Common Genetic Vulnerability for Nicotine and Alcohol Dependence in Men

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Background: Nicotine and alcohol dependence often occur together. We examined data from male twin pairs to determine whether there are genetic or environmental influences common to nicotine and alcohol dependence, and, if so, to estimate the magnitude and correlation of these influences.

Methods: Subjects were 3356 male-male twin-pair members of the Vietnam Era Twin Registry who participated in a 1992 telephone administration of the Diagnostic Interview Schedule Version 3 Revised. Genetic model fitting was performed to estimate the magnitude and correlation of genetic and environmental contributions to lifetime nicotine and alcohol dependence.

Results: The heritability of nicotine dependence was 60.3% (95% confidence interval [CI], 55.4%-65.2%); that of alcohol dependence, 55.1% (95% CI, 49.7%-60.5%). The best-fitting model for the co-occurrence of lifetime nicotine and alcohol dependence included a substantial genetic correlation between both disorders ($r = 0.68; 95\%\ CI, 0.61-0.74$) and a modest unique environmental correlation ($r = 0.23; 95\%\ CI, 0.14-0.32$).

Conclusions: These data suggest a common genetic vulnerability to nicotine and alcohol dependence in men. This common genetic influence may partially explain the clinical and epidemiological observations that alcoholics are often dependent smokers.

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The relationship between smoking and alcoholism has long interested clinicians and researchers. Smoking is nearly universal in treatment-seeking alcoholic samples and has been reported to be as high as 85% in alcoholics identified in a general medical clinic. The average number of cigarettes consumed is also significantly higher among alcoholics compared with nonalcoholic smokers, with rates of heavy smoking (e.g., >25 cigarettes per day) among adult alcoholics as high as 90%. Tobacco use and heavy alcohol consumption represent a public health concern. Independent and combined use of these substances contribute to several types of cancer, and synergistic risks are particularly high for head and neck cancers. Smoking is also associated with increased risk for alcoholism relapse and continued problems with other substance abuse.

Genetic contributions to smoking initiation, persistent smoking, and alcohol dependence have been established in many twin studies. Heritability estimates for smoking initiation in male twins range from 46% to 84%, and estimates of the genetic contribution to long-term persistent smoking range from 58% to 74%. Evidence from twin studies performed in Scandinavia, Australia, and the United States indicates that genes account for 50% to 60% of the variance in risk for alcohol dependence in women and men, including data from our study sample, members of the Vietnam Era Twin (VET) Registry. Although we have previously estimated the genetic contribution to alcohol dependence in the VET Registry, we have not addressed the heritability of nicotine dependence or its relationship with alcohol dependence.

A close relationship between smoking and the excessive use of alcohol has been recognized for many years, but the underlying mechanisms have received little investigation. Studies in rodents have found that strains of mice bred for alcohol sensitivity have also been observed to be sensitive to nicotine. However, there has been little investigation of potential common genetic influences on nicotine and alcohol dependence in humans. Swan

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SUBJECTS AND METHODS

SAMPLE

The VET Registry consists of 7375 male-male twin pairs born from January 1, 1939, through December 31, 1955, of whom both siblings served on active military duty during the Vietnam era (1965-1975). The characteristics of the VET Registry have been reported elsewhere.26-28 In 1992, approximately 5000 twin pairs of the VET Registry were invited to participate in a computer-assisted telephone administration of the Diagnostic Interview Schedule Version 3 Revised (DIS-3R),29 which allowed derivation of psychiatric diagnoses according to DSM-III-R criteria.30 Interviewers contacted twins and began interviewing after verbal informed consent was obtained, a method approved by the institutional review boards at participating universities.

Lifetime nicotine and alcohol dependence diagnoses were obtained by applying standard DIS-3R computer algorithms to the data. To assess reliability of the nicotine and alcohol dependence diagnoses, a subset of 146 individual twins were reinterviewed by a second interviewer. The mean time between interviews was 466 days (SD, ± 50.5 days). Reliability was assessed using the κ statistic. According to the guidelines for rating reliability of Fleiss,31 the test-retest reliability of the nicotine dependence diagnosis was excellent (κ = 0.76), and the test-retest reliability for alcohol dependence was good (κ = 0.61).32

The DIS-3R diagnosis of alcohol dependence in VET Registry members has been reported to have good criterion validity, with 90% of patients treated for alcoholism in a Veterans Affairs hospital also receiving a diagnosis of alcoholism using the DIS-3R algorithm.34 Although similar data are not available for nicotine dependence, the content validity of the DIS-3R diagnosis of nicotine dependence appears good. For example, et al24 reported a genetic correlation between smoking and alcohol consumption of 0.47 in male World War II US veteran twins. In a cohort of female twins, Prescott and Kendler25 found family environmental experiences modestly contributed to nicotine and alcohol dependence, with only very small genetic influences common to both substances. These contrasting studies suggest further research is needed to elucidate the genetic and environmental influences common and specific to nicotine and alcohol dependence.

From the perspective of prevention of smoking- and alcohol-related diseases, the co-occurrence of nicotine and alcohol dependence is an important priority for study. To address this issue, we investigated whether there are common genetic and/or family environmental contributions to lifetime history of nicotine and alcohol dependence in 3356 male-male twin pairs from the VET Registry.

STATISTICAL ANALYSIS

Three sources of influences accounting for individual differences are additive genetic effects (denoted A for statistical analysis), shared environmental effects (denoted C for statistical analysis), and unique environmental effects (denoted E for statistical analysis).35 Additive genetic influences are correlated 100% between members of an MZ twin pair and 50% between members of a DZ twin pair. Shared environmental influences are experiences that twins have in common such as exposure to parental smoking or drinking, attending the same school or church, or living in the same neighborhood. Shared environmental influences are assumed to contribute to similarity equally in MZ and DZ twin pairs. Finally, unique environmental influences are among nicotine-dependent veterans, 43.1% reported failed cessation attempts, and 41.8% were heavy smokers (>30 cigarettes per day) and reported a mean of 3.75 nicotine withdrawal symptoms. In comparison, 19.6% of non–nicotine-dependent smokers were unable to quit, and 7.1% were heavy smokers and reported a mean of 0.39 withdrawal symptoms.

Eligibility criteria for the present analyses were the following: (1) both members of the twin pair were identified from Department of Defense computer files26; (2) both members of the pair completed all tobacco and alcohol use questions from the 1992 interview; and (3) zygosity could be definitively assigned. The final analyses were conducted using a sample of 3356 twin pairs (1864 were monozygotic [MZ]; 1492, dizygotic [DZ]).

The mean age of respondents at interview in 1992 was 46.6 years (SD, ±2.8 years; range, 36-55 years). Most (90.4%) were non-Hispanic white; 4.9%, African American; 2.7%, Hispanic; 1.3%, native American or Alaskan native; and 0.7%, other. High school graduates accounted for 33.3%; college graduates, 38.6%. Most (92.6%) were employed full-time; 1.8% were employed part-time; and 5.6% were not employed at the time of interview.

RESULTS

Among those who met criteria for nicotine and alcohol dependence, the mean ages of onset for regular smoking and alcohol dependence were 17.1 years (SD, ±3.1 years) and 20.4 years (SD, ±7.7 years), respectively. The lifetime prevalence of nicotine and alcohol dependence was 47.8% and 35.2%, respectively. Lifetime prevalence of nicotine dependence for MZ twins was 46.2%; for DZ twins, 49.7%. Lifetime prevalence of alcohol dependence for MZ twins was 34.8%; for DZ twins, 35.8%. Among those with nicotine dependence, 50.9% met criteria for alcohol dependence compared with those without nicotine dependence, among whom 20.8% had a diagnosis of alcohol dependence. Among persons with a lifetime diagnosis of nicotine dependence, 62.6% were current smokers at interview. Characteristics of smoking and drinking behaviors were similar for MZ and DZ twin pairs (Table 1).

For MZ twin pairs, the tetrachoric correlation for nicotine dependence was 0.61; for DZ twin pairs, 0.31. For alcohol dependence, the tetrachoric correlation for MZ twin pairs was 0.55; for DZ twin pairs, 0.29. In each case, the MZ twin pair correlation was approximately twice that of the DZ twin pair correlation, which suggested that both phenotypes were influenced by additive genetic effects.
nonshared experiences that contribute to differences within MZ and DZ twin pairs. Unique environmental influences are uncorrelated between twin pairs and include measurement error. The greater similarity for a phenotype among MZ twins compared with DZ twins, as shown by a higher correlation coefficient, suggests genetic influences, as found in our analysis.

Therefore, we used model fitting to resolve competing hypotheses that nicotine and alcohol dependence are influenced by genes and environment, with environmental influences across a pair being uncorrelated (AE); environmentally determined with some environmental elements resulting from experiences shared equally by both members of a twin pair (CE); or influenced by genes, shared environment, and unique environment (ACE).

We began by computing twin-pair contingency tables separately for nicotine and alcohol dependence. Tetrachoric correlations calculated for each disorder by zygosity were computed under the assumption of a multifactorial threshold model in which multiple unmeasured genetic and environmental risk factors determine an underlying continuous liability for development of nicotine or alcohol dependence. The liability threshold model assumes that there is a single normally distributed dimension of liability with abrupt thresholds. Above a given threshold, the disorder is expressed, and below the threshold, the disorder does not develop.

Univariate genetic path models were fit to the contingency tables using maximum likelihood. A univariate model estimated the proportion of variance attributable to additive genetic, shared environmental, and unique environmental effects, including error. Submodels were fit that deleted genetic (CE) or shared environmental parameters (AE). The goodness of fit of full models (ACE) and submodels (AE or CE) was determined using likelihood ratio χ², with degrees of freedom for the χ² difference between the full model and submodel computed as degrees of freedom of the submodel minus degrees of freedom of the full model.

As shown in Table 2, a full model that allowed for additive genetic, shared, and unique environmental influences on liability to nicotine dependence (ACE) and a reduced model that did not allow for shared environmental influences (AE) produced good fits to the nicotine dependence data (χ² = 6.79 [P = .08] and χ² = 6.80 [P = .15], respectively). The AE model was chosen as the best-fitting univariate model for nicotine dependence, since it gave a more parsimonious fit to the data and was not significantly worse fitting than the full model (Δχ² = 0.01 [P > .10]). A model that did not allow for additive genetic contributions (CE) gave a significantly poorer fit to the data compared with the full model and was rejected at P < .001.

For alcohol dependence, the full and reduced models produced good fits to the data (χ² = 4.20 [P = .24] and χ² = 4.38 [P = .36], respectively). The more parsimonious reduced model was not significantly worse fitting than the full model (Δχ² = 0.18 [P > .10]) and was chosen as best fitting the data. A model that did not allow for additive genetic contributions resulted in a poor fit (P < .001).

A bivariate genetic model was fitted to estimate the genetic and environmental correlations between nicotine and alcohol dependence. For bivariate modeling, a 4 × 4 correlation matrix was calculated for nicotine and alcohol dependence data of MZ and DZ twin pairs. This resulted in 2 within-diagnosis cross-twin correlations, 2 within-twin cross-diagnosis correlations, and 2 cross-twin cross-diagnosis correlations.

Bivariate analyses compared the fit of the full model (ACE) for nicotine and alcohol dependence with that of reduced models that removed 1 or more genetic (A) or environmental (C and E) parameters. A χ² difference statistic again determined the best fitting model. If 2 or more reduced models were observed to give an adequate fit for the data, the model with the lowest Akaike information criterion was accepted as the best fitting model. MX software was used for the genetic modeling, and the PRELIS 2 program was used to compute tetrachoric correlations and asymptotic covariance matrices.

DATA WEIGHTING TO ACCOUNT FOR RESPONSE BIAS

Since nonresponse may introduce bias in our genetic model fitting, we computed weights to account for systematic nonresponse to the 1992 interview. Nonresponders were twins who responded to a 1987 survey but not to the 1992 interview. Responders were twins who participated in both data collection efforts. Nonresponders in 1992 were more likely than responders to be persistent smokers (64.9% vs 57.1%), to have ever smoked (74.1% vs 68.7%), to report drinking more than 3 times per week (39.3% vs 31.8%), and to report heavy drinking (≥6 drinks per drinking occasion) (25.4% vs 20.3%). A response propensity analysis approach was used to generate sampling weights to account for response bias effects. We calculated tetrachoric correlations by zygosity for nicotine and alcohol dependence to compare weighted and unweighted correlations. Since no differences were observed, all analyses were reported using unweighted data.

Under the full univariate models, genes accounted for 59.6% (95% confidence interval [CI], 41.5%-65.4%) and 51.5% (95% CI, 32.1%-60.5%) of the variance in risk for nicotine and alcohol dependence, respectively. Under the full models, shared family environmental influences did not significantly account for variance in risk for nicotine (1.0% [95% CI, 0.0%-16.5%]) or alcohol dependence (3.5% [95% CI, 0.0%-20.0%]). The remainder of variance for both disorders was due to unique environmental factors that included measurement error.

Bivariate analyses determined the degree to which additive genetic and environmental contributions to nicotine and alcohol dependence were correlated. The bivariate model-fitting results are portrayed in Table 3. A model that allowed for genetic and unique environmental influences to nicotine and alcohol dependence but did not allow for shared environmental influences produced the most parsimonious fit to the data (χ² = 12.73 [P = .12]; Akaike information criterion, −3.28).

For the best-fitting bivariate model, we calculated the variance due to genetic and environmental influences and the genetic and environmental correlations for...
lifetime nicotine and alcohol dependence. The best-fitting bivariate model (Figure) included a substantial genetic correlation between both disorders \( r = 0.68 \) and 95% CI, 0.61-0.74) and a modest unique environmental correlation \( r = 0.23 \) and 95% CI, 0.14-0.32). Under this model, genes accounted for 60.3% (95% CI, 55.4%-65.2%) and 53.1% (95% CI, 49.7%-50.5%) of the variance in risk for lifetime nicotine and alcohol dependence, respectively. Unique environmental influences, which included measurement error, accounted for 39.7% (95% CI, 34.8%-44.6%) and 44.9% (95% CI, 39.5%-50.3%) of the variance in risk for lifetime nicotine and alcohol dependence, respectively.

Under this model, we computed the amount of genetic variance in risk for alcohol dependence that is common to nicotine dependence, where \( r_{xy} \) is the genetic correlation coefficient and \( h^2 \) is the total genetic variance in risk for alcohol dependence. Thus, \( \left( r_{xy} \times h^2 \right)^2 = 0.68 \times (55.1\%)^2 = 25.5\% \) of the total variance in risk for alcohol dependence overlaps with the genetic risk for nicotine dependence. Similarly, we found 2.4% of the variance in risk for alcohol dependence overlapped with the unique environmental influences to nicotine dependence.

The co-occurrence of lifetime nicotine and alcohol dependence among middle-aged male twins was best explained by a model that included a substantial genetic correlation \( r = 0.68 \) between both disorders, allowed for no shared family environmental influences, and evidenced considerable additive genetic contributions to nicotine and alcohol dependence (60.3% and 55.1%, respectively). Unique environmental influences were modestly correlated for both disorders \( r = 0.23 \). Of the total variance in risk for alcohol dependence, 25.5% was common with the genetic influence to nicotine dependence, but only 2.4% of the total variance in risk for alcohol dependence was common with the unique environmental influences to nicotine dependence.

Heritability estimates of 55% obtained in this sample for alcohol dependence are within the range of 39% to 60% previously reported in other twin studies.14-17 We are not aware of previous reports of the heritability of DSM-III-R nicotine dependence, but heritability estimates of 58% to 74% have been reported for smoking persistence.11,13 which may be related to the heritability of nicotine dependence estimated in our study. We recognize that the heritability estimates obtained may be limited by the reliability of each diagnosis. The estimate of the common genetic contribution to alcohol and nicotine dependence may vary with the reliability of the diagnoses.

Our finding that the liability for alcohol dependence is partially explained by additive genetic influences.
References in common with nicotine dependence is consistent with reports from other researchers that alcoholics are often nicotine dependent,39,40 heavy smokers,2,41 and less successful at smoking cessation compared with non-alcoholics.41,42

Limitations of this study should be considered when interpreting our results. First is potentially decreased generalizability due to the high rates of nicotine and alcohol dependence among VET Registry respondents, perhaps associated with the ubiquitous exposure to tobacco and alcohol in the military. The prevalence of lifetime nicotine (47.8%) and alcohol dependence (35.2%) among VET Registry twins is greater than that reported from other epidemiologic samples. We are aware of only 1 other study of the prevalence of DSM-III-R lifetime nicotine dependence, which found that 20.0% of young adult (median age, 26 years) members of a Michigan health maintenance organization met lifetime DSM-III-R criteria for nicotine dependence.43 The high prevalence of nicotine dependence in our sample is consistent with the high rates of lifetime and current smoking in other veteran cohorts.44

The lifetime prevalence of 35.2% for alcohol dependence in the VET Registry is greater than the 20.1% reported by the National Comorbidity Study.45 Reanalyses of National Comorbidity Study data, limited to men aged 34 through 55 years, yielded a lifetime prevalence of 21.1%. The prevalence of alcohol dependence in the VET Registry is close to the 39.2% lifetime prevalence of alcohol abuse and dependence reported by veterans in the National Vietnam Veterans Readjustment Study.46 Our prevalence data may not generalize to nonveteran populations, including populations of persons who are too ill to be eligible for military service. However, the variances due to genetic influences on nicotine (60.3%) and alcohol dependence (55.1%) found in our analyses are similar to results from other twin panels.11,12,15,16

Second, our results should not be applied to women, since there may be a sex difference in the role of genes in the tobacco-alcohol relationship.23,47 No nationally distributed female twin registry has been constructed for comparison with VET Registry data.

A basic assumption of twin studies is that MZ twin brothers are not treated differently than DZ twin brothers. This equal-environments assumption asserts that family environmental influences for MZ twins do not differ from those for DZ twins in their importance in the etiology of psychiatric disorders. Our analyses do not include a test of the equal-environments assumption; however, the equal-environments assumption has been shown to hold true for nicotine and alcohol dependence in other large twin populations.48

There are several strengths of our study. Our data were derived from a structured interview, and diagnoses of nicotine and alcohol dependence were derived according to standardized DSM-III-R criteria. Estimates of reliability of the nicotine and alcohol dependence diagnoses were good to excellent. Variance component estimates derived under best-fitting models were precise.
yielding narrow 95% CIs. Data were collected from a large, nationally distributed, nonclinical population, which increased generalizability.

The combined use of tobacco and alcohol is a serious public health concern. Tobacco use alone is responsible for more than 400,000 deaths per year in the United States.49 Hurt and colleagues50 found that tobacco-related conditions were associated with 50.9% of deaths among addicted persons and were twice those expected for the general population. Alcohol-related conditions were associated with 36.0% of deaths and were more than 4 times those expected in the general population. Their study emphasized the importance of the nicotine-alcohol relationship as a serious risk factor for increased mortality among substance-dependent persons. Our observation that these 2 dependencies have substantial common genetic causes suggests that lifetime nicotine and alcohol dependence comorbidity may be heritable, and for some nicotine-dependent alcoholics, smoking may be a trait co-inherited with alcoholism. In such cases, smoking behavior would not be purely coincidental and may be construed as part of the larger risk for becoming dually addicted.

Although recent studies suggest smoking cessation is associated with continued abstinence from alcohol8,42 and that smoking cessation efforts do not undermine alcoholism treatment,24 the clinical research has recognized the lack of evidence for a mechanism driving these changes. Our results do not resolve the biological mechanisms of the nicotine-alcohol dependence relationship; however, possible mechanisms suggested by others include cross-tolerance to nicotine and alcohol,25,26 common neural reward pathways,24,55 and cued responding.56,57 Our analyses identified a common genetic contribution to these dependencies that may underlie and influence some of the mechanisms of the nicotine-alcohol relationship.

**CONCLUSIONS**

Others have already reported that smoking initiation and alcohol consumption have familial risk factors in common that are in part due to genetic influences, especially in young adults.39 Our data suggest that among tobacco and alcohol users, genetic influences also contribute to the risk for dual dependence. Adolescents beginning to experiment with cigarettes and alcohol have little understanding of the powerful role that genes play in determining the risk for becoming an addicted smoker and alcohol dependent. It may be a prudent practice to stress the common genetic risk for dual addiction to nicotine and alcohol in efforts to prevent smoking and teenage drinking.

We have confirmed other reports of the high heritability of alcohol dependence, and we have identified a large genetic contribution to nicotine dependence. Most important, we have identified a genetic correlation between nicotine and alcohol dependence and genetic variance in risk for alcoholism that overlaps risk for nicotine dependence.

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