZ as in DZ twins. If all the comorbidity is due to genes, then because MZ twins share all of their genes with one another, the cross-variable correlation in MZ twins should be the same (within sampling error) as the within-twin cross-variable correlation. If, on the other hand, the two traits are more highly correlated within an individual than across MZ twins, this suggests that some individual environmental experiences contribute to comorbidity.

Tetrachoric correlations are estimated by means of the B test version of the program PRELIS, assuming a liability-threshold model. Model fitting to these correlations of liability was performed by the computer program LISREL with the use of asymptotic weighted least squares. Nested models were tested against one another by the chi-square difference test, where the df equals the difference in the number of parameters in the two models. The best-fitting model was chosen by means of Akaike's information criterion (AIC), which equals chi-squared minus twice the df, and reflects both the goodness of fit and parsimony of the model. The goal was to produce the model with the most negative value for AIC. Dominance genetic variance was not included in our analyses because our previous univariate analyses of MD and alcoholism failed to demonstrate consistently their importance for either disorder. Analyses were performed incorporating age into the bivariate twin model without a major change in results (available on request). The correlations between MD and alcoholism due to genetic, common environmental, and individual-specific environmental factors that influence the risk of both disorders can be calculated from the best-fitting model and equal, using the terminology depicted in Figure 1, aDfSe, aDfSe, and aDfSe, respectively.
two noteworthy reviews of family studies of alcoholism and depression.2,9 These reviews both concluded that alcoholism and depression are not, from a familial perspective, the same disorder. The pattern of coaggregation that would be expected if this were true, (1) the risk of alcoholism is equally elevated in relatives of probands with depression and with alcoholism and (2) the risk of depression is equally elevated in relatives of alcoholic and depressed probands, is not consistently seen. It is less clear how much (if at all) familial risk factors are shared between MD and alcoholism. While a number of studies demonstrate little or no familial coaggregation of the two disorders,9,12 others show substantial coaggregation.13-17

Both twin and adoption studies can disentangle familial environmental from genetic sources of comorbidity. We are aware of a twin study18 and four adoption studies9,11-15 that have explicitly examined the comorbidity between alcoholism and depression. In a sample of 56 alcoholic twins ascertained through hospital treatment, Gurling et al18 reported high rates of depression both in the alcoholic proband twins and cotwins and in the nonalcoholic cotwins of alcoholic proband twins. However, the results were not presented separately by zygosity, nor were they compared with a control group. Goodwin et al19,20 found no increased risk of depression in the adopted-away children of biologic parents with alcoholism. Cadoret et al21 found that a biologic background of alcoholism produced a small and nonsignificant increased risk of depression in adoptees. Von Knorrin et al22 also found weak and inconsistent evidence of a relationship of alcohol problems in biologic parents and depression in adoptees. By contrast, Wender et al22 found a clear and significant excess rate of alcohol abuse or dependence in the biologic relatives of adoptees with affective disorder vs control adoptees.

Most clinical, epidemiologic, and family/genetic studies of alcoholism either focus solely on men or include small samples of affected women. Our knowledge of the impact of gender on the magnitude and causes of comorbidity between alcoholism and depression is therefore limited. What evidence is available, however, suggests that both the overall rate of comorbidity between the two disorders and the etiologic role of familial/genetic factors in that comorbidity may be stronger in women than in men. Despite the higher population rates of major MD in women, epidemiologic studies suggest that the relative risk of MD given a diagnosis of alcoholism is substantially higher in women than in men.24-23 Furthermore, the pattern of comorbidity may differ, with MD usually preceding the onset of alcoholism in women, but occurring after the onset of alcoholism in men.24 Several family studies have suggested that the risk of alcoholism is increased in the relatives of female but not male probands with depression.20,25 In the Stockholm adoption study,21 nearly all the evidence of a genetic relationship between depression and alcoholism was a significant excess rate of alcohol and other drug abuse problems in the biologic mothers of adopted-away daughters with depression.

An important methodologic limitation of nearly all previous family, twin, and adoption studies of alcoholism and depression is their reliance on probands ascertained in treatment settings. Since having more than one disorder may alter the likelihood of treatment seeking, clarifying causes of comorbidity from such samples may be problematic. In particular, there may be substantial gender differences in the probability of treatment seeking given the presence of alcoholism, MD, or both conditions.

In this report, we examine the comorbidity between alcoholism and MD in women from female-female pairs ascertained from a population-based twin register. In particular, we seek to address the following specific questions: (1) What is the magnitude of comorbidity between alcoholism and MD in women from a general population sample? (2) To what extent is the observed comorbidity due to genetic, family environmental, or individual-specific environmental factors that predispose to both disorders? (3) How much does the magnitude of the causes of comorbidity between alcoholism and MD vary if alcoholism and/or MD is narrowly vs broadly defined?

**RESULTS**

**PREVALENCE**

In the 2163 interviewed female twins, the lifetime prevalence of depression as defined by the broad DSM-III-R and the narrow Gershon criteria were 31% and 23%, respectively, and for our three definitions of alcoholism were as follows: narrow, 6.2%; intermediate, 8.8%; and broad, 17.0%.26,34
Table 1. Magnitude of Comorbidity Observed Between Major Depression and Alcoholism for Varying Diagnostic Approaches

<table>
<thead>
<tr>
<th>Diagnostic Criteria for Major Depression</th>
<th>Diagnostic Approach to Alcoholism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Narrow</td>
</tr>
<tr>
<td>DSM-III-R</td>
<td>OR: 3.55 (2.46-5.00)</td>
</tr>
<tr>
<td>Gerston (11)</td>
<td>6.02 (4.19-8.65)</td>
</tr>
</tbody>
</table>

*OR indicates odds ratio; CI, confidence interval; and r, tetrachoric correlation.

THE MAGNITUDE OF COMORBIDITY

The odds ratio (OR) with 95% confidence limits and the tetrachoric correlations (± SE) between the two definitions of MD and our three diagnostic approaches to alcoholism are seen in Table 1. All the ORs were highly significant and ranged from 2.68 (between broadly defined MD and broadly defined alcoholism) to 6.02 (between narrowly defined MD and narrowly defined alcoholism). In general, the ORs were higher for narrower definitions of MD or of alcoholism. A similar trend was seen with tetrachoric correlations between the liability to alcoholism and MD, which ranged from +.33 to +.50.

BIVARIATE TWIN ANALYSIS

We will examine in detail the results obtained with the use of the DSM-III-R definition of MD (broad MD) and alcohol dependence (intermediate alcoholism). As outlined previously, the tetrachoric correlations for MD and alcoholism were much higher in MZ twins (+.44 and +.54, respectively) than in DZ twins (+.19 and +.36, respectively). In addition, the cross-twin correlations between MD and alcoholism (i.e., MD in twin 1 and alcoholism in twin 2 and vice versa) were substantially higher in MZ twins (mean, +.29) than in DZ twins (mean, +.11), suggesting that genetic factors play a role in the comorbidity between MD and alcoholism. However, the within-individual correlation between MD and alcoholism (mean, +.38 in both twin groups) was higher than the cross-twin correlations of MD and alcoholism in MZ twins (mean, +.29), suggesting that genetic factors cannot account for all of the observed correlation in liability between MD and alcoholism.

Bivariate model fitting began with the full model, allowing for additive genes (A), common environment (C), and individual-specific environment (E) for both MD and alcoholism, and genetic, common environmental, and individual-specific environmental correlations between them: rA, rC, and rE, respectively. For DSM-III-R MD and intermediate alcoholism, this model, termed model 1, fitted well (χ²=7.55, df=5, P=.18, AIC=−2.43) (Table 2). In model 2, we set three parameters to 0: common environment for MD, common environment for alcoholism, and the path between them (rE). This model fit nearly as well as model 1 (χ²=8.97, df=8, AIC=−7.03) and produced a better AIC score because of its considerably greater parsimony. In model 3, we set rE to 0, forcing the model to explain all of the comorbidity between MD and alcoholism.

Table 2. Results of Bivariate Model Fitting for Varying Definitions of Major Depression (MD) and Alcoholism

<table>
<thead>
<tr>
<th>Model</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD</td>
<td>ACE</td>
<td>AE</td>
<td>AE</td>
<td>AE</td>
<td>AE</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>ACE</td>
<td>AE</td>
<td>AE</td>
<td>AE</td>
<td>AE</td>
</tr>
<tr>
<td>rA</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>rC</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>0</td>
<td>F</td>
</tr>
<tr>
<td>rE</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>0</td>
<td>F</td>
</tr>
<tr>
<td>df</td>
<td>5</td>
<td>8</td>
<td>9</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>DSM-III-R MD</td>
<td>Plus narrow alcoholism</td>
<td>χ²</td>
<td>5.2</td>
<td>6.3</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>AIC</td>
<td>−4.8</td>
<td>−9.7</td>
<td>−10.0</td>
<td>+6.9</td>
</tr>
<tr>
<td></td>
<td>Plus intermediate alcoholism</td>
<td>χ²</td>
<td>7.6</td>
<td>9.0</td>
<td>11.3</td>
</tr>
<tr>
<td></td>
<td>AIC</td>
<td>−2.4</td>
<td>−7.0</td>
<td>−6.7</td>
<td>+13.7</td>
</tr>
<tr>
<td></td>
<td>Plus broad alcoholism</td>
<td>χ²</td>
<td>7.3</td>
<td>7.3</td>
<td>12.4</td>
</tr>
<tr>
<td></td>
<td>AIC</td>
<td>−2.7</td>
<td>−8.7</td>
<td>−5.6</td>
<td>+10.5</td>
</tr>
<tr>
<td>Gerston MD</td>
<td>Plus narrow alcoholism</td>
<td>χ²</td>
<td>3.0</td>
<td>3.1</td>
<td>9.2</td>
</tr>
<tr>
<td></td>
<td>AIC</td>
<td>−7.0</td>
<td>−12.9</td>
<td>−8.8</td>
<td>+7.7</td>
</tr>
<tr>
<td></td>
<td>Plus intermediate alcoholism</td>
<td>χ²</td>
<td>3.1</td>
<td>3.9</td>
<td>12.8</td>
</tr>
<tr>
<td></td>
<td>AIC</td>
<td>−6.9</td>
<td>−12.1</td>
<td>−5.3</td>
<td>+10.8</td>
</tr>
<tr>
<td></td>
<td>Plus broad alcoholism</td>
<td>χ²</td>
<td>8.7</td>
<td>9.2</td>
<td>18.7</td>
</tr>
<tr>
<td></td>
<td>AIC</td>
<td>−1.3</td>
<td>−6.8</td>
<td>+0.7</td>
<td>+9.5</td>
</tr>
</tbody>
</table>

*AIC indicates Akaike's Information Criterion; A, additive genetic factors; C, common or familial environmental factors; E, individual-specific environmental factors; rA, additive genetic correlation, rC, common environmental correlation, rE, individual-specific environmental correlation; F, free (parameter free to take any value); and 0 or 1, parameter fixed at 0 or 1.
†Best-fitting model by AIC.
Table 3. Parameter Estimates of the Best-Fitting Bivariate Models for Major Depression and Alcoholism

<table>
<thead>
<tr>
<th>Definition of Major Depression</th>
<th>Alcoholism</th>
<th>r_A</th>
<th>r_E</th>
<th>a^2</th>
<th>\sigma^2</th>
<th>a^2</th>
<th>\sigma^2</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSM-III-R</td>
<td>Narrow</td>
<td>+.57</td>
<td>+19</td>
<td>.56</td>
<td>.06</td>
<td>.44</td>
<td>.56</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>.24</td>
<td>.24</td>
<td>.56</td>
<td>.44</td>
<td>.43</td>
<td>.57</td>
</tr>
<tr>
<td></td>
<td>Broad</td>
<td>+.61</td>
<td>+.61</td>
<td>.56</td>
<td>.39</td>
<td>.43</td>
<td>.57</td>
</tr>
<tr>
<td>Gershon</td>
<td>Narrow</td>
<td>+.63</td>
<td>+.63</td>
<td>.52</td>
<td>.48</td>
<td>.46</td>
<td>.54</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>+.56</td>
<td>+.56</td>
<td>.57</td>
<td>.43</td>
<td>.46</td>
<td>.54</td>
</tr>
<tr>
<td></td>
<td>Broad</td>
<td>+.51</td>
<td>+.51</td>
<td>.56</td>
<td>.45</td>
<td>.45</td>
<td>.56</td>
</tr>
</tbody>
</table>

*r_A* indicates genetic correlation; *r_E*, individual-specific environmental correlation; \(a^2\), proportion of variance in liability to alcoholism due to additive genetic factors; \(\sigma^2\), proportion of variance in liability to alcoholism due to individual-specific environmental factors; \(a^2_E\), proportion of variance in liability to depression due to additive genetic factors; and \(\sigma^2_E\), proportion of variance in liability to depression due to individual-specific environmental factors.

**Figure 2.** The parameter estimates from the best-fitting bivariate model (model 2, Table 3) for intermediate alcoholism (equals DSM-III-R alcohol dependence) and major depression according to DSM-III-R criteria. Path coefficients must be squared to equal the proportion of variance accounted for in the dependent variable. \(r_A\), \(a^2\), \(\sigma^2\), and \(E_S\) are explained in the legend to Figure 1.

Table 4. Tetrachoric Correlations Between Major Depression and Alcoholism due to Shared Genetic vs Shared Individual-Specific Environmental Factors

<table>
<thead>
<tr>
<th>Definition of Major Depression</th>
<th>Definition of Alcoholism</th>
<th>Genes</th>
<th>Individual-Specific Environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSM-III-R</td>
<td>Narrow</td>
<td>.32</td>
<td>.10</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>.28</td>
<td>.76</td>
</tr>
<tr>
<td></td>
<td>Broad</td>
<td>.22</td>
<td>.66</td>
</tr>
<tr>
<td>Gershon</td>
<td>Narrow</td>
<td>.31</td>
<td>.64</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>.29</td>
<td>.62</td>
</tr>
<tr>
<td></td>
<td>Broad</td>
<td>.21</td>
<td>.57</td>
</tr>
</tbody>
</table>

The parameter estimates for the best-fitting model (model 2) are given in Table 3 and illustrated in Figure 2. The genetic correlation between depression and alcoholism \(r_A\) equaled +.57 and was substantially higher than the estimated environmental correlation \(r_E\) of +.19. Another way to view the role of genes and environment in influencing the comorbidity of MD and alcoholism is to calculate the tetrachoric correlation between the two disorders that occurs via shared genetic vs shared environmental risk factors (Table 4). For these definitions of MD and alcoholism, the tetrachoric correlation between the two disorders due to shared genetic factors was +.28 compared with +.09 due to individual-specific environmental risk factors that influence the liability to both disorders. Of the total “phenotypic” tetrachoric correlation here estimated from this model, 74% was due to genetic and 24% to environmental risk factors common to the two disorders.

The model-fitting results for the other five combinations of definitions of MD and alcoholism are seen in Table 2. With broadly defined MD and broadly defined alcoholism and for narrowly defined MD and all three definitions of alcoholism, the pattern of model fitting was identical to that outlined above for DSM-III-R MD and the intermediate definition of alcoholism. That is, model 2 was the best-fitting model. However, for narrowly defined alcoholism and broadly defined MD, model 3 fit only slightly worse than model 2 and had a slightly superior AIC \((-10.0\) for model 3 vs -9.7 for model 2).

The parameter estimates of the best-fitting models for the other combinations of definitions of MD and alcoholism are seen in Table 3. Two trends are noteworthy. First, the environmental correlations are consistently higher with the narrow (Gershon) than the broad (DSM-III-R) criteria for MD. Second, the genetic correlations are consistently higher with the narrower than the broader criteria for alcoholism.

These results are viewed from another perspective in Table 4. The tetrachoric correlation between alcoholism and MD due to genetic factors decreased as the diagnostic approach to alcoholism became broader. Furthermore, the tetrachoric correlation between alcoholism
and MD that was due to individual-specific environmental factors was consistently greater with the narrow than the broad criteria for MD. The percentage of the total phenotypic correlation between the two syndromes due to genetic factors that influence the liability to both disorders, according to the best-fitting model, ranged from 100% for narrowly defined alcoholism with broadly defined depression to 57% for broadly defined alcoholism with narrowly defined depression.

COMMENT

We sought in this study to quantitate the magnitude of comorbidity between alcoholism and MD in a population-based sample of female twins, to clarify the causes of this comorbidity, and to determine whether the magnitude or causes of this comorbidity varied as a function of the breadth of the diagnostic approach to alcoholism and MD. We review our major results in turn.

THE MAGNITUDE OF COMORBIDITY

Our epidemiologic sample of female twins revealed highly significant comorbidity between MD and alcoholism, with ORs ranging from 2.7 to 6.0. With DSM-III-R definitions, the OR was 3.6, similar to the 3.7 found in women in the Epidemiologic Catchment Area Study between MD and alcohol abuse/dependence as defined by DSM-III. 4,6

THE CAUSES OF COMORBIDITY

For all definitions of MD and alcoholism, we consistently found substantial cross-twin cross-trait correlations; that is, liability to alcoholism in one twin was significantly correlated with liability to depression in her cotwin. Consistent with some,13-17 but not other,8,12 family studies, these results suggest that familial factors contribute to the comorbidity of MD and alcoholism. Our investigation differs from previous family studies of the these two disorders in being restricted to women and ascertaining probands independent of treatment seeking. Since selection into treatment is affected by comorbidity39 and may be influenced by the presence of disorders in family members (eg, a family history of alcoholism leading to more rapid treatment of problem drinking), unbiased estimates of coaggregation may be more easily obtained in population-based than treatment-based samples. As others have suggested that the familial coaggregation of MD and alcoholism may be greater in women than in men,26,27 our findings from an entirely female sample may not contradict those previous studies that found little or no coaggregation in samples that are entirely or predominantly male.

We then used bivariate twin analysis to clarify the causes of comorbidity between alcoholism and MD. Our results suggest that, in women, genetic factors that influence the risk of both alcoholism and MD are responsible for most of the observed comorbidity between the two disorders. Due to differences in sample and methods, these results are difficult to compare directly with previous twin and adoption studies of this question.18-23 except to note that they are consistent with several studies that found trends in women for a genetic relationship between MD and alcoholism.21,22

However, our results also clearly show that MD and alcoholism are not, from a genetic perspective, the same disorder. The best estimate of the genetic correlation between these two disorders in women is probably in the range of +.50 to +.60. Furthermore, for all definitions of MD and alcoholism, models in which the genetic correlation between the two disorders was unity could be easily rejected. These results are in contrast to those found in this same sample for MD and generalized anxiety disorder,27 where the best-fitting models consistently indicated that all the genetic factors that influenced liability to MD also influenced liability to generalized anxiety disorder and vice versa. Our results support the hypothesis that in women, different genetic factors exist that (1) solely influence the liability to alcoholism, (2) solely influence the liability to MD, and (3) jointly influence the liability to both disorders.

With nearly all definitions of MD and alcoholism, individual-specific environmental risk factors also contributed modestly to the observed comorbidity. However, for all definitions of MD and alcoholism, the environmental correlation was less, and often substantially less, than the genetic correlation. That is, the genetic risk factors for alcoholism and MD appeared to be more closely related to one another than are the environmental risk factors. While a twin's environmental experiences not shared with her cotwin can influence the liability to both alcoholism and MD, our results suggest that most of the environmental experiences that increase the risk of MD do not influence the risk for alcoholism and vice versa.

THE EFFECT OF VARYING DEFINITIONS OF MAJOR DEPRESSION AND ALCOHOLISM

For many disorders in DSM-III-R,39 including MD and alcohol dependence, diagnostic thresholds were set more by informed opinion than by empiric evidence. Therefore, we explored the impact of differing diagnostic approaches to these two syndromes on the magnitude and causes of comorbidity. The magnitude of comorbidity was sensitive to the diagnostic approach taken, with increasing ORs found with a narrower diagnostic approach to either alcoholism or MD. This result is consistent with findings from the Epidemiologic Catchment Area, where the OR between MD and alcohol dependence was substantially higher than between MD and alcohol abuse.3

With one exception, however, the best-fitting bivariate twin model was constant across all the combinations
of diagnostic approaches. In the one exception to this (narrow alcoholism and broad MD), the best-fitting model for all the other diagnostic combinations (model 2) came within 0.3 $\chi^2$ units of being the best fit—a modest difference. From a qualitative perspective, our results suggest that all the diagnostic combinations provide the same picture of the causes of comorbidity between MD and alcoholism.

However, two general effects of diagnostic approaches were seen on the quantification of the etiologic roles played by genetic and environmental factors in the comorbidity of MD and alcoholism. First, the narrower the diagnostic approach to alcoholism, the higher was the observed genetic correlation between alcoholism and MD. Genetic factors that influence MD appear to have more of an impact on liability to narrow forms of alcoholism (eg, alcohol dependence) than broader forms encompassing “problem drinking.” By contrast, the genetic correlation between alcoholism and MD appeared to be independent of the diagnostic approach taken to MD; narrowly defined MD had no more of a genetic relationship with alcoholism than did broadly defined MD.

The second general effect was that the diagnostic approach to MD influenced the environmental correlation between alcoholism and MD. The environmental precipitants of more narrowly defined MD (the Gershon criteria) appear to have more in common with alcoholism than do those of more broadly defined MD. Unlike the DSM-III-R criteria, the Gershon criteria require a longer period of illness (4 vs 2 weeks) and impairment in functioning. Further research will need to clarify why the environmental precipitants of longer or more disabling depressions are more pathogenic for alcoholism than the environmental precipitants of shorter, nondisabling depressions.

Although in need of replication before serving as the basis for extensive speculations about the etiologic relationship between MD and alcoholism, these results do illustrate the way in which genetic epidemiologic approaches can provide hitherto unexpected insights into the problem of comorbidity. Examined at a phenotypic level, narrowing the diagnostic approach to MD and to alcoholism has a similar effect on comorbidity. However, our twin sample suggests that the narrowing the diagnostic approach to MD and alcoholism actually has a different impact on the causes of comorbidity. The comorbidity between MD and alcoholism increases with the use of narrow definitions of alcoholism because of higher genetic correlations between the two disorders. Comorbidity between MD and alcoholism increases with the narrow definition of MD because of higher environmental correlations between the two disorders.

LIMITATIONS

These results should be interpreted in the context of six potentially significant methodologic limitations. First, the study was conducted entirely in women. Since the genders may differ both in the magnitude and in causes of comorbidity between alcoholism and MD, the results cannot be assumed to apply to men.

Second, the presence or absence of a lifetime history of both MD and alcoholism was assessed at the same time during a single structured interview. It is unlikely that a single such interview, no matter how skillfully conducted, can fully clarify the often complex interrelationship that can exist between depression and alcoholism during a lifetime. Furthermore, because we were restricted to a single time of assessment, we were unable to incorporate unreliability of assessment into our models. In fitting bivariate twin models, unreliability of measurement could have a substantial impact if a “self-report bias” is substantially correlated for disorders assessed in an individual at the same interview (eg, MD and alcoholism), but not highly correlated in twin pairs. For example, if, as a result of interviewer-respondent interactions, some respondents felt willing and others hesitant to admit to any psychopathology, this would lead to an overestimation of the individual-specific environmental correlation between the two disorders.

Third, we instructed our interviewers to avoid scoring depressive symptoms when they were “clearly” the result of alcohol consumption or withdrawal. However, the accuracy with which this can be done when assessing lifetime prevalence is questionable. It is possible that some of the observed comorbidity between MD and alcoholism in this and other epidemiologic samples results from diagnosed episodes of MD that were, largely or entirely, due to alcohol abuse or withdrawal.

Fourth, we have not explicitly evaluated “causal” models in this report that assume that the comorbidity between MD and alcoholism arises by alcoholism directly predisposing to MD or vice versa. Although conceptually attractive, causal models cannot be rigorously evaluated in twin studies unless three sources of variation are found for the two disorders (eg, additive genetic and individual-specific environmental factors plus either family environmental or nonadditive genetic factors) or assessments are obtained at two or more points of time. Some information about the plausibility of this model is provided by evaluating the ages at onset of the two conditions in comorbid cases. One previous epidemiologic study that reported results separately for women found that in those with a diagnosis of both MD and alcoholism, 66% of women reported that MD was the antecedent diagnosis. Our results were similar, with 63 of the comorbid cases having had the onset of MD before the onset of alcoholism. However, for a significant proportion of the sample, either the two disorders began within the same year (12%) or the
onset of alcoholism preceded that of MD (25%). In cotwins of twins with both diagnoses, neither the risk of MD nor the risk of alcoholism was significantly predicted by the order of onset reported by the proband twin. Although we consider it unlikely that most of the comorbidity between alcoholism and MD in women is due to direct causal effects, this issue can only be rigorously resolved with additional follow-up of our sample that would provide additional assessments of both MD and alcoholism.

Fifth, our model implicitly assumes etiologic homogeneity—that MD is the “same” disorder in the presence or absence of alcoholism and that alcoholism with MD is the “same” disorder as alcoholism without MD. The latter, in particular, has been questioned. This hypothesis can be evaluated qualitatively from our data. For example, does MD in a proband twin predict an increased risk of MD in the cotwin regardless of the presence or absence of alcoholism in the proband twin? With the use of the intermediate definition of alcoholism and the DSM-III-R definition of MD, the risks of MD and alcoholism in the cotwin of MZ proband twins as a function of the proband diagnosis of alcoholism plus MD, alcoholism only, MD only, or neither are seen in Table 5. These results support our assumption of etiologic homogeneity, as do the results with DZ twins (available on request). The diagnosis of MD in a proband twin conveys an increased risk of MD in the cotwin regardless of the presence or absence of alcoholism in the proband twin. Alcoholism in the proband twin conveys an increased risk of alcoholism in the cotwin regardless of the presence or absence of MD in the proband twin. Model fitting was applied to the full 4x4 table, classifying both twins and cotwins into those with alcoholism plus MD, alcoholism only, MD only, and neither. Results supported the above-mentioned qualitative conclusions.

Finally, our results are incomplete in several ways. Two particularly deserve mention. First, can we characterize the genetic vulnerability common to both alcoholism and MD? How much, for example, might genes influence the risk of these two common psychiatric disorders through their effect on personality? Second, given the clinical heterogeneity of the depressive syndrome, will it be possible, on the basis of symptoms, age at onset, associated features, or course, to delineate depressive syndromes in women that reflect high vs low levels of genetic liability to alcoholism?

Accepted for publication December 29, 1992.

This study was supported by grants AA-09095 and MH-40828 from the US Alcohol, Drug Abuse and Mental Health Administration, Bethesda, Md. The Virginia Twin Registry, established and maintained by W. Nance, MD, PhD, and L. Corey, PhD, is supported by National Institutes of Health (Bethesda, Md) grants HD-26746 and NS-25630.

John Myers, MS, and Leroy Thacker, MS, assisted in the data analysis.

Reprint requests to Department of Psychiatry, Medical College of Virginia, Box 710, Richmond, VA 23298-0710 (Dr Kendler).

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