A Population-Based Twin Study of Alcoholism in Women

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Objective.—To clarify the role of genetic factors in the etiology of alcoholism in women.

Design and Setting.—Personal structured psychiatric interviews conducted by researchers "blinded" to the status of the co-twin in an epidemiologic sample of 1030 female-female twin pairs of known zygosity from the population-based Virginia Twin Registry.

Measures.—Three definitions of lifetime prevalence of alcoholism based on Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised criteria: (1) alcoholism with tolerance or dependence; (2) alcoholism with or without tolerance-dependence; and (3) alcoholism with or without tolerance-dependence or problem drinking.

Results.—Using narrow, intermediate, or broad definitions, the probandwise concordance for alcoholism was consistently higher in monozygotic than in dizygotic twin pairs. Multifactorial threshold models suggested that the heritability of liability to alcoholism in women is in the range of 50% to 60%.

Conclusions.—The results support the hypothesis that genetic factors play a major role in the etiology of alcoholism in women. Women should be well represented in the efforts currently under way to elucidate the molecular basis of the genetic susceptibility to alcoholism.

The prevalence, age at onset, clinical features, course, and outcome of alcoholism differ substantially in men and women, therefore, risk factors for alcoholism in men cannot be assumed to apply to women. Compared to what has been learned from studies of alcoholism in men, our knowledge of the role of genetic factors in the etiology of alcoholism in women is sparse and contradictory. Of the three adoption and three twin studies that have examined this issue, three suggest that genetic factors are etiologically unimportant for alcoholism in women. Two studies suggest that, although significant, genes are less important as risk factors for alcoholism in women than in men. In one of these investigations, genetic factors were shown to be etiologically important in women only when alcoholism was narrowly defined.

Only one study based on a small sample of female adoptees with alcoholism suggests that genetic factors play a major role in the etiology of alcoholism in women comparable with or greater than that observed in men.

In this report, we extend previous research in this area by examining the role of genetic and environmental factors in the etiology of narrowly and broadly defined alcoholism in members of 1030 personally interviewed female-female twin pairs ascertained from the population-based Virginia Twin Registry.

METHODS

Sample and Diagnostic Methods

Data for this report come from a study of genetic and environmental risk factors for common psychiatric disorders in white female-female twin pairs from the Virginia Twin Registry. The Virginia Twin Registry is a population-based register formed from a systematic review of all birth certificates from 1918 onward in the Commonwealth of Virginia. Current addresses of twins are obtained by matching to state records and from the co-twin or other relatives.

Twins were eligible to participate in this study if they were born between 1934 and 1971 and if both members of the pair had previously responded to a mailed questionnaire, to which the individual response rate was 64%. Interviews were completed with both members of 1038 of the 1176 eligible pairs. In 46 pairs, neither twin was successfully interviewed; in 97, only one twin was interviewed. The individual and pairwise cooperation rates were 91.9% and 87.8%, respectively. Of the completed interviews, 89.3% were completed face to face (almost always in the twin's...
home), and 10.7% (mostly twins living outside Virginia) were interviewed by telephone. Interviews were completed by individuals with a master's degree in social work and/or at least 2 years of clinical experience, who were "blind" to the psychopathologic status of the co-twin. All interviewers were initially trained for 80 hours and received bimonthly review sessions over the course of the study. The mean (±SD) age of the sample was 30.1 ± 7.6 years with a range of 17 to 55 years. The mean years of education were 13.5 ± 2.0 at the time of interview. Monozygotic (MZ) twins were significantly younger and better educated than the dizygotic (DZ) twins, but the average differences were small (1.4 years and 0.2 years of education, respectively).

All zygosity information from the 1083 pairs where both members were interviewed was reviewed by two experienced twin researchers who were blinded to information about the psychiatric status of the twins. The information reviewed included data on physical similarity and frequency of confusion as children (these data have been shown to be capable of determining zygosity with around 95% accuracy) and in over 80% of cases, photographs of both twins. On the basis of this review, twin pairs were classified into five groups: definitely MZ, definitely DZ, probably MZ, probably DZ, and zygosity uncertain. We attempted to obtain blood samples from both members of all pairs in the final three categories and were successful in 119 of the 186 pairs. Zygosity was determined by the examination of DNA polymorphisms, using eight highly informative probes, which, if all identical, produced a probability of monoygosity of 0.9997. Final zygosity determination, which used blood samples where available and otherwise a definite or probable zygosity diagnosis, yielded 590 MZ twin pairs, 440 DZ twin pairs, and three pairs classified as of uncertain zygosity. DNA methods validated our zygosity diagnosis in 87 (88%) of 105 twin pairs in the "probable" category. DNA or previously obtained blood-group–based zygosity diagnoses confirmed our assignment in 26 of 26 pairs in the "definite" category. Thus, the error rate in zygosity assignment in the total sample is probably less than 2%. In this report, our analyses focused on members of the 1030 complete twin pairs with known zygosity.

The personal interview contained the section for alcohol dependence from the structured clinical interview for Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) diagnosis. Because the role of genetic factors in the etiology of alcoholism in women may differ as a function of severity and because DSM-III-R criteria for alcohol "dependence" are relatively broad and can be met by an individual who displays neither tolerance nor dependence, we defined three levels of severity of the syndrome: (1) alcoholism with dependence/tolerance (meets DSM-III-R criteria for alcohol dependence and endorses items relating to alcohol tolerance and/or dependence); (2) alcoholism without dependence/tolerance (meets DSM-III-R criteria for alcohol dependence but denies symptoms of tolerance or dependence); and (3) problem drinking (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. Interview reliability was measured among 53 randomly chosen cases assessed at a single interview by two raters. Eight of these twin met criteria for broadly defined alcoholism from the ratings of both interviewers, and 46 did not (κ = 1.0 ± 0.5). For the 72 individual DSM-III-R criteria from these eight twins, the two interviewers agreed on their presence or absence with high reliability (κ = 0.97 ± 0.04).

The Presentation of Results From Twin Studies

In previous twin studies of alcoholism, affected twins have been selected through treatment facilities or medical records. Those twins (who are termed probands) and their co-twins were then systematically evaluated to determine who had a history of alcoholism. In such studies, the results in MZ and DZ twins can be summarized in a statistical term probandwise concordance, defined as the proportion of co-twins of proband twins who are themselves affected with alcoholism. In this report, by contrast, twins were selected from the general population and not from a treatment facility. Probandwise concordance can be determined in such a study, but it provides an incomplete picture of the data because it reflects only the degree to which twins resemble one another for their chances of having had alcoholism.

In this general population sample, we also have additional important information—the degree to which twins resemble one another for their chances of not having had alcoholism. We have this information because, in contrast to samples in which twin pairs are selected through a treatment facility where at least one twin is always affected, our sample contains all types of twin pairs, including those where neither twin is affected with alcoholism.

Although we present probandwise concordance rates for alcoholism in this report, our analyses will emphasize a more appropriate and efficient statistic that uses all the information available: the tetrachoric correlation, or, as it is sometimes termed, the correlation of liability. This statistic assumes that, underlying the observed division of twins into those with and without alcoholism, there exists a latent distribution of what may be termed the liability or vulnerability to alcoholism. We assume that a threshold exists on this liability distribution such that individuals with a liability above the threshold develop alcoholism while those with a liability below the threshold remain free of the disorder. The tetrachoric correlation represents the correlation in twins for this underlying liability to alcoholism. This model further assumes that alcoholism has a multifactorial etiology involving a number of genetic and environmental risk factors of small to moderate effect. Under these circumstances, the distribution of the liability to alcoholism in the general population will be approximately normal.

If twins are simply grouped into those with and without alcoholism, it will not be possible to test the goodness of fit of this liability-threshold model. The model can be tested, however, if the twins can be divided into three or more groups. In particular, this can be done when we examine whether our definitions of alcoholism represent different levels of severity on the same continuum of liability (Fig 1). Herein, twins are divided into four categories: unaffected, problem drinking, alcoholism without tolerance-dependence, and alcoholism with tolerance-dependence. A χ² goodness-of-fit test is available for testing whether the multifactorial liability threshold model provides a good fit to the observed data.

Statistical Analysis

The impact of age at interview, type of interview (phone vs face to face), the interview status of the co-twin, and zygosity (MZ vs DZ) on the risk of alcoholism were assessed by logistic regression. Since twins resemble one an-
other for the risk to alcoholism, if twins with alcoholism were less likely to agree to the personal interview, then the rate of alcoholism should be higher in twins whose co-twin refused vs those whose co-twin cooperated with the personal interview. The tetrachoric and polychoric correlations and their SEs were calculated separately for MZ and DZ twins by the computer program PRELIS. 23 Models were fitted to these correlations by the computer program LISREL using the asymptotic-weighted least squares method. 23-31

In the full model used in this report (Fig 2), resemblance in twins is assumed to result from two sets of latent factors: (1) additive genetic factors, which contribute twice as much to the correlation in MZ twins as in DZ twins (because MZ twins share all their genes identical by descent, while DZ twins, like nontwin siblings, share on average half of their genes) and (2) family or “common” environment, which contributes equally to the correlation in MZ and DZ twins. In addition to common environment (those environmental factors, such as social class of rearing or parental behavior, that make members of a twin pair similar for liability to alcoholism), the model also contains individual-specific environment, which, in addition to measurement error, is a measure of the impact of those environmental experiences that may make members of a twin pair different for liability to alcoholism.

Those persons unfamiliar with the use of latent variables in structural equation modeling may wonder how it is possible to reach conclusions about the role of genetic and environmental risk factors without actually measuring them directly. As in all latent variable models, the impact of genes and environment on the liability to alcoholism is inferred from the pattern of observed correlations in relatives, which are in turn predicted from mendelian theory.

Our formal analysis of the twin correlations began with fitting an ACE model. This includes additive genetic factors (A) and common or familial environment (C), both of which contribute to twin similarity for liability to alcoholism, and individual-specific environment (E), which is responsible for twin differences in liability to alcoholism. We then fit two simpler models. One of these, the AE model, contains only additive factors and individual-specific environment, and assumes that all familial aggregation results from additive genetic factors. The other, the CE model, contains only common environment and individual-specific environment and assumes that all observed familial aggregation is the result of shared environmental influences. The fit of each model is assessed by a goodness-of-fit χ² test, which for the AE and CE model has 1 df.

The goal in model fitting is to explain the observed data as well as possible with as few parameters as possible. We operationalized this goal with the use of Akaike’s Information Criterion, 32 which equals the χ² value minus twice the degrees of freedom. The model with the lowest value of Akaike’s Information Criterion reflects the best balance of goodness of fit and parsimony. In addition, the fit of the ACE model can be directly compared with that of the ACE model by a χ² difference test with 1 df. Further details of the application of biometrical genetic models to twin data are outlined elsewhere. 33,34 The final step in twin analysis is to estimate, based on the best-fitting model, the proportion of variance in liability to alcoholism due to individual-specific environment (e²) and, depending on the results of model fitting, additive gene action (a²) or common environment (c²).

The proportion of variance in liability due to additive genetic effects is often termed heritability.

RESULTS

Prevalences, Probandwise Concordance Rates, and the Multiple Threshold Model

Of the 2000 personally interviewed twins, 128 (6.2%) met criteria for a lifetime diagnosis of alcoholism with dependence-tolerance, 57 (2.8%) met criteria for alcoholism without dependence-tolerance, and 172 (8.3%) met criteria for problem drinking. Using, as an example, our intermediate definition of alcoholism, the lifetime probability of illness was unrelated to age (χ²=1.39, df=1, P value was not significant [NS]), zygosity (χ²=2.91, df=1, P=NS), interview status of the co-twin (χ²=0.87, df=1, P=NS) or mode of interview (χ²=0.07, df=1, P=NS). Thus, the rates of alcoholism do not significantly differ in MZ vs DZ twins, in twins whose co-twin refused vs those whose co-twin agreed to be interviewed, or in twins interviewed in person vs those interviewed by telephone.

The lifetime prevalence and probandwise concordance rates in MZ and DZ twins for the narrow, intermediate, and broad definitions of alcoholism are shown in Table 1. The probandwise concordance for alcoholism was higher in MZ than in DZ twins for all definitions of illness.

The multiple threshold model fit well in both MZ (χ²=7.36, df=8, P=0.50) and DZ twins (χ²=7.11, df=8, P=0.50), indicat-
Table 1.—Population Prevalence and Probandswide Concordance in Monozygotic (MZ) and Dizygotic (DZ) Twins for Three Definitions of Alcoholism

<table>
<thead>
<tr>
<th>Definitions of Alcoholism</th>
<th>MZ Twins</th>
<th>DZ Twins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population Prevalence, %</td>
<td>Probandwise Concordance, %</td>
<td>Population Prevalence, %</td>
</tr>
<tr>
<td>Narrow</td>
<td>5.2</td>
<td>28.2</td>
</tr>
<tr>
<td>Intermediate</td>
<td>8.1</td>
<td>31.0</td>
</tr>
<tr>
<td>Broad</td>
<td>16.3</td>
<td>45.9</td>
</tr>
</tbody>
</table>

Table 2.—Tetrachoric Correlations, Fit of Twin Models, and Parameter Estimates for Best-Fitting Models for Three Definitions of Alcoholism and the Multiple Threshold Model

<table>
<thead>
<tr>
<th>Definitions of Alcoholism</th>
<th>Tetrachoric Correlations, rSE</th>
<th>Fit of Model in x² Units†</th>
<th>Parameter Estimates of Best-Fitting Models</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MZ</td>
<td>DZ</td>
<td>AE (df=0)</td>
</tr>
<tr>
<td>Narrow</td>
<td>0.53±0.11</td>
<td>0.15±0.15</td>
<td>0.56</td>
</tr>
<tr>
<td>Intermediate</td>
<td>0.54±0.09</td>
<td>0.36±0.11</td>
<td>0.01</td>
</tr>
<tr>
<td>Broad</td>
<td>0.61±0.05</td>
<td>0.30±0.09</td>
<td>0.00</td>
</tr>
<tr>
<td>Multiple threshold</td>
<td>0.58±0.05</td>
<td>0.29±0.09</td>
<td>0.00</td>
</tr>
</tbody>
</table>

*aZ indicates monozygotic; DZ, dizygotic; A, additive genetic factors; C, common or familial environment; E, individual-specific environment; a², proportion of variance in liability to alcoholism due to additive genetic factors (equals heritability); and a², proportion of variance in liability to alcoholism due to individual-specific environmental factors.
†The higher the x² value, the poorer the fit of the model to the data.
‡x² Values can exceed zero because all parameters are constrained to be greater than or equal to zero.
§Best-fitting model by Akaike's Information Criterion.

The Tetrachoric Correlations and Fit of Twin Models

In this study, the tetrachoric correlation represents the best single measure of the degree of twin resemblance for the liability to alcoholism. As seen in Table 2, the tetrachoric correlations for alcoholism were substantially higher in MZ than in DZ twins for all definitions of illness. For MZ twins, these correlations ranged from 0.53 to 0.61. For DZ twins, these correlations ranged from 0.15 to 0.36 (Table 2). The results were similar using the multiple threshold model, which expresses the overall liability to broadly defined alcoholism as assessed by our three categories of increasing severity of illness (Fig 1). Using the multiple threshold model, the tetrachoric correlation in MZ twins (+0.58±0.06) was exactly twice that found in DZ twins (+0.29±0.09).

We next used model fitting to find the most parsimonious explanation of the observed pattern of resemblance for the liability to alcoholism in the twins. For all three definitions of alcoholism, the AE model provided the best overall fit to the data (Table 2) as indicated by Akaike's Information Criterion. In fact, the x² values found for the AE model were, in every case, less than 1, indicating an excellent fit. The AE model is a simple one, and it suggests that the liability to alcoholism results solely from genetic effects and individual-specific environment. This model does not include familial environmental effects but predicts that all familial resemblance for alcoholism is due to genetic factors. For all three definitions of alcoholism, the AE model provided a substantially better fit that the CE model, which postulates that the liability to alcoholism is entirely environmental in origin, due partly to shared family environment and partly to individual-specific environment. By a x² difference test, the CE model could be rejected against the ACE model at nearly significant levels for narrowly defined alcoholism (x²=3.69, df=1, P=0.06) and at highly significant levels for broadly defined alcoholism (x²=8.46, df=1, P=0.004). These results mean that, compared with the full model, the CE model, but not the AE model, provided a poor explanation of the observed data. The same pattern of results was found with the multiple threshold model, where the AE model had a perfect fit (goodness of fit x²=0.00), and the CE model could be confidently rejected against the full model (x²=7.79, df=1, P=0.005).

In the best-fitting AE model, the estimated heritability of liability to alcoholism ranged, for the three definitions of illness, from 50% for the narrow definition to 61% for the broad definition. Using the multiple threshold model, the heritability of liability to alcoholism was estimated at 58%.

COMMENT

The goal of this study was to clarify the role of genetic factors in the etiology of alcoholism in women. Our results, which are consistent across different definitions of illness, suggest that genetic factors play a major etiologic role in alcoholism in women. Furthermore, contrary to a recent report,4 our results suggest that the role of genetic factors in women is similar for both narrowly and broadly defined alcoholism.

These results are also inconsistent with those of previous twin and adoption studies, which suggest that genetic factors play at best a minor role in the etiology of alcoholism in women.15,17-18 Several methodological differences between this study and previous investigations might be responsible for these discrepant findings.

First, the size of both our total sample (2060 individuals from 1090 complete female-female twin pairs) and that portion of the sample who are affected (185 women who met DSM-III-R criteria for alcohol dependence and 357 who met broad criteria for alcoholism) is substantially greater than samples contained in previous studies. The three previous twin studies of alcoholism in women examined, respectively, 2115, 54, and 87 pairs. The two adoption studies examined 49 adopted-away daughters of alcoholics, of whom 16 had broadly defined alcoholism,19 and a total adoption sample of 913 adopted women, of whom 31 had abused alcohol.9 Secondly, in all the previous adoption studies, proband twins25 or biologic parents with alcoholism were selected through psychiatric hospitalization or...
registration with temperance authorities. By contrast, in the present study, twins were selected through a population-based twin register independent of treatment status. Third, in three of the previous reports, assessment of alcoholism was made solely or largely by medical or governmental records or by self-report questionnaire. By contrast, in this study, all twins were personally evaluated by clinically experienced interviewers. Finally, the diagnostic approach to alcoholism varied widely across the studies, with the present study being the only one to use DSM-III-R criteria.

The elucidation of the precise cause of the varying results from the completed twin and adoption studies of alcoholism in women must await further research. One plausible hypothesis is that the genetic loading for alcoholism in the modest proportion of women who seek treatment may not be typical of that found in the entire population of women with alcoholism. It is possible, for example, that patients seen in treatment settings may have been particularly influenced by social or familial environmental factors. In addition, conclusions about the heritability of alcoholism in women may differ substantially depending on the diagnostic criteria used and whether the diagnostic assessment is based on medical records or on structured personal interviews.

Although our population-based twin study examined only women, our heritability estimates for alcoholism in women are similar to those found by Pickens et al. in the largest and methodologically strongest twin study of alcoholism in men conducted to date. Indirectly, our findings suggest that genetic factors are of similar etiologic importance for alcoholism in women and in men.

Estimates for the heritability of liability to alcoholism in women in this sample ranged from 50% to 61%, depending on the definition of illness. These findings suggest that the role of genetic factors in the etiology of alcoholism is substantial and that at least half of the total liability to alcoholism is a result of genetic factors. Our estimates for the heritability of liability to alcoholism are generally somewhat higher than those previously estimated from twin studies for coronary artery disease, stroke, peptic ulcer disease, and major depression; in the range of those previously reported for hypertension; and somewhat lower than those previously found for schizophrenia or bipolar illness.

Twin studies can also provide insight into the nature of environmental risk factors. For all three definitions of alcoholism, as well as for the multiple threshold model, no evidence was found for shared environmental risk factors. By contrast, individual-specific environmental risk factors (the kind not shared by an individual with her co-twin) appeared to play an important etiologic role in alcoholism. Our study suggests that 40% to 50% of the total variance in liability to alcoholism is due to environmental experiences that are not shared by both members of a twin pair. These results are not consistent with hypotheses that familial-environmental factors, such as social class, parental disciplinary practices, or parental drinking behavior, play a major etiologic role in alcoholism.

Equal Environment Assumption

Twin studies assume that MZ and DZ twins are equally correlated for exposure to disease-predisposing environmental experiences. However, if MZ twins are more highly correlated than DZ twins for exposure to environmental risk factors for alcoholism, then our estimates of the heritability of alcoholism will be biased upward. As previously reported, in this twin sample, MZ twins reported more similar childhood environments and more frequent contact as adults than did DZ twins. Similarity of childhood environment in this sample was, however, unrelated to similarity for alcoholism (results available from the authors on request). By contrast, frequency of contact as adults and similarity for the presence or absence of alcoholism were significantly related. The causal interpretation of this finding is uncertain. Do twins in frequent contact develop more similar drinking habits or are twins with more similar drinking habits likely to have more frequent contact with each other? Although no data exist to evaluate these two interpretations for alcoholism, for quantity of alcohol consumed, studies have supported both hypotheses. However, studies of other behavioral traits have, with considerable consistency, suggested that the greater similarity in the social environment of MZ vs DZ twins is a result rather than a cause of the greater behavioral similarity of MZ twins.

We reanalyzed our data incorporating frequency of contact, assuming that contact causes similarity for alcoholism (details available from the authors on request). The estimated heritability for the liability to alcoholism decreased modestly and was, for example, with our broad definition of alcoholism, estimated at 46%. If, as we consider implausible, all of the relationship between frequency of contact and resemblance for alcoholism results from contact influencing resemblance, then the heritability of liability to alcoholism in women may be in the range of 40% to 50% rather than 50% to 60%.

Limitations

The results of this study should be interpreted in the context of three potentially significant methodological limitations. First, while based on a complete search of birth certificates from 1934 onward, our final study sample is unlikely to be completely representative of the entire twin population. Twins who moved out of state or did not return earlier questionnaires were less likely to be included in our sample. However, our results did suggest that the risk for alcoholism was unlikely to be strongly related to the probability of cooperation with the personal interview.

Second, our results should be interpreted in the context of the statistical power of this sample. In particular, in the presence of the substantial heritability found for alcoholism, familial environmental influences that accounted for only a modest proportion of the total variance in liability would presumably be undetectable. Therefore, we can appropriately conclude only that we were unable to detect major familial environmental influences on the liability to alcoholism in women.

Finally, our assessments of alcoholism were performed at only one point in time. Previous studies with other psychiatric disorders have suggested that the reliability of such assessments is far from perfect. In our twin model, error of measurement in twin pairs is indistinguishable from individual-specific environment. Had we corrected for the unreliability of measurement or included interviews conducted at multiple time points, it is possible that we would have found the heritability of liability to alcoholism in women to be even higher than reported herein.

CONCLUSION

Contrary to the findings of most previous adoption and twin studies, our results support the hypothesis that in women, genetic factors play a major etiologic role in alcoholism. These findings are consistent with evidence that the association between alcoholism and the D4 dopamine receptor locus may be of similar magnitude in both genders. As major efforts are now underway to elucidate the molecular basis of the genetic susceptibility to alcoholism, these results suggest that women, along with men, should be well represented in these investigations.
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