The Genetics of Alcohol Intake and of Alcohol Dependence

John B. Whitfield, Gu Zhu, Pamela A. Madden, Michael C. Neale, Andrew C. Heath, and Nicholas G. Martin

Background: Because alcohol has multiple dose-dependent consequences, it is important to understand the causes of individual variation in the amount of alcohol used. The aims of this study were to assess the long-term repeatability and genetic or environmental causes of variation in alcohol intake and to estimate the degree of overlap with causes of susceptibility to alcohol dependence.

Methods: Data were used from three studies conducted between 1980 and 1995 on volunteer adult male and female Australian twin subjects. In each study, alcohol intake was reported both as quantity $\times$ frequency and as past-week data. Repeatability was calculated as correlations between occasions and between measures, and the effects of genes and environment were estimated by multivariate model fitting to the twin pair repeated measures of alcohol use. Relationships between mean alcohol use and the lifetime history of DSM-III-R alcohol dependence were tested by bivariate model fitting.

Results: Repeatability of the alcohol intake measures was between 0.54 and 0.85, with the highest repeatability between measures within study and the lowest repeatability between the first and last studies. Reported alcohol consumption was mainly affected by genetic factors affecting all times of study and by nonshared environmental factors (including measurement error) unique to each time of study. Genes that affect alcohol intake do affect alcohol dependence, but genetic effects unique to dependence are also significant; environmental effects are largely unique to either intake and dependence.

Conclusions: Nearly all the repeatable component of variation in alcohol intake is due to genetic effects. Genes affecting intake also affect dependence risk, but there are other genes that affect dependence alone. Studies aiming to identify genes that affect alcohol use disorders need to test loci and candidate genes against both phenotypes.

Key Words: Alcohol Intake, Alcohol Dependence, Repeatability, Genetic Effects, Twin Study.

ALTHOUGH ALCOHOL CONSUMPTION and alcohol dependence are closely related, the causes of variation in the amount and patterns of alcohol intake and the causes of variation in susceptibility to alcohol dependence are not necessarily the same. Definition of the common underlying causes and of those that are unique to either consumption or dependence is an important step toward identifying social or personality factors or genetic polymorphisms that influence either or both of these significant phenotypes.

From the Department of Clinical Biochemistry, Royal Prince Alfred Hospital, and University of Sydney, Sydney, Australia (JBW); Queensland Institute of Medical Research, Brisbane, Australia (JBW, GZ, NGM); Missouri Alcoholism Research Center, Department of Psychiatry, Washington University School of Medicine, St. Louis, Missouri (PAM, ACH); and Department of Psychiatry and Human Genetics, Virginia Commonwealth University, Richmond, Virginia (MCN).

Both alcohol use and dependence have significant effects on many aspects of health, but on the whole, the psychological and social problems associated with alcohol cluster within the concept of dependence, whereas the biomedical consequences are more closely associated with the quantity of alcohol consumed. There is substantial evidence on the relationships between total quantity of alcohol consumption and the more common forms of harm, particularly alcoholic liver disease (Bellentani et al., 1997; Corrao et al., 1999; Pequignot et al., 1978; Savolainen et al., 1993), but also alcohol-related cancers (Corrao et al., 1999) and accidental or violent injury (Dawson, 2001). The dose-response relationships between alcohol and cardiovascular disease and the variation in the size of cardioprotective effects with age and sex have also been the subject of many large studies (e.g., Corrao et al., 2000; Thun et al., 1997; White, 1999).

A large amount of survey and epidemiological data is available on both alcohol use and dependence, but research on causes of variation in susceptibility to alcohol dependence has tended to overshadow research on the causes of variation in consumption or patterns of consumption. This is particularly true of recent genetic linkage and association studies, in which the most compelling results come from the Consortium on Genetics of Alcoholism. They have concentrated, as the name implies, on the phenotype of alcohol dependence or on en-

dophenotypes closely associated with dependence (Edenberg et al., 2004; Saccone et al., 2000). Research on dependence can easily be justified, but the biological (and, ultimately, pathologic) effects of alcohol are caused by the substance itself and are not a direct consequence of dependence as currently defined. In the general community, the association between lifetime dependence and current alcohol use is significant but not overwhelming, with a substantial overlap of intake between ever-dependent and never-dependent subjects. Quantitative measures of alcohol intake have been found to be poor predictors of past-year DSM-III-R alcohol dependence (Dawson, 1994).

Because the pathologic effects of alcohol accumulate over a long period, stability or fluctuation in alcohol use over time is another important issue. The average of a number of measurements on different occasions will give a better estimate of exposure to risk over the long term. For estimates of heritability or environmental effects, as well as for genetic association or linkage studies, data from multiple occasions put any observed effects in a better context of the repeatable component of variation.

Our previous publications have addressed variation in both consumption and dependence (Heath et al., 1997, 1999, 2001; Heath and Martin, 1994; Whitfield et al., 1998b, 2001) and have in part aimed to clarify the relationships between them. Following these themes, this study used longitudinal data from male and female twin subjects on self-reported alcohol consumption: we considered the stability of the measures over time, their heritability, and their relationship with lifetime alcohol dependence history within a community-based sample.

MATERIALS AND METHODS

Subjects were originally recruited from the Australian Twin Registry, a volunteer registry begun in 1978. In 1980 to 1982, a questionnaire was mailed to all 5,867 registered pairs of twins (11,734 individuals) over the age of 18 years (Heath et al., 1995; Jardine and Martin, 1984). In almost all cases, the subjects were of European descent. Information was obtained in three phases, with the second phase approximately 9 years and the third approximately 13 years after the first. Each of these studies was performed with the informed consent of the participants and after approval by appropriate ethics review committees.

Responses to the initial questionnaire were received from 8184 individuals. Included in this questionnaire were items regarding frequency of having consumed alcoholic drinks in the past year, the usual number of drinks taken, and a table for respondents to complete indicating how many glasses of beer, wine, spirits, sherry, and other alcoholic drinks they had consumed in the past week. Glass volumes were quoted (7 oz for beer, 4 oz for wine, and 1 oz for spirits) to standardize quantities of alcohol. This phase is referred to as the 1980 Study.

The next wave of data collection occurred in 1988 to 1991, when a follow-up questionnaire was mailed to all twin pairs for which one or both of them had completed the 1980 Study (Heath et al., 1994). Responses were obtained from 6570 individuals. Questionnaire items similar to those in the 1980 Study regarding frequency of alcohol consumption and usual quantity in the past year and actual consumption of each type of alcoholic beverage in the past week were included. This phase is referred to as the 1989 Study.

Third, a telephone interview–based study using a modified version of the Semi-Structured Assessment for the Genetics of Alcoholism instru-

ment was conducted during 1992 and 1993 with 5996 individuals who had participated in the earlier studies outlined previously. Details of the interview procedure and instrument are described elsewhere (Bucholz et al., 1994; Heath et al., 1997; Statham et al., 1998). In addition to items similar to those in the mailed questionnaires regarding the usual quantity and frequency of alcohol consumption, the interview also allowed a lifetime diagnosis of alcohol dependence according to DSM-III-R criteria. During 1993 to 1995, blood was collected from 3378 subjects who had participated in the telephone interviews (Whitfield et al., 1998a); at that time they filled in a chart showing the number of drinks taken in the previous week, categorized as beer, wine, spirits, sherry, and other. Data from the telephone interview and the subsequent blood collection session are referred to in this article as the 1993 Study.

Therefore, we had data on six measures of alcohol intake: (1) the quantity $\times$ frequency estimate for the previous year in the 1980 Study; (2) the number of drinks in the previous week in the 1980 Study; (3) the quantity $\times$ frequency estimate for the previous year in the 1989 Study; (4) the number of drinks in the previous week in the 1989 Study; (5) the quantity $\times$ frequency estimate for the previous year in the 1993 Study; and (6) the number of drinks in the previous week in the 1993 Study. The two measures of intake from the 1980 study were provided at the same time, as were those from the 1989 Study, but there was an interval of some months between the two measures from the 1993 interview and blood collection phases.

There was some attrition of subjects through the series of studies. The most serious issues would arise if there was differential attrition so that either the abstainers and lighter drinkers were more likely to drop out or the heaviest drinkers were more likely to do so. We tested this by logistic regression, by using alcohol intake data from the first study as the predictor variable and participation versus nonparticipation is the subsequent studies as dependent variables. This showed that reported intake did not significantly predict participation in the later studies, either for women or men. Conversely, we compared the alcohol intakes of participants and nonparticipants in the first two studies by using intake data from the Semi-Structured Assessment for the Genetics of Alcoholism telephone interview (which is central because it is the source of the alcohol dependence data, and only those with these data could be included in the bivariate intake/dependence analysis). Because of the smaller numbers participating in the blood collection phase, the greatest concern would be if the alcohol intake declared at the time of telephone interview differed substantially between participants and nonparticipants in the blood collection. This was not the case; the values differed by 0.9% in women and 3.7% in men, and neither difference was statistically significant.

Relevant characteristics of the participants are given in Table 1, and their reported previous-week alcohol consumption is summarized in Fig. 1. Zygosity was determined by self-report questionnaire; comparisons with multilocus genotyping have shown approximately 98% accuracy for these questions. Because the distributions of measures of alcohol intake were positively skewed, they were subjected to log transformation [$\log_{10}(x+1)$, to allow inclusion of 0 values] before analysis. We used SPSS 9 (SPSS Inc., Chicago, IL) for exploratory compilation of summary statistics, frequency tables, and cross-tabulations. Model fitting for estimation of genetic and environmental causes of variation and of covariation between intake values from different occasions and between mean intake level and alcohol dependence was performed with Mx (Neale, 1999). This was designed for analysis of twin and family data and is not subject to problems associated with nonindependence of related subjects. Furthermore, the full information maximum likelihood method that Mx uses is especially useful for handling missing data. Whenever data are missing completely at random or when missingness is predicted by other variables used in the analysis (or both), the parameter estimates are unbiased.

The model-fitting process for the alcohol intake data commenced with inclusion of six factors for additive genetic effects (A1 to A6), six for shared environmental effects (C1 to C6), and six for nonshared environmental effects (E1 to E6). In each case, the first factor (A1, C1, or E1) could affect all six intake measures (i.e., the quantity $\times$ frequency measure and the number of drinks in the previous week, on three occasions each, as listed previously), the second factor could affect the second to sixth

Table 1. Characteristics of Subjects and Comparison With National Alcohol Consumption at the Times of Study

Variable	Men	Women
Age at time of 1980 questionnaire (years)		
Mean ± SD	32.9 ± 13.9	34.5 ± 14.2
n	2964	5220
Range	18–82	18–88
Drinks per week, 1980 (mean ± SD)	14.4 ± 18.8	5.0 ± 8.1
Average for Australia, 1981	14.9[a]	
Age at time of 1989 questionnaire (years)		
Mean ± SD	40.2 ± 12.6	41.9 ± 13.0
n	2309	4261
Range	24–87	24–86
Drinks per week, 1989 (mean ± SD)	10.9 ± 13.5	4.6 ± 7.1
Average for Australia, 1989	13.4[a]	
Age at time of interview (years)		
Mean ± SD	43.2 ± 11.8	45.3 ± 12.6
n	2087	3909
Range	28–90	28–90
Age at time of blood collection (years)		
Mean ± SD	44.8 ± 11.0	46.5 ± 12.0
n	1135	2243
Range	30–86	30–92
Drinks per week, 1993 (mean ± SD)	9.6 ± 11.8	3.9 ± 5.7
Average for Australia, 1993	11.5[a]	

[a] Estimated from data in "Consumption of Alcohol, Australia, 1961–2000." Australian Institute of Criminology, 2003: http://www.aic.gov.au/research/drugs/stats/consumption/alcohol.html. This is calculated from sales data and is not adjusted for sex or age effects.

intake measures, and so on until the sixth factor represented influences unique to the sixth of the intake measures. The intake measures were listed chronologically, with the quantity × frequency value first within each time point. This so-called triangular decomposition is equivalent to estimating genetic and environmental variances for each measure and genetic and environmental correlations between all pairs of variables. Effects of sex and age were included. Path coefficients, proportions of variance explained, and genetic and environmental correlations between the intake measures were estimated under this full model.

To maximize the number of subjects for analysis of the relationships between alcohol consumption variables and alcohol dependence, means of all available measures of total intake (up to six measures) were calculated. Because our main focus in this part of the analysis was on the relationship between the long-term, repeatable component of the intake-related measures and the likelihood of dependence, this procedure does not detract from the results. Relationships between genetic and environmental sources of variation in alcohol intake and dependence were tested with a threshold model in which alcohol dependence was viewed as occurring once the underlying continuous variable, likelihood of dependence, passed a threshold for expression. Similarly, in this analysis, mean alcohol intake was subject to threshold-based analysis so that the underlying construct was the likelihood of falling into the top quartile of alcohol intakes. For this group of subjects, the 75th percentile of mean alcohol intake was 4.2 drinks per week for women and 12.2 drinks per week for men. An initial model containing all potential sources of variation was simplified in stages, with assessment of goodness of fit at each stage. Terms allowing for sex differences and age effects were included. Because the pattern of within-pair correlations initially suggested that the sources of variation in likelihood of heavy drinking might vary between men and women, the full model contained additional terms for genetic influences on intake and dependence that were unique to men.

RESULTS

Stability of Alcohol Consumption Across Time

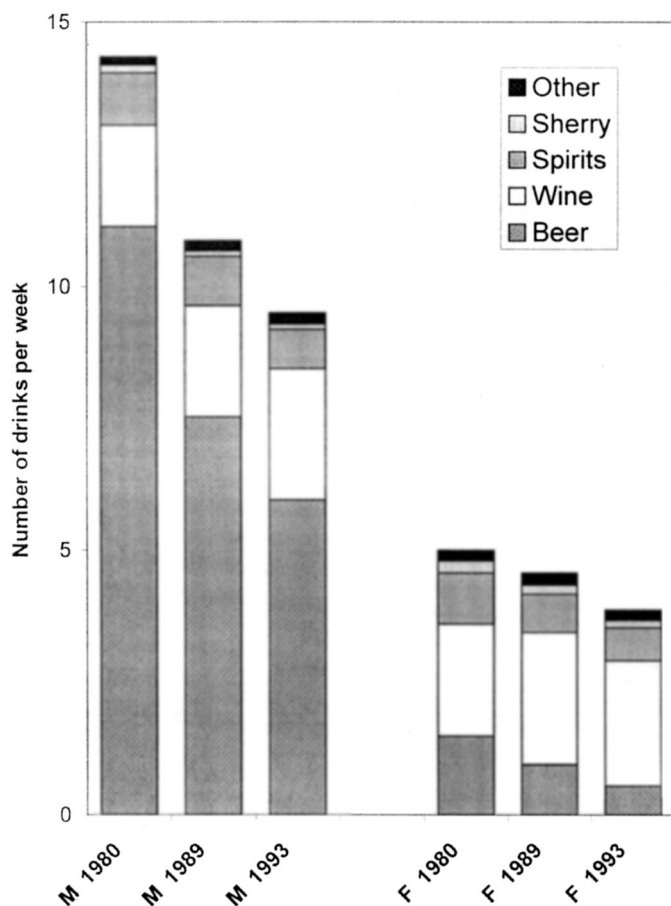Correlations between the estimates of alcohol intake are shown in Table 2. Taking all subjects together, the

Fig. 1. Consumption of alcoholic beverages, by category, for men and women at three times. M = male, F = female, in 1980, 1989 and 1993.

correlations between measures within studies were higher than those between studies, but the correlations between the two measures across studies were equivalent. Comparing the results by age group, the stability of alcohol intake across studies was greater in the older subjects (older than 30 years at the time of the first study), and comparison by alcohol dependence status showed greater variation (particularly between the results from the first and last studies) in the ever-alcohol-dependent group (data not shown).

Repeatability and Heritability of Alcohol Intake

The pattern of genetic, shared environmental, and non-shared environmental influences on alcohol intake measures is summarized in Table 3. This shows the proportions of variance ascribed to the possible sources of variation. The heritability of the alcohol intake measures varied between 0.40 and 0.54. A small proportion of variation (up to 10%) was ascribed to shared environmental effects; this could be dropped from the model with a marginally significant ($p = 0.055$) deterioration in goodness of fit but was retained for completeness. Most of the additive genetic effects on intake were ascribed to a genetic factor (A1) that acted on all six intake measures, but there was also a

Table 2. Stability of Alcohol Intake Across Time

Variable	1980 QF	1980 PW	1989 QF	1989 PW	1993 QF	1993 PW
1980 QF	—	0.83	0.57	0.54	0.54	0.56
1980 PW	0.85	—	0.58	0.57	0.54	0.59
1989 QF	0.60	0.58	—	0.78	0.66	0.70
1989 PW	0.54	0.54	0.74	—	0.62	0.70
1993 QF	0.56	0.54	0.69	0.60	—	0.76
1993 PW	0.60	0.60	0.73	0.67	0.80	—

Correlations between self-reported alcohol intake on three occasions and by the past-week (PW) and quantity × frequency (QF) measures, are shown. Results for women are above the diagonal, and for men, below.

Table 3. Percentage of Variance in Self-Report Measures of Alcohol Intake Due to Additive Genetic (A), Shared Environmental (C), and Nonshared Environmental (E) Effects

Variable	A1	A2	A3	A4	A5	A6	Total	C1	C2	C3	C4	C5	C6	Total	E1	E2	E3	E4	E5	E6	Total
1980 QF	54						54	4						4	41						41
1980 Past week	46	2					48	6	0					6	20	25					45
1989 QF	28	0	12				40	1	0	0				1	6	1	52				59
1989 Past week	28	2	13	0			43	4	0	0	0			4	6	1	14	32			53
1993 QF	26	0	14	0	0		40	10	0	0	0	0		10	6	1	7	2	34		50
1993 Past week	28	0	15	0	0	0	43	6	1	1	0	0	0	8	3	1	3	2	8	31	48

A1 to A6, C1 to C6, and E1 to E6 represent factors that affect all intake measures, all except the first-listed measure, all except the first and second measures, etc., to A6, C6, and E6, which affect only the last-listed measure. The Total columns sum A1–A6, C1–C6, and E1–E6 for each measure and represent the heritability, shared-environment effect, or nonshared-environment effect for each. Certain factors can be dropped from the full model (A4 to A6; C2 to C6) because the fit between the data and the model was not significantly worse after they were set to 0.

QF, usual number of drinks per week calculated from quantity and frequency data; Past week, total number of drinks reported for the previous 7 days.
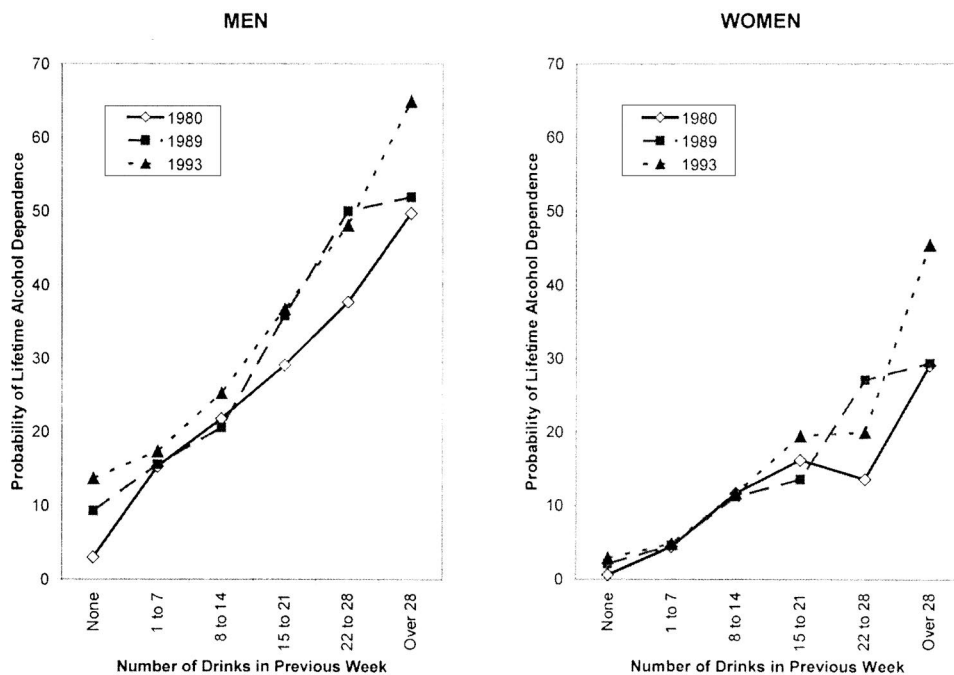

Fig. 2. Probability of lifetime DSM-IIIR alcohol dependence for men and women, by self-reported alcohol intake in the previous week in 1980, 1989 and 1993.

significant but slight genetic effect (A2) on the past-week intakes in the first and second studies and a genetic factor (A3) acting on intake measures from the second and third studies (1989 and 1993), but not the first (1980) study. The nonshared environmental effects (E1–E6) were mainly specific to the individual measures but also affected the other type of measure within the same occasion (e.g., E1 accounted for 41% of the variance in the quantity × frequency intake measure in the 1980 Study and also for 20% of the variance in the past-week measure for that occasion, but only for 3–6% of the variance in intake reports from the other occasions).

The genetic correlations among the six intake measures were high, ranging from 0.79 to 0.99, whereas the between-occasion nonshared environmental correlations were substantially lower (range, 0.25–0.35). For the two measures of alcohol intake obtained on the same occasions, the nonshared environmental correlations were 0.6, indicating that recent departures from long-term intake patterns were well reported by the subjects.

Table 4. Proportions of Subjects With Lifetime DSM-III-R Alcohol Dependence by Approximate Quartiles of Mean Alcohol Intake: Alcohol Intake Estimates were Derived From up to Six Self-Reports From Three Studies

Variable	Men				Women			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Mean of the quartile (drinks per week)	0.5	3.6	8.9	22.6	0.1	0.9	3.0	9.4
Number of subjects	520	546	541	454	1015	980	981	902
Number (%) with lifetime DSM-III-R alcohol dependence	32 (6.2%)	90 (16.5%)	153 (28.3%)	216 (47.6%)	10 (1.0%)	18 (1.8%)	66 (6.7%)	141 (15.6%)
Odds ratios (relative to lowest quartile, Q1)	1.00	3.01	6.00	13.8	1.00	1.88	7.24	18.6

The number of subjects in each quartile varies because the frequency distribution of the mean number of drinks per week does not allow definition of interquartile boundaries giving the same number of subjects in each quartile.

Table 5. Pairwise Tetrachoric Correlations and Cross-Correlations for Likelihood of Heavy Drinking and Alcohol Dependence by Zygosity

Variable	Monozygotic same-sex pairs (female above diagonal, male below)				Dizygotic same-sex pairs (female above diagonal, male below)				Dizygotic opposite-sex pairs (female = twin 1, male = twin 2)			
	Twin 1 HD	Twin 1 AD	Twin 2 HD	Twin 2 AD	Twin 1 HD	Twin 1 AD	Twin 2 HD	Twin 2 AD	Twin 1 HD	Twin 1 AD	Twin 2 HD	Twin 2 AD
Twin 1 HD	—	0.505	0.735	0.471	—	0.505	0.442	0.207	—			
Twin 1 AD	0.501	—	0.471	0.518	0.501	—	0.207	0.199	0.505	—		
Twin 2 HD	0.665	0.373	—	0.505	0.438	0.239	—	0.505	0.267	0.177	—	
Twin 2 AD	0.373	0.680	0.501	—	0.239	0.222	0.501	—	0.072	0.383	0.501	—

Within-subject correlations between intake and dependence liabilities are constrained to be equal regardless of zygosity (although they may differ between men and women), and the cross-correlations of alcohol intake for twin 1 and alcohol dependence for twin 2 are constrained to be equal to those for intake of twin 2 and dependence in twin 1 (although they are free to differ by zygosity).

HD, heavy drinking (in top 25% of sample); AD, alcohol dependence (lifetime, DSM-III-R).

Alcohol Intake and Dependence

The proportion of subjects who were ever alcohol dependent increased with increasing alcohol intake, as illustrated in Fig. 2. This shows data from the 1980, 1989, and 1993 estimates of number of drinks in the week before data collection for men and women. The probability of lifetime alcohol dependence and calculated odds ratios, by quartiles of the summary measure of alcohol intake derived from all six intake measures, are shown in Table 4.

Sources of Variation and Covariation for Alcohol Intake and Dependence

The estimated tetrachoric correlations and cross-correlations for likelihood of heavy drinking and likelihood of alcohol dependence, by zygosity, are shown in Table 5. Note that the within-subject correlations between intake and dependence liabilities were constrained to be equal regardless of zygosity (although they may differ between men and women) and that the cross-correlations of alcohol intake for twin 1 and alcohol dependence for twin 2 were constrained to be equal to those for intake of twin 2 and dependence in twin 1 (although they were free to differ by zygosity).

Initial inspection of the data in Table 5 suggested that the cross-correlations between alcohol dependence and heavy drinking were similar in male and female monozygotic pairs and, again, similar (but lower, as expected) in male and female dizygotic pairs. However, this cross-correlation was lower in the opposite-sex dizygotic pairs, raising the possibility of sex-specific genetic effects. This led us to compare a model containing additive genetic, shared environmental, and non-shared environmental effects and also male-specific genetic effects with progressively simplified models from which sex-specific genetic effects and shared-environmental effects were absent. The results of stepwise simplification of the full model are shown in Table 6. The male-specific genetic effects, the different parameter estimates for men and women, and the shared-environmental effects could each be dropped without significant deterioration in goodness of fit between the model and the data. However, genetic effects, and, importantly, both common and unique genetic effects had to be retained. This led to the final model shown in Fig. 3. The genetic and environmental variances and covariances

Table 6. Comparison of Nested Models for Bivariate Genetic Analysis of Heavy Drinking and Alcohol Dependence

Model	Compared with		$-2LL$	$\Delta\chi^2$	$\Delta\,df$	p Value
1	—	Full bivariate ACE model with sex-specific parameter estimates (A, C, E) and male-specific genetic effects (m)	11787.79	—	—	—
2	1	Drop male-specific genetic effects	11789.81	2.024	3	0.567
3	2	Constrain male and female parameter estimates to be equal	11801.27	13.48	12	0.335
4	3	Drop C (AE model)	11802.02	0.75	3	0.861
5	3	Drop A (CE model)	11884.98	83.71	3	$<10^{-6}$
6	4	Drop common A on alcohol dependence	11936.97	135.70	1	$<10^{-6}$
7	4	Drop unique A effect on alcohol dependence	11842.99	41.72	1	$<10^{-6}$

At each step, the effect of elimination of a potential cause of variation was tested by estimating the log-likelihood ($-2LL$) and testing the change by using the χ^2 test with the appropriate number of degrees of freedom ($\Delta\,df$).
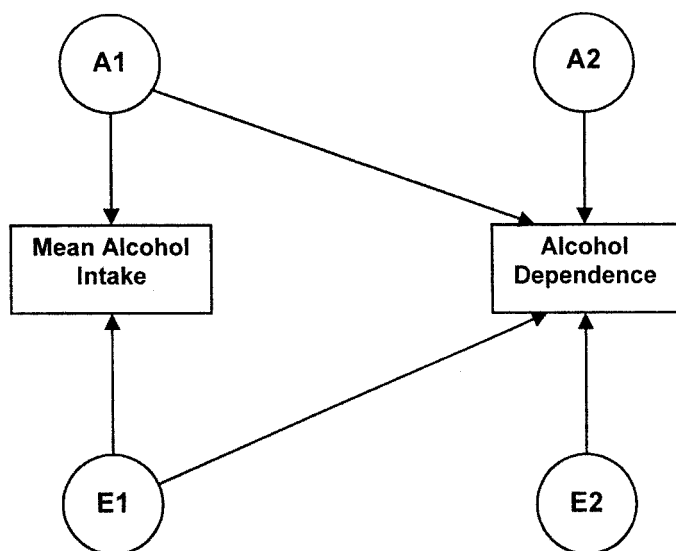
Fig. 3. Model of genetic and environmental sources of covariation between liability to high alcohol intake (top quartile of average of six measures from three occasions) and DSM-IIIR diagnosis of lifetime alcohol dependence. A1 and A2, and E1 and E2, are independent additive genetic factors, and non-shared environmental factors, respectively. A1 and E1 potentially affect both consumption and dependence, while A2 and E2 potentially affect only liability to alcohol dependence.

DISCUSSION

The main aims of this article were to define the genetic and environmental factors that influence alcohol intake, their continuing effects across time, and their relation to alcohol dependence risk. Overall, we found that genetic effects continue to affect consumption across time but that nonshared environmental effects are essentially occasion specific. Similarly, some genes affect both use and dependence, whereas others affect only one, but environmental influences show little overlap between these domains.

Total Alcohol Consumption

Average alcohol consumption reported by the participants was very similar to the average per-capita consumption in Australia in 1980, but it decreased by approximately half over the 13-year period covered by these studies. This is probably a result of aging rather than a secular trend, because per-capita alcohol consumption in Australia decreased only by approximately a quarter in this period. As expected, men and younger subjects reported substantially greater alcohol intake than women and older subjects, particularly for beer (Fig. 1).

It is important to consider how much these subjects are representative of the Australian population and whether any deviations would affect the conclusions about constancy or variation of alcohol intake across time, about the relationship between alcohol intake and alcohol dependence, or about genetic and environmental causes of variation. The Australian Twin Registry, which was the original resource for recruitment of subjects, is a volunteer panel, and the subjects were not a random sample of the population in the epidemiological sense. Either the original cohort or the approximately 75% who proceeded to the 1993 phase might not be representative. However, a number of comparisons with the Australian Bureau of Statistics data have been made, and we have found that deviations with respect to education, socioeconomic status, and prevalence of psychiatric symptoms are slight (Baker et al., 1996; Heath et al., 1997; Jardine and Martin, 1984). The prevalence of lifetime alcohol dependence was high but comparable to that observed in other studies using the DSM-III-R or DSM-IV criteria. Even if some differences from the overall population do exist, the aim of this study was to assess genetic and nongenetic sources of covariation be-

of the likelihoods of high alcohol intake and of alcohol dependence are shown in Table 7.

It will be seen that alcohol dependence is affected partly by genes that also affect alcohol consumption and partly by genes that are unique to dependence. The genetic correlation between likelihood of heavy drinking and likelihood of alcohol dependence was 0.63, and the 95% confidence interval (0.53–0.72) excluded both 0 and 1. The nonshared environmental correlation was 0.27 (95% confidence interval, 0.10–0.43), which reflects the comparatively low proportion of environmental liability that was common to both dependence and high alcohol use (Table 7).

In this analysis, the heritability of the mean alcohol intake was just over 70%, whereas it was between 40 and 54% for the six individual measures of intake. This difference is due to the reduction in measurement error, which forms part of the nonshared environmental (E) component of variance, which occurs when the mean alcohol intake across measures and occasions is used.

Table 7. Final Bivariate Model of Genetic and Environmental Causes of Variation and Covariation in Likelihood of Heavy Drinking (Top Quartile of Sample) and Alcohol Dependence

Variable	A1	A2	E1	E2
Heavy drinking	0.72 (0.67–0.76)		0.28 (0.24–0.33)	
Alcohol dependence	0.42 (0.35–0.48)	0.61 (0.51–0.70)	0.09 (0.03–0.15)	0.39 (0.30–0.48)
Genetic and environmental correlations	r_G = 0.63 (0.53–0.72)		r_E = 0.27 (0.10–0.43)	

A1 and E1 represent paths from the first genetic and nonshared-environmental factors to likelihood of heavy drinking and alcohol dependence, whereas A2 and E2 represent paths from the second genetic and nonshared-environmental factors to alcohol dependence. Note that common estimates are used for both men and women. The table shows the genetic and environmental covariance matrices and the genetic and environmental correlations (r_G and r_E) between likelihood of heavy drinking and alcohol dependence: 95% confidence intervals are shown in parentheses.

tween alcohol intake at different times and between alcohol intake and alcohol dependence, and these aims would not be affected by the deviations that are likely to be present.

Our results are based, like most studies of alcohol use, on self-reports by the participants. The repeatability, validity, and bias of methods for estimating alcohol intake from questionnaires have been considered in many articles. This topic was reviewed by Feunekes et al. (1999), who examined data on quantity × frequency, extended quantity × frequency, retrospective and prospective diary, and 24-hr recall methods. The test-retest reliability of each method was approximately 0.8, whereas comparison between methods gave correlations in the 0.6 to 0.7 range. They concluded that both the quantity × frequency and the retrospective diary methods were able to provide a reliable ranking of subjects but that questions remained about their ability to estimate the true amount of alcohol consumed, and they commented that "for the purposes of epidemiologic research, we need particularly a valid ranking. . .to advise the population we need in addition a valid estimation of level." For our analysis of these twin data, which concentrated on causes of variation, both the quantity × frequency and retrospective diary methods that we used are suitable.

For our subjects, estimates of repeatability of total alcohol intake were in the range 0.74 to 0.85 within occasions (by the two methods quantity × frequency and drinks in the past week) and 0.54 to 0.73 across occasions. The between-occasion correlations were essentially the same whether comparisons were made within the same method or across methods (Table 2), which increases our confidence in the validity of both approaches for estimation of total alcohol intake. The meta-analysis of Feunekes et al. showed test-retest correlations between 0.75 and 0.99 for the quantity × frequency method, but there was no information on the length of time between measurements. In our results, repeatability by either method was higher over 4 years (0.6 to 0.7 for 1989–1993) than over 9 years (0.5 to 0.6 for 1980–1989).

The finding that the repeatability of intake estimates across time was poorer in younger people (aged 30 or younger at the time of the first study) and in those who became or had been alcohol dependent is not surprising. Correlations between results from different occasions were greater when the elapsed time was less, as, for example, between 1989 and 1993, but the subjects were older and possibly more stable in their drinking habits for that reason. In addition, there was evidence for a genetic factor that affects alcohol intake in the second or third studies but not the first, which is again probably age related. Further investigation of age-related (rather than study-based) changes in the balance between shared environmental and additive genetic sources of variation in alcohol intake is needed, incorporating data on the age of onset of alcohol dependence for those participants who meet the lifetime dependence criteria.

Most of the genetic variation in alcohol intake could be ascribed to two factors, A1 and A3 in Table 3, that affected alcohol intake in all studies or in the second and third

studies, respectively. The small contribution of shared environmental sources of variation was also due to a single factor that affected the three times studied. In contrast, the nonshared environmental factors either were specific to one of the intake measures or affected only one occasion. This is consistent with the existence of measurement error, poor recall, and short-term fluctuation in alcohol consumption. It also implies that very little of the repeatability of alcohol intake measures over time is due to nongenetic factors, and we may infer that variation in lifetime alcohol intake within this community is almost entirely due to genetic differences.

Alcohol Use and Dependence

Lifetime history of DSM-III-R alcohol dependence was clearly related to alcohol intake, although the direction of causation between these two phenomena is not established and is likely to be complex. Reported total alcohol intake, at all times and by both methods, was strongly associated with the risk of lifetime alcohol dependence in both men and women. As can be seen in Fig. 2, the probability of dependence increased monotonically with increasing alcohol use, and, in particular, we did not find a U-shaped curve in which alcohol-dependent subjects clustered at the high intake or no-intake ends of the spectrum. On the contrary, a substantial number of people who had met the diagnostic criteria for alcohol dependence at some stage in their lives were apparently drinking alcohol regularly and staying within the accepted safe consumption limits. This finding from a population-based sample contrasts with what might be anticipated for a sample recruited through treatment facilities and emphasizes the need for both kinds of studies of the genetic epidemiology of alcohol use disorders.

Both total alcohol intake and the likelihood of alcohol dependence are subject to genetic influences. We have previously shown that the heritability of likelihood of alcohol dependence in this cohort is 64% (95% confidence interval, 32–73%) for both men and women (Heath et al., 1997). In this analysis, we found that approximately a quarter of the variation in likelihood of alcohol dependence was due to genes that also affect alcohol intake and a third to genes that have no influence on intake but are unique to dependence. Nonshared environmental factors account for some 40% of the likelihood of alcohol dependence, and this is consistent with the finding that significant numbers of genetically identical monozygotic pairs are discordant for this condition; these factors also account for approximately 30% of variation in the mean alcohol intake. However, the nongenetic effects were essentially unique to either intake or dependence (Table 7).

The full model, which included shared environmental effects and sex-specific genetic effects, was examined to assess whether the overlap between genetic influences on heavy drinking and on alcohol dependence differed between women and men or whether different genes affected

heavy drinking in women and men. There was no significant deterioration in the goodness of fit when such differences were excluded, and the confidence intervals for both the shared environmental and the sex-specific genetic effects were wide and included 0. At least with the sample size available to us and for people born mainly in the 4th, 5th, and 6th decades of the 20th century and living in Australia, the simple bivariate model containing only genetic and nonshared environmental effects best explains the observed patterns of alcohol intake and dependence.

Analysis of twin data, without genotypes, cannot establish which genes or what type of genes are relevant to consumption, dependence, or both. Clearly, efforts toward greater refinement of phenotype and distinction between associated phenotypes are important for gene-hunting studies, and it will be necessary to test which aspects of alcohol-related behavior are affected by candidate polymorphisms or candidate loci revealed by linkage studies. Better definition of phenotype is expected to increase power and lead to a more appropriate interpretation of results.

It is tempting to speculate that some genes affect the transition from comparatively heavy but nondependent alcohol use to alcohol dependence; these would be the genes contributing to the unique genetic effects on dependence in this analysis. Such genes may also affect other types of drug dependence, smoking, or aspects of personality such as conduct disorder, which are known to show associations with alcohol dependence (Hettema et al., 1999; Slutske et al., 1998; Swan et al., 1997), but further work will be needed to clarify this point.

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