Rapid Communication

Smoking and Intoxication after Alcohol Challenge in Women and Men: Genetic Influences

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In an earlier analysis, men and women who were current or former smokers were found to report feeling less intoxicated on average than nonsmokers after ingestion of a challenge dose of alcohol. Here, we examine whether differences in subjective response to alcohol and a tendency to smoke cigarettes are transmitted together in families; and, if so, whether this association might be entirely explained by the same heritable factors that influence alcohol intake (as we might expect if both smoking and subjective intoxication are influenced by some general susceptibility for substance use). Alcohol challenge data on 388 Australian male and female twins (194 complete pairs) were reanalyzed using multivariate genetic analysis to evaluate the association between cigarette smoking and self-report intoxication after a standard dose of alcohol. In women, we could not reject the hypothesis of complete genetic overlap between effects on intoxication rating and history of smoking, and a significant residual genetic correlation between smoking and postalcohol intoxication persisted even when genetic influences on alcohol consumption were controlled for. In men, the familial association seemed to be largely environmentally mediated and associated with differences in drinking history. These findings prompt the question of whether, in some individuals, cigarette smoking may contribute to the development of tolerance to the effects of alcohol.

Key Words: Alcohol Intoxication, Alcohol Challenge, Smoking, Genetics.

Findings from most twin and adoption studies of alcoholism, reviewed elsewhere, are consistent with an important genetic influence on alcoholism risk in both women and men. Evidence from both cross-sectional and prospective research supports the hypothesis that less intense subjective reactions to alcohol, assessed in an alcohol challenge paradigm, predict increased vulnerability to alcohol and its effects of alcohol and nicotine, we found that men and women who were current or former smokers were found to report feeling less intoxicated on average than nonsmokers after ingestion of a challenge dose of alcohol. Here, we examine whether differences in subjective response to alcohol and a tendency to smoke cigarettes are transmitted together in families; and, if so, whether this association might be entirely explained by the same heritable factors that influence alcohol intake (as we might expect if both smoking and subjective intoxication are influenced by some general susceptibility for substance use). Alcohol challenge data on 388 Australian male and female twins (194 complete pairs) were reanalyzed using multivariate genetic analysis to evaluate the association between cigarette smoking and self-report intoxication after a standard dose of alcohol. In women, we could not reject the hypothesis of complete genetic overlap between effects on intoxication rating and history of smoking, and a significant residual genetic correlation between smoking and postalcohol intoxication persisted even when genetic influences on alcohol consumption were controlled for. In men, the familial association seemed to be largely environmentally mediated and associated with differences in drinking history. These findings prompt the question of whether, in some individuals, cigarette smoking may contribute to the development of tolerance to the effects of alcohol.

Key Words: Alcohol Intoxication, Alcohol Challenge, Smoking, Genetics.
smoking men (but not women) in our sample had increasingly lower blood alcohol concentrations (BACs) as recovery from alcohol progressed, the differences in perceived intoxication by smoking status could not be explained by the disparities in BACs between the smokers and nonsmokers (never or ex-smokers).

In a number of experimental studies, cigarette smoking has been demonstrated to increase with alcohol use in women,

and in men.

Laboratory measures of the amount and the intensity of cigarette use have been observed to be greatest in subjects with a history of alcohol-related problems.

Unfortunately, there has been little experimental study of the effect of nicotine on levels of alcohol consumption in humans. However in a laboratory study, rodents were found to drink substantially more alcohol during a period of subcutaneous administration of nicotine or amphetamine [but not caffeine, phenylcyclidine (PCP), secobarbital, LSD, methamphetamine, or haloperidol] than before drug treatment.

We may hypothesize that cigarette smoking enhances tolerance to alcohol either by counteracting performance deterioration (perhaps through the stimulatory effects of smoking) or by cross-tolerance to alcohol. Experimental studies on the effects of alcohol and nicotine, consumed both separately and jointly, suggest that nicotine counteracts certain detrimental effects of alcohol on cognitive skills, such as reduction in alertness

and speed of decision-making.

Short-term

and chronic treatment with nicotine has been demonstrated to produce cross-tolerance to ethanol in mice; and, in humans, a similar interaction between substances might contribute to the tendency of susceptible individuals to use nicotine and alcohol together.

We know of no previous examination of the familial relationship (be it genetic or environmental) between the use of tobacco and differences in subjective response to alcohol. In the present study, we reanalyzed the alcohol challenge data obtained from Australian male and female twins
to determine whether there is a familial association between a history of smoking and post-alcohol intoxication and, if so: (1) whether the same genetic (and/or shared environmental) factors influence history of alcohol consumption, smoking history, and subjective intoxication, as might be expected if the association between smoking and drinking alcohol is regulated by some general susceptibility to substance use (e.g., the same heritable personality traits or a depressive disorder); or (2) whether a significant genetic residual correlation persists between a history of smoking and post-alcohol intoxication even when genetic influences on alcohol consumption are controlled for.

**METHODS**

**Sample**

Data used in these analyses were obtained from an alcohol challenge study conducted by Martin and colleagues from 1979 to 1981
to using male and female adult volunteers recruited from the Australian NH & MRC Twin Registry. Subjects were not screened for family or personal history of alcoholism or alcohol consumption. Excluded from the study were recruits with co-twins who did not participate or complete the experiment. Fewer than 5% of the twins accepted into the study failed to complete the protocol, and this was usually due to nausea after the ingestion of alcohol. The zygosity assigned to the twin pairs was determined by tests that compared blood group, serum proteins, and certain enzyme systems. Almost all subjects were of European descent. The mean age of subjects completing the challenge study was 23 years (range: 18 to 34 years). Deletion of cases with missing data left 202 female and 186 male twins from complete pairs of twins (42 female and 41 male pairs of identical twins; 40 female and 33 male pairs of like-sexed fraternal twins; and 38 fraternal male-female pairs of twins).

Many of the alcohol challenge women (n = 148) and men (n = 128) participated in a survey conducted by mailed questionnaire in 1980 to 1982 ("1981 survey"), shortly after the experimental study. This allowed a small number of comparisons to be made between the experimental subjects who completed the 1981 survey and a subsample of twins of the same ages who had participated only in the survey (women: 3129; men: 1903).

**Measures**

Protocol and laboratory procedures are described more completely elsewhere.

Subjects completed a questionnaire that obtained sociodemographic information (i.e., age, education, religion, and marital history); measures of personality (the Eysenck Personality Questionnaire); history of alcohol consumption, including frequency of consumption (every day or most days, a couple of times a week, every week or so, or very rarely), a lifetime estimate of the number of occasions alcohol has been consumed (10 times or less, between 10 and 50 times, 51 to 100 times, 101 to 500 times, 501 to 1000 times, or >1000 times), the average number of drinks consumed per week (the sum of the number of glasses of beer, cider, wine, fortified wine, and spirits reported), a measure sensitive to heavy drinking (i.e., average number of drinks consumed per drinking occasion (9 or more, 6 to 8, 3 to 5, or 2 or less drinks)), frequency hung over, and frequency drunk (with the last two variables rated on three levels: often,
sometimes, or never); and history of cigarette smoking (whether the subject was a current or former smoker or had never smoked).

The experimental protocol included a battery of psychomotor tests, blood drawings, and ratings of subjective intoxication. Subjects were permitted to smoke when not otherwise occupied throughout the experimental protocol. Unfortunately, smoking by subjects during the protocol went undocumented.

For the purposes of this article, we analyzed data on self-report history of cigarette smoking and self-ratings of intoxication. Feelings of intoxication were measured by having subjects rate "How drunk do you feel now?" on a scale from 1 to 10, where 1 = "completely sober" and 10 = "the most drunk I have ever been."

Subjects were instructed to eat a nonfatty meal at about 8:00 AM. Procedures were begun at 9:00 in the morning. After completing the baseline questionnaire and psychomotor tasks, subjects were asked to drink an alcohol dose of 0.75 g of ethanol/kg body weight diluted to 10% (v/v) in sugarless "lemon squash" within 20 min at a steady pace. The battery of psychomotor tests was administered at 20, 80, and 140 min after alcohol intake, over a 25-min testing cycle. Intoxication ratings and blood alcohol levels were obtained at the end of each testing cycle, with three additional blood samples taken between cycles.

**Data Analysis**

**Generalizability Tests.** As a check on the generalizability of results from the alcohol challenge sample, the extent to which participation in the alcohol challenge sample was associated with previous exposure to alcohol, and cigarette use was examined using data from participants who responded to the 1981 mailed questionnaire survey. History of smoking and alcohol use was compared with 1981 survey respondents from the same birth years who did not participate in the alcohol challenge study, by χ² test. No attempt was made to correct for statistical nonindependence of observations on twin pairs, because these would be conservative (i.e., would lead to overreporting of differences between the alcohol challenge and 1981 survey samples). In addition, using methods described elsewhere, data from the alcohol challenge sample were weighted so that within each of the five psychosis groups, the proportion of participants in the alcohol challenge study had frequency distributions similar to those observed in the 1981 survey sample. The potential effect of sampling bias on estimates of genetic and environmental parameters was explored by comparing twin correlations generated from the weighted and unweighted data (see Ref. 37 for a discussion of the representativeness of the 1981 sample with respect to alcohol consumption variables).

**Genetic Influences on Subjective Intoxication.** In a previous analysis of these data, Neale and Martin determined that at least 35% of the observed variance for subjective intoxication may be accounted for by additive genetic effects, but they did not assess whether different genetic or environmental factors influenced the intensity of feelings of intoxication at different time points over the course of recovery from alcohol.

Therefore, before examining the association between cigarette smoking and postalcohol intoxication, we used multivariate genetic analysis to test whether variance in subjective intoxication reflects a single genetic common factor with effects that persist throughout recovery or, rather, the influence of two or three additive genetic factors expressed at different phases of recovery from alcohol (i.e., whether independent genetic factors determine (1) initial postalcohol intoxication and (2) extent of recovery at later time points).

The basic principles underlying the genetic analysis of twin data are straightforward (for a detailed technical account, see Ref. 39). In a univariate genetic analysis, variance is decomposed into three sources: additive genetic effects, shared environmental effects (i.e., influences that are shared by individuals reared in the same household, such as neighborhood, schooling and family, and environmental effects), and nonshared environmental effects. This decomposition rests on the assumption that identical twin pairs are no more highly correlated for their environmental experiences than fraternal twin pairs. If variance in a trait is entirely environmentally determined, equal monozygotic (MZ) and dizygotic (DZ) correlations are predicted; whereas if it is influenced by genetic as well as shared and nonshared environmental effects, the DZ correlation should be less than the MZ correlation, but still greater than half the MZ correlation; and if explained only by genetic plus nonshared environmental effects, a 2:1 ratio of the DZ to MZ correlation is predicted (or a greater than 2:1 ratio if some of the genetic variance is nonadditive; i.e., due to genetic dominance or epistasis). These same comparisons extend to the case of multivariable analyses. If genetic and environmental influences on two traits are entirely trait-specific, then the traits are predicted to be uncorrelated, and zero cross-correlations are predicted between one trait measured in one twin and the second trait measured in the second twin. If, in contrast, both genetic and shared as well as nonshared environmental influences contribute to the correlation between, say, smoking and subjective intoxication after alcohol challenge, then it is predicted that the cross-correlation between smoking and subjective intoxication rating will be lower in DZ than in MZ twin pairs, although still greater than one-half the MZ cross-correlation; and if there are only effects of genetic and nonshared environmental influences, then a 2:1 ratio of the MZ and DZ cross-correlations is predicted.

In practice, hypothesis testing is conducted not by visual inspection, but by fitting models to summary covariance matrices (for continuous variables) or polychoric correlation matrices (for binary or ordinal variables) by maximum-likelihood or by asymptotic weighted least squares, using the same methods used in structural equation modeling. This is particularly important for the multivariate case, because even with 3 variables, there will be 9 within-variable and cross-variable twin pair correlations for each twin group, in addition to 6 within-person (phenotypic) correlations between traits. Our approach involves fitting genetic "triangular decomposition" models. It can be shown (e.g., Ref. 39) for the general n-variable case that, under certain assumptions (either nonadditive genetic effects or nonshared environmental effects, but no shared environmental effects), the 2n × 2n covariance matrices for MZ twin pairs, DZ twin pairs, or other relatives can be decomposed into n orthogonal additive genetic factors, n orthogonal shared environmental factors, and n orthogonal nonshared environmental factors, whereas the first factor for each source (i.e., genetic, shared environmental, nonshared environmental) loads on l-n observed variables; the second factor has a zero loading on the first variable, but nonzero loadings on the remaining n-1 variables; the third factor has zero loadings on the first two variables and nonzero loadings on the remaining n-2 variables, and so on.

For the analysis of postalcohol intoxication ratings, obtained at three points in time (i.e., toward the end of 25-min testing cycles beginning at 20, 80, and 140 min after alcohol intake), summary 6 × 6 matrices of polychoric correlations were computed, separately for the five twin pair psychosis groups, using PRELIS. In the case of unlike-sex twin pairs, data were reordered so that the first three variables were always intoxication ratings given by the female twin, with the remaining three variables intoxication ratings given by the co-twin. Although subjective intoxication was measured using a 10-point scale, given the low frequency of response at some levels, we collapsed categories into four. A full triangular decomposition model, estimating orthogonal genetic, shared, and nonshared environmental factors with different loadings in men and women was fitted to the set of five 6 × 6 correlation matrices by the method of weighted least squares, yielding an overall χ² test of goodness-of-fit. Submodels were compared in which (1) genetic and shared environmental factors were constrained to be equal across sexes, and (2) the variance of each of the genetic or shared environmental factors was fixed at 0. For example, fixing the second and third genetic factors to 0 implied the hypothesis that any genetic influences on time 2 and time 3 subjective intoxication ratings could be entirely explained by genetic effects that also influenced time 1 rating; whereas finding evidence for a significant time 2 genetic factor would imply that, even after controlling for genetic effects that influenced time 1 rating, there was significant residual genetic variance in the time 2 rating, and so on. The different submodels were compared with the full model by likelihood-ratio χ² test.

**Genetic and Environmental Correlations with Smoking and Drinking Histories.** Model-fitting analyses allowed us to reject the hypothesis that
time 2-specific and time 3-specific genetic factors contribute substantially to the variation of perceived intoxication ratings at later time points. Therefore, the multivariate genetic models used to estimate genetic and environmental contributions to correlations between history of alcohol consumption, history of cigarette smoking, and level of perceived intoxication included only the measure of subjective intoxication taken during the first testing cycle post-alcohol, which previously demonstrated the strongest association with smoking history. A single score was computed for each subject to summarize history of alcohol exposure (i.e., the six measures of drinking history assessed in the baseline questionnaire) using principal components analysis. Smoking was classified as a binary variable (current or former smoker vs. never smoked). Matrices (6 × 6) of polychoric correlations were computed using PRELIS 2 and genetic tri- angular decomposition models fitted by asymptotic weighted least squares, as in the previous example.

In these analyses, variables were ordered (1) drinking history score, (2) lifetime smoking, and (3) subjective intoxication rating. Therefore, by fixing to 0 the variance of the second and third genetic factors (or the second and third shared environmental factors), it was possible to test the hypothesis that any genetic (or shared environmental) association between smoking and subjective intoxication was entirely explained by the first factor that also influenced alcohol consumption [i.e., was associated with genetic (or shared environmental) effects on drinking history].

RESULTS

Sample Representativeness

The alcohol challenge women who also participated in the 1981 survey reported drinking more heavily and somewhat more frequently than those who participated in the survey, but not the challenge study. Thirty-two percent of the alcohol challenge women vs. 21% of the women who only took part in the survey reported drinking six or more drinks per occasion (p < 0.01) in 1981, compared with 64% vs. 55% of the men (p = 0.05). Eight percent of the alcohol challenge women vs. 4% of the survey-only women reported drinking daily (p = 0.04) in 1981, in contrast to 11% vs. 9% of the men (p = 0.52). The overrepresentation of heavy drinkers was not unexpected, given that subjects were volunteering for an experiment involving the ingestion of alcohol. No significant differences in smoking history were found in men. However, compared with the survey-only women, the alcohol challenge women were more likely to have ever smoked by 1981 (prevalence of lifetime smoking was 44% and 53%, respectively; p = 0.02); but, among the lifetime smokers, women from the experimental group were no more likely to have continued smoking (i.e., the respondent was still smoking at time of 1981 survey) (prevalence of continued smoking among lifetime smokers was 66% vs. 68%, respectively; p = 0.66). Across samples, well-educated individuals were somewhat overrepresented: ~63% of the alcohol challenge participants who responded in the 1981 survey, and 47% of the survey only participants achieved >12 years of education (p = 0.001).

Analyses of weighted data indicated that sampling bias had only a minimal effect on the genetic and environmental parameter estimates. There were no significant differences between twin pair polychoric and Pearson correlations for perceived intoxication, smoking, and alcohol consumption variables using data unweighted versus weighted to account for the overrepresentation of heavy drinking and other characteristics predictive of participation in the alcohol challenge study.

Baseline Gender Differences

Figures 1a to 1c compare the drinking practices of the women who participated in the alcohol challenge study with the men. Women and men were equally likely to endorse drinking on >500 occasions (p = 0.75, not shown). More women reported drinking alcohol "once a week or so" than at any other frequency (Fig. 1a). Men were on average more frequent drinkers, with most men reporting drinking a "couple of times a week" or more. Similar numbers of male and female participants in the alcohol challenge study endorsed drinking 3 to 5 drinks on average per occasion (52% vs. 52%; Fig. 1b), but fewer women than men reported drinking heavily (i.e., >5 drinks per occasion; 14% vs. 24%, p = 0.01). Men were more likely to report being often intoxicated [often drunk: 24% vs. 8% of the women, p = 0.001, (Fig. 1c); often hungover, 16% vs. 6% of the women, p = 0.001, not shown].

Figure 1d summarizes the quantity of cigarettes typically consumed per day by smokers. Similar numbers of men and women described themselves as heavy smokers (i.e., smoke 20 or more cigarettes on a typical day; men = 22% and women = 18%; p = 0.48), and there were no significant differences in the proportions of lifetime smoker (52% in women vs. 56% in men, p = 0.42, not shown) or of those who continued to smoke (73% in women vs. 64% in men, p = 0.14, not shown).

Intoxication Ratings

Figure 2 presents the distribution of self-report intoxication obtained at the end of the first testing cycle begun 20 min after alcohol intake in the women compared with the men. The mean intoxication self-rating was higher in the women (6.6 vs. 5.3, p < 0.001), as was the percentage of women reporting to feel "the most drunk I have ever been" (21% vs. 12% of the men, p = 0.01).

Table 2 presents unweighted twin correlations for the ratings of subjective intoxication obtained at the end of 25-min testing cycles begun at 20, 80, and 140 min after alcohol intake. Ninety-day test-retest correlations are also shown in the last two rows of Table 2. The female MZ correlation for the intoxication rating taken during the first testing cycle was ~70% of the reliability estimate, suggesting that ~70% of the longitudinally stable variance (nearly 100% at time 2 and 80% at time 3) is caused by factors responsible for family resemblance (i.e., either genetic or environmental influences that are shared between twin and cotwin), compared with ~50% in men (~30% at time 2 and 75% at time 3). It seems that, during recovery from alcohol, more of the longitudinally stable variance in subjective intoxication was explained by familial factors in women
than in men. There was no evidence in our data for sex differences in the magnitude of the test-retest correlations obtained during the first testing cycle (0.81 in each sex), although differences between men and women were observed in the test-retest correlations derived from ratings obtained during the second and third testing cycles. Across all three points in time, the DZ correlation for self-rating of intoxication was less than one-half of the corresponding MZ correlation in both women and men, consistent with the hypothesis that family resemblance was determined by shared genetic rather than by shared environmental influences.

**Genetic Influences on Subjective Intoxication**

Despite the higher MZ correlations in women than men, the magnitude of estimated additive and shared environmental effects did not differ significantly by sex. The model with additive genetic and shared environmental parameter estimates constrained to be equivalent across sexes did not provide a significantly worse fit to the data, compared with the full model where these parameters were estimated separately for men and women (additive genetic effects: χ² = 3.72, df = 6, p = 0.71; shared environmental effects: χ² = 1.53, df = 6, p = 0.96). The best-fitting model, with parameter estimates constrained to be the same in men and women, allowed for genetic, shared environmental, and nonshared environmental effects that were common to all three testing cycles, as well as additional nonshared environmental influences (which would include measurement error) at cycles 2 and 3. Allowing for new genetic (or shared environmental) influences occurring late in recovery gave no discernible improvement in fit (χ² = 0.00).

Genetic and environmental factor loadings under the best-fitting model are shown in Fig. 3. A substantial proportion of the variance in intoxication ratings was determined by the genetic common factor (46% for cycle 1, 59% for cycle 2, and 44% for cycle 3), whereas familial influence due to environmental circumstances shared by twin and co-twin was small (0%, 1%, and 18% for each testing cycle, respectively), but increased by the end of recovery from alcohol.
SMOKING AND INTOXICATION

**Fig. 2.** Self-ratings of intoxication obtained during testing cycle 1 begun at 20 min postalcohol in women vs. men. Ratings on a scale from 1 to 10, with 10 "the most drunk I have ever been."

<table>
<thead>
<tr>
<th>Group</th>
<th>No.†</th>
<th>Time 1</th>
<th>Time 2</th>
<th>Time 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MZ females</td>
<td>44</td>
<td>0.56 (0.14)</td>
<td>0.54 (0.13)</td>
<td>0.53 (0.17)</td>
</tr>
<tr>
<td>DZ females</td>
<td>42</td>
<td>-0.14 (0.18)</td>
<td>-0.01 (0.19)</td>
<td>0.25 (0.25)</td>
</tr>
<tr>
<td>MZ males</td>
<td>42</td>
<td>0.30 (0.17)</td>
<td>0.25 (0.16)</td>
<td>0.38 (0.25)</td>
</tr>
<tr>
<td>DZ males</td>
<td>35</td>
<td>0.16 (0.19)</td>
<td>0.10 (0.22)</td>
<td>-0.07 (0.30)</td>
</tr>
<tr>
<td>DZ opposite-sex</td>
<td>39</td>
<td>0.10 (0.19)</td>
<td>0.32 (0.17)</td>
<td>0.19 (0.21)</td>
</tr>
<tr>
<td>Retest sample</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>36</td>
<td>0.81 (0.08)</td>
<td>0.53 (0.14)</td>
<td>0.67 (0.15)</td>
</tr>
<tr>
<td>Males</td>
<td>42</td>
<td>0.81 (0.07)</td>
<td>0.76 (0.09)</td>
<td>0.50 (0.18)</td>
</tr>
</tbody>
</table>

* Self-rating taken during testing cycle begun at 20 min postalcohol.
† Number of pairs for the twin groups and number of individuals for the retest samples. Numbers of pairs differ from those given under methods that were derived by deleting pairs with missing data on smoking and alcohol exposure, as well as on subjective intoxication.

**Table 2.** Sample Sizes and Twin Pair and Test-Retest Polychoric Correlations (Standard Error) for Self-Rating of Intoxication*

**Partitioning the Genetic Variance**

When multivariate genetic models were fitted to the data on alcohol exposure, smoking, and subjective intoxication, dropping additive genetic and shared environmental factors specific for intoxication did not change the fit of the model ($\chi^2 = 0.00$). Equating additive genetic or shared environmental parameter estimates across sex gave significantly worse fits to the data (additive genetic effects: $\chi^2 = 19.93$, df = 9, $p = 0.02$; shared environmental effects: $\chi^2 = 24.70$, df = 9, $p = 0.003$); consequently, the magnitude of the genetic and shared environmental estimates were allowed to differ in men and women.

Findings under the best model suggest complete overlap between genetic influences on risk of cigarette smoking and decreased sensitivity to alcohol intoxication in the women (genetic correlation $R_G = 0.98$, 95% confidence interval (CI): 0.85–1.00). Indeed, the genetic correlation between alcohol intoxication and smoking history was as strong as that between alcohol intoxication and drinking in the women ($R_G = 0.86$, 95% CI: 0.60–1.00). Genetic and environmental factor loadings under the best fitting model are presented in Fig. 4. In women, a substantial proportion, but NOT ALL of the genetic variance in intoxication ratings $[75\% = 0.57^2/(0.57^2 + 0.33^2)]$ and in smoking $[56\% = 0.64^2/(0.64^2 + 0.57^2)]$ was determined by the first genetic common genetic factor (the same genes influencing drinking history). Controlling for genetic influences on alcohol consumption history (the first genetic factor), the point estimate (and 95% CI) for the partial additive genetic covariance between lifetime smoking and perceived intoxication in women was 0.33 (0.02–0.57), but only a trivial 0.03 (0.00–0.35) in men. Approximately 25% of the genetic variance in perceived intoxication rating in women $[0.33^2/(0.57^2 + 0.33^2)]$ was due to genetic effects shared only with smoking.

In contrast to findings in the women, estimates of genetic parameters in men were not significant, but we could not reject the hypothesis of a familial environmental association between intoxication rating and smoking and drinking history in men. All estimates of the genetic effect on smoking in the men in this sample (but not women) could be dropped from the model (men: $\chi^2 = 0.00$, df = 2, $p < 0.001$) without a significant change in fit. Likewise, the estimate of the 95% CI for the genetic correlation between drinking history and subjective intoxication did not differ significantly from 0 (0.98, 95% CI: 0.00–1.00).

Our data suggest that environmental factors shared by twin and co-twin play an important role in determining the familial association between a tendency to smoke cigarettes, history of exposure to alcohol, and subjective intox-
Fig. 3. Results of fitting a genetic decomposition model to the post-alcohol intoxication rating data. The observed variables are self-rated measures of perceived intoxication obtained during each of the three test cycles (INTOX_T1–INTOX_T3). Latent variables are genetic (AG1–AG3), shared environmental (SHE1–SHE3), and nonshared environmental factors not shared with other family members (NSE1–NSE3) that contribute to the variance and covariance of the observed variables in each model, where the subscript denotes testing cycle. Parameter estimates are genetic and environmental factor loadings. Nonsignificant loadings have been fixed to 0. Squaring parameter estimates provide estimates of the proportions of observed variance in intoxication that is due to genetic or environmental effects.

Fig. 4. Results of fitting a genetic decomposition model to data on drinking history ("alcohol exposure"), smoking history, and subjective intoxication at test cycle 1. The observed variables are exposure to alcohol (ALCOHOL EXPOSURE), lifetime smoking (SMOKER), and subjective feelings of intoxication measured at test cycle 1 (INTOX_T1). Parameter estimates for men are in parentheses. Latent variables are latent genetic (AGa, AGs, and AG1), shared environmental (SHEa, SHEs, and SHE1), and nonshared environmental factors (NSEa, NSEs, and NSE1). Parameter estimates are genetic and environmental factor loadings in women and, given in parentheses, in men.

In a previous article, we reported analyses showing an apparent direct effect of history of cigarette smoking on ratings of intoxication after an acute dose of alcohol.20 Smokers reported feeling less intoxicated. Here, we examine whether the source of this association might be transmitted in families.

Consistent with the previous analyses of Neale et al.,38 we found evidence to support the hypothesis that differences in the level of perceived intoxication after the ingestion of alcohol is in part under genetic regulation (accounting for ~44 to 59% of the variation in response). In analyses restricted to the three post-alcohol intoxication ratings, only a minor contribution was observed from environmental factors shared with other family members (~0 to 18% of the variation in response). Our results suggested that a single genetic factor, operative during all phases of recovery, contributes to the variation in intensity of perceived intoxication. Although women on average reported being more intoxicated than men, the relative impact of genetic and environmental influences on subjective intoxication was the same in men and women. Genetic effects...
seemed to play a substantial role on reported level of intoxication consistently throughout alcohol recovery. However, the influence of environmental factors shared between the twins (e.g., day-of-testing effects) was only apparent late in recovery (i.e., during the third test cycle begun ~140 min after alcohol intake).

Results of the multivariate genetic analyses, including data on smoking and drinking history, suggested that a common genetic influence may in part underlie the association between subjective response to alcohol and smoking, at least in women. The genetic correlation between smoking and perceived intoxication in women was 0.98 (95% CI: 0.85–1.00). Because a high percentage of the experimental subjects with a history of cigarette smoking were current smokers (74% of female and 65% of male lifetime smokers), we were unable to rule out the possibility that our results were an effect of acute cigarette use (i.e., undocumented smoking during the alcohol challenge session) rather than a chronic effect.

Controlling for the genetic factor influencing alcohol consumption, our results for women suggested that as much as 25% of the genetic variance for intoxication could be attributed to the independent effect of genes influencing smoking behavior. Results from the present study are consistent with our earlier findings on shared genetic risk between smoking and problems with alcohol in women; both suggest that the relationship between smoking and problems with alcohol cannot be entirely explained by some general susceptibility for substance use, such as heritable personality traits or a depressive disorder. Interestingly, once we controlled for history of alcohol consumption and cigarette smoking, there was no evidence of familial risk specific to perceived alcohol intoxication in either women or men.

In contrast with the women, we could not rule out the possibility that familial risk for becoming a smoker in this sample of men was entirely due to environmental factors. These results are inconsistent with our finding of a substantial genetic effect on lifetime smoking in Australian twin volunteers of the same ages from a much larger sample of 1318 men (where the percentage of variance in lifetime smoking explained by additive genetic factors was found to be 36%, with ~38% due to shared environmental factors), and the findings of most but not all other studies on the heritability of smoking behavior in men. To examine the possibility that our power to detect a genetic contribution to smoking behavior was insufficient in the men, compared with the women in the alcohol challenge sample, we conducted a power analysis. Assuming a male MZ correlation of 0.7, a male DZ correlation of 0.5, and a prevalence of 47% for ever smoking (consistent with findings from the Australian 1981 survey for men born from 1944 to 1963), we had at least 95% power to reject (with $\alpha = 0.05$) the hypothesis of no familial influences from any source (i.e., either from genetic or shared environmental factors) on lifetime cigarette use in men. However, data from at least 500 pairs each of MZ and DZ male like-sex twins would have been needed to provide even 80% power for rejecting the more specific hypothesis of no genetic influence. By comparison in the women, assuming an MZ correlation of 0.85, a DZ correlation of 0.5 (i.e., estimating that 70% of the variance in lifetime smoking can be explained by additive genetic factors and only 15% by shared environmental factors) and a prevalence of 44% (again, consistent with results from the Australian 1981 questionnaire survey for women born 1944 to 1963), data from a substantially smaller number of pairs (~125 pairs each of MZ and DZ pairs) were found to be sufficient to achieve 80% power for rejecting the hypothesis of no genetic influence. The greater importance of shared environmental influences on the initiation of cigarette use in the young Australian men reduced our power to evaluate the contribution of genes, compared with the women.

Our analyses of the male data did confirm a significant familial association between smoking and subjective intoxication after alcohol challenge, although due to shared environmental rather than shared genetic influences. Nonetheless, in men (but not women), the familial association between perceived alcohol intoxication and cigarette smoking was found to be entirely explained by the same factors that influence the quantity and frequency of alcohol intake. Therefore, we cannot rule out the hypothesis that the familial association observed between smoking and perceived intoxication was determined by some general susceptibility to substance use in the men. Failure to find evidence for a specific familial association between smoking and subjective intoxication in men may in part have been a function of the dose of alcohol administered.

How do we explain these differences in men and women? There is much that remains unknown about biological processes associated with alcohol and nicotine, and still less known about sex differences. However, assuming that similar mechanisms underlie perceived intoxication for alcohol in men and women, perhaps the disparity in our findings is in part due to physiological differences affecting tolerance to alcohol. For example, there is evidence to suggest that women on average require less alcohol to achieve similar BACs and levels of intoxication as men because of having a lower amount of body water and less gastric metabolism of alcohol. Dosing in the alcohol challenge study was based on total body weight (i.e., not adjusted for differences in amount of body water and reduced gastric metabolism). Women alcohol challenge study participants, although on average heavier drinkers than other female twins from the Australian twin panel (see also Ref. 36), had less experience of drinking large amounts of alcohol than the male participants. Higher BACs in the women, as well as higher subjective ratings of intoxication were observed. We may speculate that, if smoking decreases feelings of alcohol intoxication, cigarette use would make a substantially larger contribution to the reduction in level of alcohol intoxication experienced by the women, making it easier to
demonstrate a specific familial association between smoking and post-alcohol intoxication.

In interpreting the results of this study, several potential limitations must be borne in mind. The essence of the twin method is to compare the degree of phenotypic resemblance in identical twins to that of fraternal twins. However, if greater concordance between MZ twins is partly due to greater similarity in experience (e.g., peer influences), the result is an overestimation of the importance of genetic influences and an underestimation of environmental experiences shared by twin and co-twin. Such excess environmental similarity, particularly if more important in women than men, could cause us to overestimate any genetic association between smoking and subjective intoxication. The reverse may result from assortative mating. That is, if individuals in the parental generation with reduced sensitivity to alcohol were more likely to marry smokers than nonsmokers, the estimated contribution of familial influences from environmental effects shared between family members will be overestimated and the genetic influences underestimated in twin data (e.g., see Ref. 39). Because questions about parental use of alcohol and tobacco were not asked, or questions about the degree to which the twins shared similar social environments at the time of the alcohol challenge experiment, we were not able to examine the effects of these factors on the genetic and environmental estimates derived from our data. Lastly, our power to evaluate the contribution of genes in men may have been insufficient. It should be noted, the statistical power for detecting shared environmental effects are greater than for detecting genetic effects in the classical twin study.51

Our research suggests a specific familial association between smoking and subjective intoxication after alcohol administration (i.e., not explained by history of alcohol consumption) in women that is in part genetically mediated. It does, however, give few clues as to the possible biological underpinnings of such an effect. It seems plausible that there are genetic effects that jointly influence both response to nicotine and response to alcohol. In rodent studies, acute30-32 and chronic33 nicotine-alcohol cross-tolerance effects have been demonstrated, and at least some strains of mice selected for differences in alcohol response also exhibit differences on some measures of response to nicotine.22,53 Human studies have shown an important genetic correlation between smoking and the onset of alcohol use,15 alcohol consumption,16-18 and alcohol-related problems.9 Our findings raise the possibility that reduced intoxication would be observed even in non-smokers who carry genetic risk factors for smoking (e.g., have co-twins who are heavy smokers). Because of the very high degree of twin pair concordance for smoking, the random sampling design used in the alcohol challenge study would be very inefficient for investigating such an effect. These deficiencies point to the need for a new generation of laboratory-based studies, using more efficient sampling designs (e.g., oversampling smoking-discordant twin pairs), and a broader range of doses of alcohol, to investigate the relationship between smoking and subjective response to alcohol, and its genetic underpinnings.

In conclusion, if the hypothesis that low alcohol sensitivity predicts vulnerability to alcohol-related problems is true, then our findings suggest that this may represent one mechanism by which cigarette smokers come to have an elevated risk for alcoholism, at least in women. These findings support continuing efforts to determine the role of smoking in the development of tolerance to alcohol, and suggest that sex differences in the effects of smoking on vulnerability to alcohol-related outcomes be an important priority for future research.

REFERENCES

17. Swan GE, Carmelli D, Cardon LR: The consumption of tobacco,


