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Correlations of Alcohol Consumption with Related Covariates and Heritability Estimates in Older Adult Males Over a 14- to 18-Year Period: The NHLBI Twin Study

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Consistent maximum-likelihood heritability estimates of consumption of alcoholic beverages were observed at three separate times during a 14- to 18-year period in adult twin males initially aged 42–56 years in 1969–1973. Log transformation of the average number of drinks/week of the returnees to all three examinations was examined relative to potential covariates representing both antecedents of drinking alcohol and consequences of alcohol consumption. Significant relationships were noted for 38 of the covariates at one or more of the separate examinations, including positive correlations with smoking, coffee consumption, high-density lipoprotein cholesterol, mean corpuscular volume, systolic blood pressure, uric acid and behavioral measures, and negative correlations with blood urea nitrogen, red blood cell count, tea consumption, and tricep skinfolds. Analysis of the average alcohol consumption adjusted for nine independent covariates selected from multiple stepwise regression resulted in a modest decline in maximum-likelihood heritability estimates compared with unadjusted data, but little difference from heritability estimates obtained when abstainers from alcohol (no alcoholic beverages consumed at all three examinations) were excluded. The most striking effect of omitting abstainers from alcohol was the decline in the intraclass correlations in dizygotic twins. Bivariate analyses of alcohol and individual covariates revealed the phenotypic correlation between alcohol consumption and a measure of hostility was primarily environmental, that for high-density lipoprotein, smoking and coffee drinking with alcohol was primarily genetic, and the phenotypic correlation between alcohol consumption and mean corpuscular volume had both significant genetic and environmental correlations. Comparison with other twin studies in males suggested relatively consistent estimates of genetic variance, despite wide variation in subject characteristics, study design and methods, and measure of alcohol consumption.

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IT IS WELL-established that there are familial influences in the propensity toward alcoholism.[1–10] The evidence can be summarized into three main categories: (1) family or kinship studies in which the risk of alcoholism is increased over expected; (2) adoption or half-sibling comparisons in which the rate of alcoholism in siblings reared by nonalcoholic versus alcoholic parents is compared; and (3) increased concordance of alcoholism in identical or monozygous (MZ) twins compared with fraternal or dizygotic (DZ) twins.

The importance of genetic influences on the amount of alcohol consumed in the general population has primarily been examined utilizing comparisons of MZ and DZ twins. Kaprio et al.[11] recently reported consistent heritability estimates over a 6-year period for the amount and frequency of alcohol consumed in both male and female twins initially aged 24–43, paralleling studies of stable patterns of consumption in adult men and women.[12,13] The present work examined heritability estimates of alcohol consumption in adult male twins as assessed by questionnaire three separate times over a 14- to 18-year period. It was hypothesized that the most accurate assessment of drinking level over this time period would be the average reported consumption of the three questionnaires. In addition, the availability of a large number of other variables allowed for an estimation of the consistency of the association of covariates with reported alcohol drinking at each exam. Heritability estimates were performed before and after adjustment for significant covariates and bivariate analyses examined phenotypic correlation of covariates with average alcohol consumption.

METHODS

The National Heart, Lung and Blood Institute (NHLBI) twin study is a collaborative, longitudinal study of the genetics of cardiovascular risk factors in White World War II and Korean War veteran male twin-pairs born between 1917 and 1927. The twins were members of the National Academy of Sciences/National Research Council (NAS/NRC) twin registry.[14] A total of 514 twin-pairs volunteered and lived within 200 miles of 1 of the 5 examining centers in Framingham, MA; Indianapolis, IN;

and Los Angeles, San Francisco, and Davis, CA. The twins were first examined between 1969 and 1973.[15] At the second examination, in 1981–1982, 792 members of the cohort, including 363 complete twin-pairs, were seen.[16] The latest examination of the twins was in 1986–1987, where 622 individuals, including 268 complete pairs, participated.[17]

Consumption of alcoholic beverages, including beer, wine, and spirits, was assessed at all three examinations during an interview with a physician. At exam 1, participants were asked for the number of bottles, cans, or glasses of beer/week; number of glasses of wine/week; and the number of cocktails, highballs, or straight drinks/week. Their responses were categorical to a question of how often do you drink. The conversions are given below in parentheses. Responses indicating consumption of seldom or less than once/week were recorded as 0 drinks/week.

1 or 2 times/week (1.5)
3–6 times/week (4.5)
1 or 2 times/day (10.5)
3 or 4 times/day (24.5)
>4 times/day (35)

At exams 2 and 3, the questions were open-ended (coded to a maximum of 98). A 0 code indicated persons who never drank, and a 1 was coded for drinking 1 or fewer drinks/week. For this study, the total alcohol consumption was the sum of the drinks/week of beer, wine, and spirits. Table 1 gives the mean number of drinks/week for all individuals at each of the examinations and the average consumption for individuals who were seen at all three examinations (returnees). An abstainer in the returnee group was defined as one who reported no alcohol consumption at all three examinations. The percentage of abstainers at exam 1 was higher because the categories of seldom or less than once/week were converted to 0. This contributed to a lower mean consumption for exam 1, in addition to the truncation of higher amounts consumed into a single category. Mean ages for the returnees was virtually identical to the total cohort seen at each examination.

Because the distributions of total alcohol consumption were skewed, log (base e) transformation was used to reduce skewness. Pearson correlation coefficients of the log-transformed alcohol consumption at each exam were strongly positively correlated (Table 1), and intraclass correlation coefficients were also very consistent in both MZ and DZ from exam to exam (Table 2). These trends were particularly apparent in the returnees. For this study, we principally focus on the log-transformed mean alcohol consumption of the returnees to best reflect the actual drinking level over the 14- to 18-year period and to reduce error variance in reported level of drinking at each of the single examinations.

Univariate twin analyses were conducted with LISREL using maximum-likelihood estimation,[18,19] or TWINAN90,[20] which performs both maximum-likelihood estimation of parameters, including standard errors of the heritability estimates, and analysis of variance-based twin methods. Univariate analyses conducted on alcohol consumption compared an unshared environmental model (E) versus a model with additive genetic effects and unshared environmental effects (A+E). Additive genetic effects (A) combine independently over different alleles at the same locus and over different loci. As a result, the expected additive genetic variance of DZ pairs is half of the additive variance shared by MZ twins. The A+E model assumes that all phenotypic resemblance is due to additive genetic effects. The E model was also compared with a purely environmental model, assuming only shared (common) environmental effects and unshared environmental effects (C+E). Common environmental effects (C) are shared by both twins and influence both twins in the same way. The A+E and C+E models were further compared with a model that fitted all three effects (A+C+E). If the estimate of common environmental variance in the A+C+E model had a negative coefficient, then estimates from a fit of a model, including A+D+E, was used instead of the A+C+E model. Dominant effects (D) arise from gene interactions, either between alleles at the same locus (dominance) or from interaction of genes at different loci (epistasis).

The relationship of other variables, both antecedents of alcohol consumption (e.g., smoking, years of education) and potential consequences of alcohol consumption [e.g., mean corpuscular volume (MCV), plasma high-density lipoprotein (HDL) cholesterol], were compared with reported alcohol consumed at each examination and for the average consumption of the returnees over the 14- to 18-year period. Many of the covariates were known to be associated with alcohol consumption; others were examined to see if there was a relationship to alcohol drinking. Some variables were available at all three examinations, others were recorded at two of the visits, and still others were only determined at a single examination. A tabulation of the covariates by exam is given in the Appendix.

The effects of other variables on average alcohol consumption were examined by two different approaches. First, using average alcohol consumption over all three exams in the returnees as the dependent variable, backward stepwise multiple regression analyses were performed with covariates at exam 3. Nine independent covariates ($p < 0.05$) were used to adjust drinking levels for these related variables. Because of suggestions that the genetic influence on the decision to abstain from alcohol use may be different from genetic influences on the level of drinking,[21–23] a twin analysis of average alcohol consumption was repeated, eliminating individuals who abstained from alcohol consumption over the 14–18 years. Data were further stratified based on how often the twins got together. Responses of both twins on a scale of 1 = daily to 5 = less than once/year were averaged for the first and last exams. If the pair mean was 2 or less (equal to or greater than 1–4 times/week), the pairs were classed as getting together most. If the pair mean was 4 or more (occasionally but less than 1–3 times/month), the pair was categorized as getting together least.

The second approach examined the nine independent covariates and highly correlated variables (e.g., for HDL we also compared the HDL_2 subfraction and apoprotein A-I with alcohol consumption), using bivariate twin analyses with LISREL. Bivariate genetic analyses seek to explain the phenotypic covariance between two variables as a function of their environmental and genetic covariances. A positive phenotypic correlation between the two variables, for instance, may be due to positively correlated genetic effects, positively correlated environmental effects, or a combination of the two. If there are correlated genetic effects, partialing out the significant covariates via the regression approach may also reduce the estimate of genetic influences on alcohol consumption. Only genetically informative samples with measures of both alcohol consumption and the covariate can empirically establish the nature of the relationship.

Pearson correlation and regression analyses were performed using the SAS statistical package (SAS Institute, Cary, NC).

RESULTS

Table 2 displays the intraclass correlations of the log-transformed alcohol consumption data for each of the

Table 1. Alcohol Consumption (Drinks/Week) for the Total Cohort at Each Examination and Returnees to All Examinations

Exam	No. individuals	Age (SD)	Alcohol consumption		Pearson correlation*		
			Mean (SD)	Abstainers (%)	Ex1	Ex2	Ex3
1	910	48.0 (3.1)	6.6 (8.5)	312 (34.3)	—		
2	792	58.2 (3.0)	10.3 (13.6)	178 (22.5)	0.62	—	
3	622	63.6 (3.0)	8.4 (14.8)	172 (27.7)	0.54	0.72	—
Average (returnees)	508		8.3 (9.8)	73 (14.2)	0.82	0.89	0.83

* Log-transformed consumption; all $p < 0.0001$. Ex, exam.

Table 2. Intraclass Correlations of Log Drinks/Week in MZ and DZ Pairs at Each Examination for All Cases, Returnees to All Exams, and the Average Consumption in Returnees With or Without Abstainers From Alcohol and Before and After Adjustment for Covariates

Group/time	MZ pairs		DZ pairs		
	n	*r*	*n*	*r*	MLE h^2 (SE)*
All pairs					
Exam 1	235	0.49	220	0.31	0.49 (0.04)
Exam 2	180	0.44	183	0.34	0.48 (0.05)
Exam 3	137	0.41	130	0.19	0.42 (0.06)
Returnees					
Exam 1	116	0.44	103	0.27	0.44 (0.07)
Exam 2	127	0.46	122	0.25	0.47 (0.06)
Exam 3	126	0.43	122	0.24	0.46 (0.06)
Average consumption of returnees					
All returnees	127	0.55	122	0.29	0.56 (0.06)
No abstainers	105	0.50	90	0.13	0.47 (0.07)
Covariate adjusted					
All returnees	97	0.46	95	0.26	0.45 (0.07)
No abstainers	83	0.50	75	0.13	0.44 (0.08)

* MLE, maximum-likelihood heritability estimate based on the A+E model, all $p < 0.001$.

three examinations and maximum-likelihood heritability estimates. The top third of Table 2 includes all cases that participated at that examination. The middle third presents data for only those twin-pairs who returned to all three examinations, and the bottom third includes an analysis of the average consumption of returnees across all three of the examinations. The largest difference between the MZ and DZ intraclass correlation coefficients and largest maximum-likelihood estimate of heritability was obtained using the average drinking levels across the 14- to 18-year period.

The A+E model provided an excellent fit to the data in all analyses in Table 2, although in the case of exam 2 for all pairs, the difference in fit between the A+E and C+E models was not significant. With this one exception, all A+E models were not significantly improved, with the addition of shared common environmental effects (A+C+E), and all A+C+E models fit significantly better or approached significance (exam 1 returnees) than did the purely environmental (C+E) model. For average consumption, the A+E model χ^2 was 1.39 (4 degrees of freedom); $p = 0.85$, and the purely environmental model (C+E) provided a significantly poorer fit to the data ($\chi^2_4 = 11.41$; $p = 0.02$). The heritability estimate under the best-fitting (A+E) model was 0.56 for the average consumption and for individual exams ranged from 0.42 to 0.49.

For the 910 subjects with alcohol consumption data at exam 1, the 792 individuals at exam 2, and the 622 subjects at exam 3, the relationship of drinking level with potential covariates were examined using Pearson correlation coefficients. Table 3 displays covariates with significant ($p < 0.05$) correlations at one or more examinations with log-transformed average consumption in the 508 returnees. The covariate correlations in Table 3 were consistent with the correlations observed with alcohol consumption at each individual examination (not shown).

Table 3. Covariates With at Least One Significant Pearson Correlation at Any Exam With Log Average Drinks/Week in Subjects Who Participated at All Three Examinations (Returnees)†

Variable	Exam 1	Exam 2	Exam 3
Anthropometrics			
Triceps skinfold right (mm)	NA	−0.076	−0.112*
Triceps skinfold left (mm)	NA	−0.053	−0.135**
Abdominal/hip circumference	NA	NA	0.107*
Cholesterol			
HDL (mg/dl)‡	0.140**	0.175***	0.184***
HDL_2 (mg/dl)	NA	NA	0.140**
HDL_3 (mg/dl)	NA	NA	0.168***
Apoprotein A-I (mg/dl)	NA	NA	0.202***
Hematology			
RBC count (1,000,000/mm^3)	NA	−0.154**	−0.160***
MCV (μm^3)‡	NA	0.407***	0.270***
MCH (pg)	NA	0.314***	0.248***
MCHC (%)	NA	−0.135*	−0.004
Habits			
Smoking cigarettes/day‡	0.133**	0.190***	0.215***
Packyear smoking history	NA	0.293***	0.288***
Years smoker at home‡	NA	0.339***	0.271***
Coffee cups/day	0.172***	0.097*	0.134**
Tea cups/day‡	−0.091*	−0.078	−0.091*
Caffeine (tea + coffee)	0.124**	0.056	0.089*
Glucose/diet			
Glucose (mg/dl)	0.054	0.133**	0.035
Glucose-SMA (mg/dl)	0.008	0.119**	0.117*
C-peptide (mM/liter)	NA	NA	0.110*
Carbohydrates/day (g)	−0.098*	NA	NA
Complex carbohydrates/day	−0.100*	NA	NA
Physiologic Measures			
FEV_1	NA	NA	−0.152***
Systolic pressure (mmHg)‡	0.120**	0.145**	0.120**
Behavioral			
Cook and Medley hostility‡	NA	NA	0.179***
Paranoia subscale	NA	NA	0.130**
Cynicism subscale	NA	NA	0.171***
Adjective checklist type A	NA	0.125**	0.090*
ACL type A brother	NA	NA	0.113*
Electrolytes/other SMA			
Urea nitrogen (mg/dl)‡	−0.148***	−0.208***	−0.193***
Uric acid (mg/dl)‡	0.146**	0.167***	0.147**
Calcium (mg/dl)	−0.009	0.096*	−0.026
Globulin (g/dl)	0.048	−0.009	−0.100*
Albumin/globulin	NA	NA	0.107*
Alkaline phosphatase (IU/liter)	0.031	−0.018	−0.099*
SGOT (IU/liter)	0.106*	0.072	0.040
LDH (IU/liter)	0.010	−0.009	−0.122*
T-4 (μg/dl)	NA	−0.112*	NA

RBC, red blood cell; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; SMA, standard medical chemistry; FEV_1, forced expiratory volume; ACL, Adjective checklist; LDH, lactate dehydrogenase.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

† NA, no available data.

‡ Exam 3 variable in multiple regression of average consumption ($R^2 = 0.257$).

Multiple regression procedures were performed using the variables listed in Table 3 with the following conditions: (1) the variable was measured at exam 3; (2) the variable was significantly correlated at exam 3 with average alcohol consumption; and (3) correlations of the variable, if measured at exams 1 and/or 2, were consistent with the correlation observed at exam 3. Also included were age and years of education. Nine covariates consistently were chosen ($p < 0.05$) from multiple regression procedures and are also noted in Table 3. Nine covariates explained 25.7% of the variance in alcohol consumption. Covariate-adjusted residuals of the log-transformed average alcohol

consumption did not deviate significantly from a normal distribution.

Selection of covariates was also undertaken, omitting individuals who did not drink alcohol at all over the 14- to 18-year period between exams 1 and 3. Omitting abstainers, the exact same covariates were retained in the stepwise procedure, with the exception that the highly correlated apoprotein A-I level was substituted for HDL cholesterol. The results provide validation for the nine covariates used to adjust the average drinking level of the returnees.

The bottom part of Table 2 compares intraclass correlations and maximum-likelihood heritability estimates for log-transformed average alcohol consumption with and without covariate adjustment and similar analyses omitting study long abstainers. The correlation coefficient decreased in DZ twins when abstainers from alcohol were excluded. Maximum-likelihood heritability estimates were somewhat lower after covariate adjustment or omitting nondrinking individuals compared with unadjusted consumption levels. Comparing pairs on how often the twins got together revealed that intraclass correlations were higher in MZ than DZ pairs in all strata. For example, the difference in MZ and DZ intraclass correlations was 0.47 (r_{MZ} = 0.74, r_{DZ} = 0.27) for covariate-adjusted drinks/week in the 22 MZ and 14 DZ pairs who got together more than 1–4 times/week. The difference was 0.05 (r_{MZ} = 0.44, r_{DZ} = 0.39) in 21 MZ and 39 DZ pairs spending the least time together (<1–3 times/week), and 0.15 (r_{MZ} = 0.31, r_{DZ} = 0.16) in 53 MZ and 42 DZ pairs with intermediate contact. The sample sizes were relatively small, and both A+E and C+E models provided adequate fit to the data. For pairs getting together most, there was statistically significant improvement in fit with the addition of A to the C+E model, but no significant improvement when C was added to the A+E model. For twin-pairs who got together least, the magnitude of the improvement was greater but not statistically significant when C was added to the A+E model than when A was added to the C+E model.

Table 4 shows the results of the bivariate genetic analysis of average consumption with each of the significant independent covariates identified in the multiple regression analysis and some additional variables highly correlated with these covariates. Each analysis estimated an environmental (r_e) and an additive genetic (r_g) correlation between the two variables. Table 4 also lists the heritability of the covariate as estimated in the bivariate analysis. In general, bivariate analyses provided an excellent fit to the data. The analysis conducted on MCV provided a marginal fit. The analysis of HDL_2 provided a poor fit, which could be traced to the already reported higher HDL_2 variances for DZ pairs.[24] Similarly, poor fit in the analysis of tea consumption was due to a violation of the assumption of equal variances for the randomly assigned first and second twins. This most likely represented a chance effect, whereby the few individuals with higher levels of tea drinking happened to be the first cotwin of a pair to be entered. Most of the covariates had a significant genetic correlation with consumption, indicating significantly shared genetic variance. Only MCV, lifetime smoking history (pack years), and the Cook and Medley hostility scale shared significant environmental influences with alcohol consumption. The environmental influences on the other covariates, then, were relatively independent of the environmental influences on consumption. Only for the Cook and Medley hostility scale was the phenotypic covariance entirely explained by environmental factors.

A correlation analysis performed using the difference in average drinks/week between cotwins with cotwin differences of the covariates used in the bivariate analyses (Table 5) reinforced some of the conclusions from the bivariate analysis. The MCV and Cook and Medley hostility scale were most strongly related to intrapair differences across both zygosities, reflecting shared environmental influences with consumption. The variables showing significant shared genetic variance in the bivariate analysis had more pronounced intrapair relationships, with intrapair alcohol consumption in DZ pairs. Of the nine variables identified in the regression analysis, only systolic blood pressure did not show any correlation with intrapair differences that was at least approaching statistical significance.

DISCUSSION

Our study followed the consumption of alcohol in a group of older adult males over a 14- to 18-year period, examined the relationship of drinking level with a large number of covariates across three separate examinations, and examined these relationships including or excluding abstainers from alcohol in the study period. We found relatively consistent heritability estimates across exams; the consistency was more striking considering that exam 1 data was categorical and resulted in an excess of "abstainers," a decrease in the magnitude of the estimated consumption of the heaviest drinkers, and consequently a mean consumption lower than subsequent examinations (Table 1). Log-transformation was necessary to reduce the effect of highly disparate pairs in amount of alcohol consumed. Using the average consumption of returnees over the 14- to 18-year period between exams 1 and 3, in an effort to reduce the effect of reporting errors in drinking level at a single point in time, led to the highest MZ intraclass correlation and heritability estimates.

We utilized two different approaches to examine the relationship of covariates related to alcohol consumption. First, the effects of significant covariates were removed via multiple regression, with subsequent genetic analysis of the residuals. Second, bivariate genetic analyses were used because of concern that the adjustment for covariates may be removing positively correlated genetic effects between the covariate and the level of alcohol consumption. Our

Table 4. Bivariate Twin Analyses for Average Alcohol Consumption in Returnees for Significant Independent Covariates and Related Variables

Covariate	No. MZ	No. DZ	Heritabilities†		Correlations*		χ^2 (14 *df*)
			Alcohol	Covariate	*r*(e)	*r*(g)	
Smoking							
Packyears	126	120	0.56	0.39	0.16*	0.45**	12.96; $p = 0.530$
Cigarettes/day	123	121	0.58	0.39	0.11	0.37**	18.35; $p = 0.191$
Years smoker at home	127	122	0.57	0.20	0.07	0.63**	6.24; $p = 0.960$
Cholesterol							
ApoA-I	104	102	0.57	0.65	0.12	0.35**	18.48; $p = 0.186$
HDL_2	118	113	0.55	0.77	0.10	0.27**	40.49; $p = 0.000$
HDL	118	113	0.55	0.68	0.10	0.30**	16.86; $p = 0.264$
MCV	119	113	0.57	0.69	0.27**	0.34**	25.89; $p = 0.027$
C&M hostility	122	120	0.56	0.30	0.27**	0.00	9.80; $p = 0.777$
Uric acid	123	117	0.56	0.46	0.11	0.17	10.15; $p = 0.751$
BUN	123	117	0.56	0.54	−0.13	−0.19	10.97; $p = 0.688$
Coffee	127	122	0.57	0.27	0.08	0.36**	11.50; $p = 0.646$
Tea	126	120	0.56	0.13	−0.07	−0.19	33.40; $p = 0.003$
Systolic b.p.	123	119	0.56	0.59	0.07	0.12	5.07; $p = 0.985$

ApoA-I, apoprotein A-I; C&M, Cook and Medley; BUN, blood urea nitrogen; b.p., blood pressure.
* $p < 0.05$; ** $p < 0.01$.
† Small fluctuations in heritability of alcohol are due to small fluctuations in sample composition of each covariate; heritability of the covariates are all $p < 0.01$, except for tea consumption ($0.05 < p < 0.10$).

Table 5. Pearson Correlations of Cotwin Differences of Significant Covariates With Cotwin Difference in Average Alcohol Consumption

Variable	Full sample†		MZ twins		DZ twins	
	r	*p*	*r*	*p*	*r*	*p*
Smoking						
Packyears	0.23	***	0.13		0.32	***
Cigarettes/day	0.18	**	0.08		0.25	**
Years smoker at home	0.14	*	0.10		0.18	
Cholesterol						
Apoprotein A-I	0.22	**	0.10		0.28	**
HDL_2	0.17	**	0.09		0.21	*
HDL	0.16	*	0.10		0.19	*
MCV	0.32	***	0.24	**	0.38	***
C&M hostility	0.22	***	0.27	**	0.19	*
Uric acid	0.14	*	0.11		0.14	
BUN	−0.15	*	−0.14		−0.14	
Coffee	0.14	*	0.03		0.22	*
Tea	−0.11		−0.03		−0.17	
Systolic b.p.	0.06		0.08		0.05	

C&M, Cook and Medley; BUN, blood urea nitrogen; b.p., blood pressure.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.
† Sample size maximums: full (268), MZ (138), DZ (130).

approach provided an opportunity for cross-validation of the bivariate modeling and regression methods.

The nine covariates chosen to adjust the average alcohol consumed/week were known to reflect the consequences of drinking, as well as variables believed to influence the propensity to drink. There was greater alcohol consumption with smoking[25–27] and coffee drinking,[25,28,29] which was inversely related to tea consumption. Heavier drinkers have been reported to have a significant increases in behavioral measures, such as anger[30] and type A trait,[26] and in our study alcohol consumption was positively related to the Cook and Medley hostility scale.[31] Effects of drinking alcohol were increased MCV,[32,33] increased blood pressure,[25,27,28,34–37] increased uric acid,[26–28,32] decreased blood urea nitrogen,[33,38] and increased HDL cholesterol.[25,39–42]

Although all of the covariates in the bivariate analysis had significant phenotypic correlations with alcohol consumption, there was substantial heterogeneity in the genetic and environmental contributions to those correlations. Such results can help direct research. For instance, researchers interested in the alcoholism–hostility link cannot afford to ignore environmental effects, which may be associated with both traits; researchers interested in the smoking–alcohol or coffee–alcohol link may be misled if they ignore genetic factors contributing to the association of these variables. MCV showed a mixed pattern consistent with a model in which the drinking phenotype, which is approximately half-genetic and half-environmental, is directly driving MCV. Although causal direction cannot be established with the current analyses, it is thought that alcohol has a direct effect on red cell development.[32] Adjustment for the covariates via regression did lead to lower heritability estimates than with the bivariate analyses (0.45 vs. 0.55–0.58).

Repeating the analyses and eliminating abstainers, we observed that maximum-likelihood heritability estimates changed little with covariate adjustment (0.45–0.44); these were similar to estimates obtained when omitting abstainers with bivariate modeling approaches (0.46–0.49). Therefore, a moderate amount of the reduction in heritability estimates with covariate-adjusted residuals may relate to alcohol effects on covariates in drinkers versus nondrinkers. However, a stepwise regression using only drinkers led to the selection of the same set of significant covariates as the total sample. About the only difference noticed in bivariate model fitting after omitting abstainers was that the genetic correlation between average alcohol consumption and years living with a smoker decreased substantially. Abstainers were probably more likely to come from households with no smokers.

Table 6 summarizes our results with comparable twin studies in the literature. Regardless of the measure of alcohol consumption used, and the varying types of adjustments of the data, the intraclass correlation in MZ

Table 6. Twin Studies on Amount of Alcohol Consumption in Males

No.*	Measure	Adjustments	MZ		DZ	
			n	*r*	*n*	*r*
1	Factor score	Omit abstainers	172	0.38	557	0.11
2	g/month	None	1537	0.51	3507	0.22
3	Factor score	Age-adjusted	1537	0.54	3507	0.28
		age 18–29	731	0.58	1628	0.34
		age 30–39	351	0.53	812	0.20
		age 40–49	191	0.36	563	0.17
		age 50–59	137	0.44	300	0.14
		age 60+	127	0.23	204	0.21
4	g/month	Omit concordant abstainer pairs	841	0.37	1885	0.19
5	cl./week	Age-adjusted	79	0.79	50	0.46
6	Drinks/week	Log-transformed	NR	0.55	NR	0.50
7	oz/month	None	2390	0.40	2571	0.24
		Log-transformed		0.51		0.33
		Adjusted for education, coffee, age, smoking, rank		0.32		0.19
8	g/month	Omit abstainers	1785	0.44	1870	0.23
		Subgroup age 42–52	671	0.45	550	0.27
		Subgroup 15 yr later		0.51		0.29
9	Drinks/week	None	163	0.46	166	0.17
		By zygosity adjusted for smoking, coffee, anger, type A, contact frequency		0.39		0.17
10	Factor score	Omit abstainers, age stratified (over/under 30)	567	0.58	352	0.43
11	Drinks/week	Average over 14–18 years, log-transformed	127	0.55	122	0.29
		Covariate (9) adjusted	97	0.46	90	0.26
		Omit abstainers	105	0.50	95	0.13
		No abstainers, adjusted	83	0.50	75	0.13

* 1—Partanen et al. 1966, (Finland)[54] ages 29–38; 2—Kaprio et al. 1978 (Finland)[44] ages 18–75+; 3—Kaprio et al. 1981 (Finland)[45]; 4—Kaprio et al. 1987 (Finland)[53] ages 29–49; 5—Clifford et al. 1981 (London)[43]; 6—Clifford et al. 1984 (London)[48] ages 16+ (sample size not specified); 7—Carmelli et al. 1990 (NAS/NRC U.S.A.)[29] ages 45–56; 8—Carmelli et al. 1993 (NAS/NRC U.S.A.)[49]; 9—Swan et al. 1990 (NHLBI U.S.A.)[30] ages 52–66; 10—Heath et al. 1991 (Australia)[22]; 11—present study (NHLBI U.S.A.) ages 42–56 at entry; NR—not reported.

twins most often is 0.4–0.6. An exception is the small sample reported by Clifford et al.,[43] with an intraclass *r* of 0.79. A lower correlation in MZ pairs over age 60 in cross-sectional data, with nonsignificant estimates of genetic variance, was reported by Kaprio et al.[44,45] Jardine and Martin[46] reported no significant genetic influences on alcohol consumption in male twin-pairs over 30 years of age. However, Kaprio et al.[11] reported significant heritabilities of 0.48–0.54 in adults over 30 and Prescott et al.[47] reported that genetic factors contributed 40% of the variance in a sample of elderly twins. DZ correlations (Table 6) generally ranged from 0.15 to 0.35, with the London data[43,48] reporting DZ correlations approaching 0.50. We found a relatively stable correlation in alcohol consumption in MZ and DZ twins at 3 times when the twins were aged 42–56, 54–65, and 59–70 years of age. This is consistent with a more extensive model fitting approach of the larger NAS/NRC sample from which the NHLBI twins were drawn.[49] Kaprio et al.[11] also concluded there was significant longitudinal covariation of genetic effects in patterns of social drinking that were higher in their older age group. Despite a number of different methods of estimating heritabilities, most of the studies in Table 6 reported heritabilities between 0.3 and 0.6, consistent with our data. Some of the reports found significant common or shared environmental effects,[23,48,50] using maximum-likelihood or path analysis modeling, with somewhat lower estimates of genetic variance. Our results for the most part suggested that models, including only additive genetic and unshared environmental effects, provided an appropriate fit to the alcohol consumption data. There still may be common environmental or dominant genetic effects that cannot readily be differentiated from each other in twin data, which contribute to a greater heritability estimate in the more parsimonious A+E models. Heath and Martin[21] suggested that the decision to abstain from drinking is not genetically determined, but once a decision is made to drink alcohol, the onset and amount consumed are influenced by genetic factors. From the twin studies in Table 6, it is difficult to judge the effects of the inclusion or exclusion of abstainers, because none of the studies analyzed the data both ways. In our sample, removing abstainers lowered intraclass correlations in DZ twins, and there also was a decrease in maximum-likelihood heritability estimates. The latter were similar to heritabilities obtained after adjustment for significant covariates, regardless of whether abstainers were included or not (Table 2).

Our data are consistent with a conclusion of a maximum heritability of 45–50% for alcohol consumption over a 14- to 18-year period in men aged 42–56. Given the imprecision of our instrument to assess levels of drinking, this conclusion may be conservative, but it is in agreement with other twin studies. There is also evidence for differences in genetic and environmental correlates in twin studies between males and females.[21,23,43,46,48,51] Only with the availability of very large samples can consistent information be obtained relative to whether genetic influences on consumption patterns differ if the total alcohol con-

sumed is partitioned into that from beer, wine, or spirits[49,52,53] and further stratified by sex.

With this data set, we may also explore multivariate models for the consumption of alcohol at exams 2 and 3, when the exact same instrument was used to assess alcohol consumption, with significant covariates that were also both measured at these times. This will allow identification of underlying patterns of genetic and environmental effects linking groups of covariates with consumption. We can also utilize the longitudinal structure of the data to help understand the direction of effects, which, for our bivariate analyses, were assumed from the sign of cross-sectional correlations. Path analysis does not lead to the identification of major gene effects, and a challenge for the future is the identification of genetic factors on a molecular level that determine the amount of alcohol consumed. Perhaps only then will possible interactions of type of beverage, gender differences in consumption pattern, and longitudinal effects identified in path models be clarified. Furthermore, the genetic influences relating to alcoholism and molecular markers identified to be associated with alcoholism may not necessarily be the same as those influencing the level of consumption of alcohol by social drinkers.

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APPENDIX:

Covariates Examined for Their Relationship to Alcohol Consumption by Exam

Measure	Exam 1	Exam 2	Exam 3
Age	x	x	x
Years of Education	x	x	x
Family History Scores			
Cancer mortality	x		
Heart disease prevalence	x		
Stroke prevalence	x		
Anthropometrics			
Height (cm)	x	x	x
Weight (kg)	x	x	x
Body mass index (wt./ht.^{2})	x	x	x
Degree of obesity (category)	x		
Triceps skinfold left (mm)		x	x
Triceps skinfold right (mm)		x	x
Subscapular skinfold left (mm)		x	x
Subscapular skinfold right (mm)		x	x
Upper arm circumference left (cm)			x
Upper arm circumference right (cm)			x
Chest circumference (cm)			x
Abdominal circumference (cm)			x
Abdominal/hip circumference			x
Lipids			
Total cholesterol (mg/dl)	x	x	x
LDL cholesterol (mg/dl)	x	x	x
Triglycerides (mg/dl)	x	x	x
HDL cholesterol (mg/dl)	x	x	x
HDL_2 cholesterol (mg/dl)			x
HDL_3 cholesterol (mg/dl)			x
VLDL cholesterol (mg/dl)	x		
Frederickson classification	x		
Esterified cholesterol (%)		x	
Apolipoprotein A-I (mg/dl)			x
Apolipoprotein B (mg/dl)			x
Lp (a) presence			x
Hematology			
Hematocrit (%)	x	x	x
RBC count (1,000,000/mm^3)		x	x
MCV (μm^3)		x	x
Mean corpuscular hemoglobin concentration (%)		x	x
Mean corpuscular hemoglobin (pg)		x	x
WBC count (1,000/mm^3)			x
Habits			
Smoking cigarettes/day	x	x	x
Any smoking past 2 years	x		
Cigarette smoking now	x		
Lifetime packyear history		x	x
Years at home with smoker		x	x
Years at work with smoker		x	
Drink cups of tea (category)	x	x	x
Drink cups of coffee (category)	x	x	x
Drink cups of decaffeinated coffee		x	x
Caffeine (coffee + tea)		x	x
Glucose/Insulin/Diet			
Glucose (mg/dl)	x	x	x
Caloric intake/day	x		
Protein intake (g)/day	x		
Total fat intake (g)/day	x		
Total carbohydrate intake (g)/day	x		
Complex carbohydrates (g)/day	x		
Insulin (mM/liter)		x	x
C-peptide (mM/liter)			x
Physiologic Measures			
Systolic blood pressure (mmHg)	x	x	x
Diastolic blood pressure (mmHg)	x	x	x
Heart rate (Minnesota code)	x	x	x
Heart rate (Holter monitor)			x
Leisure time physical activity (kcal)		x	x
Forced vital capacity			x
FEV_1			x
Grip strength (kg)			x
Hand steadiness			x
Behavioral/Cognitive Measures			
Adjective checklist type A		x	x
Thurstone activity		x	
Framingham type A		x	
Jenkin's activity (standard score)		x	
CESD depression scale			x
Cook and Medley hostility scale			x
Paranoia subscale			x
Cynicism subscale			x
Iowa battery dementia score			x
Mini-Mental Test			x
Digit Symbol Substitution Test			x
Adjective checklist rating of cotwin			x
Electrolytes/Other SMAs			
Calcium (mg/dl)	x	x	x
Phosphorus (mg/dl)	x	x	x
Blood urea nitrogen (mg/dl)	x	x	x
Uric acid (mg/dl)	x	x	x
Total protein (g/dl)	x	x	x
Globulin (g/dl)	x	x	x
Albumin (g/dl)	x	x	x
Total bilirubin (mg/dl)	x	x	x
Alkaline phosphatase (IU/liter)	x	x	x

continued on next page

APPENDIX: Continued

Measure	Exam 1	Exam 2	Exam 3
Lactic dehydrogenase (IU/liter)	x	x	x
SGOT (IU/liter)	x	x	x
T-4 (μg/dl)		x	
SGPT (IU/liter)			x
Sodium (mEq/liter)			x
Potassium (mEq/liter)			x
Chloride (mEq/liter)			x
Creatinine (mg/dl)			x
Albumin/globulin ratio			x

LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; LP, lipoprotein; RBC, red blood cell; WBC, white blood cell; FEV_1, forced expiratory volume; CESD, Center for Epidemiologic Studies Depression; SMAs, standard medical chemistry.

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