Sex-Specific Genetic Influences on the Comorbidity of Alcoholism and Major Depression in a Population-Based Sample of US Twins

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Background: Alcoholism and depression frequently co-occur, but the origins of this comorbidity remain uncertain. Most previous family, twin, and adoption studies of these disorders have used cases ascertained through treatment settings, who may differ from cases in epidemiological samples. We studied the importance of genetic influences on risk for lifetime comorbidity of major depression and alcoholism by means of a population-based twin sample.

Methods: Lifetime major depression (MD), alcohol abuse, and alcohol dependence were assessed by structured interview for both members of 3755 twin pairs from the Mid-Atlantic Twin Registry. Pair resemblance was analyzed by means of structural equation models.

Results: Individuals with MD were at significantly increased risk for alcohol dependence and for a combined diagnosis of alcohol abuse and/or dependence. History of MD in a twin significantly increased the risk of cotwin alcohol dependence and alcohol abuse and/or dependence among identical male pairs and for alcohol abuse and/or dependence in identical female pairs, but not among male or female fraternal pairs. Results of structural modeling indicate that comorbidity occurs because the genetic and specific environmental sources of liability to MD overlap with those underlying alcohol dependence and alcohol abuse and/or dependence. This overlap was significant only within sex, not across sexes.

Conclusions: In this population-based twin sample, the familial transmission of MD and alcohol dependence was largely disorder specific. Comorbidity appears to be due to sex-specific genetic and environmental risk factors. The factors underlying depression in women do not appear to arise from the same factors underlying alcoholism in men.

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Alcoholism and depression co-occur at levels higher than chance in clinical and epidemiological settings. The cause of comorbidity is of substantial theoretical and clinical relevance because it complicates treatment and may alter prognosis.

The most common approach to studying the causes of comorbidity has been with family studies. Methodological variation in definition of probands, use of family interview vs family history data, and the method used to define primary vs secondary diagnoses precludes simple summaries of the results. However, studies that began with alcoholic probands generally have found that relatives are not at increased risk for depression unless the proband also has depression. These findings are consistent with a phenotypic association between the two disorders, wherein the presence of alcoholism increases risk for depression, but the vulnerability for the two disorders is transmitted independently within families.

Family studies based on probands with primary depression have yielded mixed findings. Some have found no increase in alcoholism among relatives unless the probands were also alcoholic. Others have found increased alcoholism but sometimes only among the relatives of female probands. The latter results have been used as evidence for a depressive spectrum in which women with depression plus alcoholism are viewed as having a more severe form and their relatives are at increased risk for depression and alcoholism compared with relatives of women with depression only.

Studies beginning with treated alcoholics have found that the relatives of probands with both major depression (MD) and alcoholism were not at increased risk for alcoholism compared with relatives of probands with alcoholism alone.
SUBJECTS AND METHODS

SUBJECTS

Subjects were from 2 longitudinal twin studies of psychiatric and substance-related disorders: one of female-female pairs (FF) and another of male-male and male-female pairs (MM/MF). Subjects were ascertained from the Virginia Twin Registry (now part of the Mid-Atlantic Twin Registry), which was formed by matching birth certificates to state records. Twins were eligible for participation if one or both were successfully matched and were born between 1934 (FF) or 1940 (MM/MF) and 1974. Inclusion in the FF study also required that both twins return a mailed questionnaire. Studies were limited to whites because participation levels by ethnic minority pairs were too low to permit valid estimates of genetic effects. Both studies were approved by our institutional review board. Subjects provided verbal consent for telephone interviews and written consent for in-person interviews and DNA collection.

The FF study included 2164 women interviewed in 1988 to 1989 and 276 ascertainment subsequently. Data for the current study come from the fourth FF interview, which was conducted by telephone on 1945 (79.7%) of these 2440 women. Data from the MM/MF study come from the first interview, conducted in 1993 to 1996 by telephone with 6847 subjects (3120 male, 1727 female). Subjects were 18 to 56 years old (mean, 35.1 years; SD, 9.2 years) when interviewed and had a mean education of 13.4 years (SD, 2.6 years). Subjects from the two studies did not differ in educational level, but the FF sample was on average slightly older. Further details of sample ascertainment and characteristics are presented elsewhere.36-38

The individual-level analyses in this report are based on 8733 subjects (5081 male, 3652 female). Excluded are 59 subjects with incomplete diagnostic information. Twin-pair analyses are based on 7460 subjects (4421 male, 3039 female) from complete pairs with known zygosity and diagnostic data. Excluded are 1273 subjects whose cotwins were not interviewed or had incomplete data. Same-sex pairs were classified as identical (monozygotic [MZ]) or fraternal ( dizygotic [DZ]) on the basis of a discriminant function of questionnaire responses (about physical similarity and blood type) developed in the FF sample and validated in the male sample by polymorphic markers (mean, 11.5 [SD, 11.9] markers per pair). Using this discriminant function, we could confidently assign zygosity to more than 93% of MM pairs. The remainder were assigned by genotyping (n = 65) or review of photographs, audiotapes, and interview responses (n = 32).

The complete pairs include 862 MZ male, 506 MZ female, 649 DZ male, 330 DZ female, and 1408 opposite-sex pairs. (This number includes 33 pairs created by all possible within-set pairings of members of 14 triplet sets and 1 quadruplet set. Exclusion of these pairs produced no appreciable change in the estimates, so we include them for completeness.)

MEASURES

Diagnostic criteria were adapted from standard structured interviews40-41 to permit evaluation of both DSM-III-R42 and DSM-IV43 diagnoses. Interviewers had a master’s degree in a mental health field or a bachelor’s degree plus 2 years of relevant clinical experience and received extensive training. Members of a twin pair were interviewed by different interviewers who were blind to cotwin diagnosis.

Interater reliability among 53 randomly selected FF subjects was κ = 1.0 (±0.05) for DSM-III-R AD44 and κ = 0.96 (±0.04) for DSM-III-R MD. The validity of our alcohol diagnoses is supported by their association with alcoholism treatment, alcohol consumption, and early drinking on-set.45-47

Previous analyses of this sample suggest little difference in twin resemblance for AD vs the broader AAD. However, previous research has found higher comorbidity for MD with AD than with AAD,1 so we investigated both definitions. We selected DSM-III-R definitions because they are slightly broader than those based on DSM-IV, yielding greater comorbidity.

We also created a classification of nonsecondary AD, which includes only individuals whose alcohol-related episodes did not all occur entirely within an MD episode. This was assessed by an interview item or (for 71 subjects missing this item because it was omitted from an early version of the MM/MF interview) by review of interview protocols and audiotapes. Seventeen subjects were excluded because of missing data.

TWIN MODELS

We used a standard liability-threshold model to estimate the genetic and environmental contributions to twin-pair resemblance for their liability to depression and alcoholism. Liability is an inferred trait, assumed to be continuous and normally distributed in the population, with individuals who exceed a theoretical threshold expressing the disorder.46 Individual differences in liability arise from 3 sources: additive genetic (G), genes whose allelic effects combine additively; common environment (C), all prenatal and postnatal environments shared by members of a twin pair; and specific environment (E), all remaining factors not shared within a twin pair, including measurement error (Figure 1). Comparing the resemblance of MZ and DZ twin pairs permits estimates of each source’s contribution to individual differences in liability to a disorder, or to the covariance between disorders. (It is possible to include nonadditive genetic effects in twin models, but these have not been implicated in our univariate analyses of MD rate. Grant et al23 and Dawson and Grant24 found increased alcoholism in the relatives of probands with MD and found individuals with comorbid alcohol dependence (AD) plus MD reported higher prevalences of alcoholism among their relatives than individuals with AD only. Kendler et al25 found significantly increased risk for MD among relatives of probands with alcohol abuse and/or dependence (AAD) and vice versa, although these asso-
and AD, so we do not consider them further.) There are G, C, and E sources for each diagnosis, and comorbidity can arise through a variety of mechanisms operating at the component or phenotypic level (Figure 2). These models make different predictions about the magnitudes of the cross-twin alcoholism-depression correlations in the different twin-pair types, so they will differ in how well they explain the observed data. Previous univariate results in these samples indicated significant sex differences in the genetic sources underlying MD and alcohol disorders, so we included these parameters in all models.

Our models assume random mating, equality of environmental effects for MZ and DZ twins, and no systematic biases associated with age, attrition, or pair completion. On the basis of several studies of AD and MD in spouses, a large impact of nonrandom mating seems unlikely. Among same-sex pairs in our sample, similarity for lifetime MD and AD was not associated with the twins’ similarity of childhood environment or frequency of adult social contact, supporting the validity of the assumption of equal MZ-DZ environments. A previous report from our group showed that women younger than 35 years had significantly higher prevalences of AD, but pair correlations did not differ significantly across 3 age groups (18-24, 25-34, and ≥35 years). Compared with FF pairs, women from MF pairs had similar prevalences of MD but higher prevalences of AD, probably because of methodological differences between studies. The cooperation status of one twin was unrelated to cotwin MD, AD, or AAD.

Structural models were based on tetrachoric correlations and asymptotic weight matrices estimated by means of PRELIS 2. Models were fit by means of weighted least-squares estimation with the program Mx. We compared alternative models by means of the principle of parsimony; models with fewer parameters are preferable if they do not provide substantially worse fit. We operationalized parsimony by the Akaike information criterion statistic, calculated as the likelihood-ratio , where is the difference.

For this report, we conducted several analyses investigating potential effects of age heterogeneity, study differences, attrition, and pairwise completion on comorbidity. Significance was based on for all analyses. To test for possible biases in estimated comorbidity due to incomplete ascertainment from age censoring, we used logistic regression to predict MD from alcohol diagnosis (AD or AAD), age at interview, and the interaction of age and alcohol diagnosis, separately for men and women. To test for age heterogeneity in cross-disorder cross-twin resemblance, complete pairs were divided into 13 groups of 3 age bands (19-29, 30-39, and ≥40 years) by 5 zygosity types. The fit of a model requiring the twin 1–twin 2, cross-twin covariation (model ii), and no cross-twin covariation in opposite-sex pairs (model iii). The fit of these models was compared with that of a standard baseline model requiring equal within-person depression-alcoholism correlations within sexes regardless of zygosity, and, for same-sex pairs, equal cross-twin correlations (ie, twin 1 depression–twin 2 alcoholism correlation equals the twin 2 depression–twin 1 alcoholism correlation).

We then fit models to evaluate the adequacy of 3 explanations for how comorbidity arises and 2 hypotheses related to sex differences:

1. Comorbidity arising from correlated liability posits that alcoholism and depression co-occur in families because they have the same underlying causes. The familial basis for the two disorders is identical; individual-specific processes determine which disorder is manifest (Figure 2, B).

2. Comorbidity arising from correlated liability posits that alcoholism and depression co-occur in families because the contributing factors are correlated. There are genetic and environmental factors that contribute to both disorders, as well as factors specific to each disorder (Figure 2, C).

3. Sex differences in sources of comorbidity are indicated if the cross-twin alcoholism-depression correlation is smaller for opposite-sex than for same-sex DZ pairs. If men and women have completely separate sources of comorbidity, these correlations will be 0 in opposite-sex pairs.

4. Sex differences in sources of comorbidity are indicated if the cross-twin alcoholism-depression correlation is smaller for opposite-sex than for same-sex DZ pairs. If men and women have completely separate sources of comorbidity, these correlations will be 0 in opposite-sex pairs.

5. Sex-dependent expression is when the same liability has different manifestations in men and women. If male alcoholism and female depression have common causes, they should be more strongly associated than male depression with female alcoholism.

A previous analysis of the female-female twins from the current (epidemiologically based) sample found overlapping liability for MD and AD and attributed most of this to genetic factors shared by the two disorders. Of 4 adoption studies, 2 found weak evidence of increased depression among adopted-away children of alcoholic parents, and another found increased alcoholism among biological rela-

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The magnitude of these correlations may differ for males and females. A final limitation of the existing literature is insufficient power to address potential sex effects.

We address these issues by studying the causes of comorbidity of major depression and alcoholism in a large, epidemiologically based twin sample unselected for history of depression or alcoholism.

ASSOCIATIONS OF SEX, AGE, STUDY, ATTENTION, AND PAIR STATUS WITH PREVALENCES AND COMORBIDITY

We observed substantial sex differences in prevalences, with MD being more common in women ($\chi^2 = 111, P < .001$) and alcohol disorders more prevalent in men (AD, $\chi^2 = 378, P < .001$; AAD, $\chi^2 = 524.6, P < .001$, Table 1). Among co-morbid individuals, 61% of men reported that their alcoholism preceded depression, whereas 68% of women reported that depression began first ($\chi^2 = 9.5, P = .002$). Onset of MD was significantly earlier among comorbid individuals than among subjects with MD alone. Onset of MD tended to be later in comorbid women than in those with AD alone, but there was no difference among men.

We found no evidence of biases associated with study, age, attrition, or pair status. Age did not interact with alcohol diagnosis in predicting risk for MD. Women from MM/MF and FF studies did not differ in degree of comorbidity. The twin 1–twin 2, cross-disorder correlation did not differ across age groups. The FF participants not included in the current interview did not differ from included subjects in prevalences of MD or AD at previous assessments. Twins from complete and incomplete pairs did not differ in prevalences or comorbidity.

PAIR SIMILARITY AND MODEL FITTING

Pair resemblance for MD and various definitions of alcoholism was consistently stronger among MZ pairs than same-sex and opposite-sex DZ pairs (Table 2). The degree of comorbidity was modest; the within-person correlations between MD and alcohol diagnoses ranged from 0.24 to 0.31 among men and 0.29 to 0.37 among women. The key information for uncovering the sources of comorbidity is contained in the cross-twin cross-disorder correlations. These were modest in all pairs, although highest for MZ pairs, followed by same-sex DZ pairs, and lowest for opposite-sex pairs. Excluding secondary cases of AD did not appreciably change the estimates. Therefore, we present model-fitting results for MD with AD and AAD.

As expected, the model of no MD-AD covariation fit poorly (model i in Table 3). Allowing within-person covariation (model ii) improved the fit, but it was still substantially worse than the baseline model fit. Allowing MD-AD covariation only in same-sex pairs (model
Table 1. Lifetime Prevalence of DSM-III-R Major Depression, Alcohol Abuse, and Alcohol Dependence Among 8733 Adult Twins

<table>
<thead>
<tr>
<th></th>
<th>Males (n = 5081)</th>
<th>Females (n = 3652)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Onset Age, Mean (±SD), y</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Major depression (MD) only</td>
<td>24.7 ± 10.2†</td>
<td>746 (14.7)</td>
</tr>
<tr>
<td>Alcohol dependence (AD) only</td>
<td>20.8 ± 5.3</td>
<td>810 (15.9)</td>
</tr>
<tr>
<td>Alcohol abuse (AA) only</td>
<td>21.4 ± 6.1</td>
<td>286 (5.6)</td>
</tr>
<tr>
<td>MD and AD</td>
<td>22.4 ± 9.9</td>
<td>634 (12.5)</td>
</tr>
<tr>
<td>MD and AA</td>
<td>24.3 ± 9.6</td>
<td>119 (2.3)</td>
</tr>
<tr>
<td>No MD, AD, or AA diagnosis</td>
<td>NA</td>
<td>2486 (48.9)</td>
</tr>
</tbody>
</table>

*Alcohol dependence is with or without abuse; alcohol abuse is without dependence. NA indicates not applicable.
†Differs from comorbid MD; t1496 = 7.5, P < .001, R2 = 0.7%.
‡Differs from comorbid AD; t1470 = 32.1, P < .001, R2 = 2.1%.
§Differs from comorbid MD; t1470 = 15.3, P < .001, R2 = 0.7%.

Table 2. Tetrachoric Correlations (and 95% Confidence Intervals) for Within-Person and Cross-Twin Lifetime DSM-III-R Major Depression, Alcohol Use Disorders, and Their Covariation

<table>
<thead>
<tr>
<th></th>
<th>Within-Person Correlations</th>
<th>Cross-Twin Correlations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males (n = 4430)</td>
<td>Females (n = 3080)</td>
</tr>
<tr>
<td>MD</td>
<td>0.31 (0.26 to 0.36)</td>
<td>0.37 (0.30 to 0.44)</td>
</tr>
<tr>
<td>AD</td>
<td>0.40 (0.26 to 0.22)</td>
<td>0.47 (0.23 to 0.37)</td>
</tr>
<tr>
<td>Nonsecondary AD†</td>
<td>0.54 (0.45 to 0.63)</td>
<td>0.54 (0.22 to 0.45)</td>
</tr>
<tr>
<td>MD with AD‡</td>
<td>0.21 (0.19 to 0.29)</td>
<td>0.29 (0.22 to 0.37)</td>
</tr>
<tr>
<td>MD with nonsecondary AD†</td>
<td>0.21 (0.19 to 0.29)</td>
<td>0.29 (0.22 to 0.37)</td>
</tr>
</tbody>
</table>

*MD indicates major depression; AD, alcohol dependence; AAD, alcohol abuse or dependence; ALC, AD or AAD; MZ, monozygotic; DZ, dizygotic; and NA, not applicable.
†N = 854 (MZ males), 646 (DZ males), 506 (MZ females), 330 (DZ females), and 1403 (opposite-sex DZ).
‡Correlations were estimated using equality constraints, eg, for same-sex pairs, the correlation of twin1 MD with twin2 AD is constrained to equal the correlation of twin2 MD with twin1 AD.

iiii resulted in a fit not distinguishable from the baseline model, indicating that the cross-sex MD-AD correlations did not differ from 0.

The phenotypic comorbidity models (Figure 2, A) fit the data poorly, both the one requiring relative resemblance for AD arising from familial resemblance for MD (model 1) and the one requiring resemblance for MD arising from AD (model 1a). The common-liability model (Figure 2, B) also fits poorly (model 2). In contrast, the correlated-liability model (Figure 2, C) fits well (model 3). Requiring the cross-sex MD-AD correlations to be 0 changed the fit minimally (model 4), indicating different sources of the MD-AD association for men and women. Since these correlations do not differ from 0, we did not test whether the female depression–male alcoholism association differs from that for female alcoholism with male depression.

On the basis of the results of model 3, a reduced model (3a) was fit in which all near-0 parameters were dropped. For AD, all common environment parameters could be equated to 0 with no loss of fit. On the basis of this “best-fitting” model, the MD-AD correlation for men was \( r = 0.31 \), and for women, \( r = 0.37 \) (Table 4, Figure 3). For both sexes, genetic factors were significant, accounting for 61% of this association in men and 51% in women. The remaining association was due to individual-specific sources. The large SEs around these estimates reflect the lack of precision with dichotomous categories even with large samples.
The pattern of results was the same for AAD as for AD. The best-fitting model included marginally significant residual C variation on AAD in men, but there was no evidence of common environmental contributions to the comorbidity of MD and AAD.

Our results suggest that sex-specific processes contribute to the lifetime comorbidity of depression and alcoholism. These results may help explain the lack of consistency in the results from previous studies, in which there was usually inadequate power to test for sex-specific transmission. We were able to detect these effects because we used a twin design with a large number of opposite-sex pairs.

Our results are most consistent with an explanation for comorbidity in which the causes of depression and alcoholism are overlapping but not isomorphic. There are genetic and specific environmental factors that influence both disorders and influences specific to each disorder. The overlap accounts for a relatively small proportion of the variation in liability to these disorders; the correlations of 0.29 to 0.37 translate into overlaps of 9% to 14%. Of this overlap, 50% to 60% is attributed to shared genetic factors and the remainder to specific environmental influences. We found no evidence that common environmental factors contribute to alcoholism-depression comorbidity.

The results do not support a causal model of phenotypic vulnerability in which depression causes alcoholism or alcoholism causes depression, and familial resemblance for the secondary disorder arises only from familial transmission of the first. However, there are less restrictive variations on the phenotypic model that cannot be rejected in our data. For example, a phenotypic model of MD secondary to AD that allowed residual familial resemblance for MD is mathematically similar to our correlated-liability model. The two models can be distinguished only if the pattern of genetic and environmental effects for comorbidity are disproportional to those influencing AD. In our data, these effects are close to pro-

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**Table 3. Goodness-of-Fit Results From Models for Comorbidity of Lifetime DSM-III-R Major Depression With Alcoholism**

<table>
<thead>
<tr>
<th>Model</th>
<th>Description</th>
<th>df</th>
<th>$\chi^2$</th>
<th>AIC</th>
<th>$\chi^2$</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Baseline model</td>
<td>32</td>
<td>15.5</td>
<td>48.5</td>
<td>14.3</td>
<td>49.7</td>
</tr>
<tr>
<td>i</td>
<td>No MD-ALC covariance</td>
<td>40</td>
<td>292.6</td>
<td>212.6</td>
<td>254.2</td>
<td>174.2</td>
</tr>
<tr>
<td>ii</td>
<td>No cross-twin MD-ALC covariance</td>
<td>38</td>
<td>50.6</td>
<td>25.4</td>
<td>54.0</td>
<td>22.0</td>
</tr>
<tr>
<td>iii</td>
<td>Opposite-sex cross-twin covariance = 0</td>
<td>34</td>
<td>15.7</td>
<td>52.3</td>
<td>16.0</td>
<td>52.2</td>
</tr>
</tbody>
</table>

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**Table 4. Parameter Estimates and 95% Confidence Intervals From Correlated Liability Models for the Comorbidity of Major Depression With Alcoholism**

<table>
<thead>
<tr>
<th>Model</th>
<th>Sex</th>
<th>Total</th>
<th>Additive Genetic</th>
<th>Common Environment</th>
<th>Specific Environment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3) Full model</td>
<td>Male</td>
<td>0.31 (0.26-0.36)</td>
<td>0.17 (0.00-0.26)</td>
<td>0.01 (0.00-0.17)</td>
<td>0.13 (0.04-0.21)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0.37 (0.31-0.44)</td>
<td>0.19 (0.00-0.30)</td>
<td>0.00 (0.00-0.10)</td>
<td>0.18 (0.07-0.29)</td>
</tr>
<tr>
<td>(3a) Reduced model</td>
<td>Male</td>
<td>0.31 (0.26-0.36)</td>
<td>0.19 (0.11-0.26)</td>
<td>Fixed at 0</td>
<td>0.12 (0.05-0.20)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0.37 (0.30-0.44)</td>
<td>0.19 (0.08-0.30)</td>
<td>Fixed at 0</td>
<td>0.18 (0.07-0.29)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model</th>
<th>Sex</th>
<th>Total</th>
<th>Additive Genetic</th>
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<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(3) Full model</td>
<td>Male</td>
<td>0.29 (0.24-0.33)</td>
<td>0.19 (0.08-0.26)</td>
<td>0.00 (0.00-0.10)</td>
<td>0.10 (0.03-0.18)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0.31 (0.24-0.37)</td>
<td>0.18 (0.07-0.29)</td>
<td>0.00 (0.00-0.07)</td>
<td>0.13 (0.01-0.23)</td>
</tr>
<tr>
<td>(3a) Reduced model</td>
<td>Male</td>
<td>0.29 (0.25-0.34)</td>
<td>0.18 (0.11-0.26)</td>
<td>Fixed at 0</td>
<td>0.11 (0.04-0.18)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0.31 (0.24-0.37)</td>
<td>0.18 (0.07-0.29)</td>
<td>Fixed at 0</td>
<td>0.13 (0.02-0.24)</td>
</tr>
</tbody>
</table>
portional and the MD-AD overlap is modest, so we cannot distinguish these possibilities.

One explanation for sex differences in prevalences of depression and alcoholism is sex-limited gene expression, in which the disorders have shared liability that combines with sex-specific biological or social factors to give rise to either alcoholism or depression. This could arise if males are shaped by social factors to develop drinking problems rather than to express their depressive tendencies. Studies of ethnic groups in which heavy drinking is discouraged, such as in Israel39 and among the Old Order Amish,57 provide indirect support for this hypothesis, because the men have low prevalences of alcoholism and prevalences of depression similar to those of women. This explanation is a variant of the common-liability model (Figure 2, B) and so is inconsistent with our data. However, if depression or alcoholism arises from the interaction of genetic liability with sex-specific genetic or environmental factors, the pattern of twin correlations would be similar to those we observed, with the cross-twin depression-alcoholism association in opposite-sex pairs indistinguishable from 0.

Although the phenotypic (within-person) correlation of MD with AAD was lower than for MD with AD, the estimated genetic overlap of AAD with MD was the same as for AD, suggesting that alcohol abuse also shares genetic liability with MD.

Our ability to test whether “secondary” alcoholism has a different cause was limited, as only approximately 10% of cases of AD in women and approximately 5% in men were secondary to MD. Exclusion of secondary cases of alcoholism reduced the association of depression and alcoholism within individuals, but not across twin pairs, consistent with secondary alcoholism being no less associated with familial MD. These findings are consistent with those of Schuckit et al.58 who found that alcoholics with independent MD did not differ in family history of depressive disorder from those whose MD was secondary to their alcoholism. Similarly, Andrew et al.59 found that twin pairs concordant for MD had (nonsignificantly) higher rates of alcoholism in their relatives than discordant pairs, inconsistent with a separate cause for “pure” MD. Comorbidity may have different implications depending on proband sex and family history24 or may indicate greater liability. In our sample, individuals who had MD plus AD had significantly earlier onset of MD than depressed individuals without alcoholism, suggesting greater severity.

One study limitation is that subjects were white twins born in Virginia, so the results may not be generalizable to individuals from other regions or ethnic backgrounds. Our tests for biases associated with sample, age, completion status, and attrition suggest that restricting the modeling to subjects from complete pairs with complete data is not likely to have biased our results. However, other biases are possible.

Our prevalences of depression and alcoholism are somewhat higher than those reported for white adults in some US epidemiological studies, but the degree of comorbidity is similar to that in both US5,59 and international60 studies. It could be that our methods result in a somewhat lower threshold for caseness. Use of a more stringent definition (4 of 9 symptoms for DSM-III-R alcohol dependence and 6 of 9 for DSM-III-R major depression) produced prevalences more similar to those of US studies but produced minimal changes to MD-AD comorbidity, as indicated by within-person and cross-twin correlations. Thus, even if we used more narrow definitions, we would still obtain the same pattern of results.

Some subjects were still within the risk period for developing MD and AAD when interviewed. This censoring probably has less effect than in family studies, since twins are matched for age. Furthermore, we found no aged-related differences in within-person or cross-twin MD-AD covariation. Because there are sex differences in the sequencing and onset ages of these disorders, it is possible that subsequent follow-up of this relatively young sample might result in a stronger cross-sex alcoholism-depression association. Although this association did not differ significantly across age groups, there was a trend in the predicted direction: the male AD–female MD correlation among opposite-sex pairs older than 40 years was r = 0.17 (95% confidence interval, 0.02 to 0.32), compared with the correlation of r = −0.01 (95% confidence interval, −0.04 to 0.09) among younger pairs.

Our classification of comorbid cases into secondary and nonsecondary alcoholism was based on the timing of episodes and may not correspond to what is etiologically primary. Our models are based on lifetime comorbidity of these disorders. Studies that examine the simultaneous occurrence of these disorders may find greater overlap in causes.

The models we used assume that the constructs of alcoholism and depression apply equally to men and women and to individuals with or without comorbidity. It is possible that our finding of a weaker association between alcoholism and depression in opposite-sex than in same-sex pairs is due to sex differences in measurement or clinical manifestations, rather than in causes.
Despite these limitations, this sample arguably provides the best genetically informative data from which to generalize about the causes of comorbidity of alcoholism and depression. Our findings of differences in men and women in the causes of comorbidity warrant further investigation of these complex processes.

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