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Heritability of Substance Use in the NAS-NRC Twin Registry

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Abstract. This study examines the heritability of cigarette smoking, alcohol, and coffee consumption in 4,960 adult, male twin pairs (2,390 MZ and 2,570 DZ pairs) participants in an epidemiologic survey of the NAS-NRC Twin Registry conducted in the USA during 1972-73. Heritability estimates for smoking, alcohol and coffee use were calculated both before and after adjustment for shared variance between these behaviors and other demographic characteristics including socioeconomic status and an occupational adjustment score. The objective of the analysis was to determine the impact of adjustment for covariates on heritability estimates of smoking, alcohol and coffee use. Before adjustment, genetic effects in smoking, alcohol and coffee use accounted for 53%, 36%, and 45% of the variance, respectively. After adjustment, the corresponding estimates were 35%, 29%, and 36%. The fact that these estimates remained significant after adjustment for covariates leads to increased confidence about the role of genetic factors in substance use behaviors.

Key words: Smoking, Alcohol, Coffee, Heritability, Covariate-adjustment

INTRODUCTION

The significant contribution of genetic factors to the variation in alcohol and tobacco use has been demonstrated repeatedly in studies using various designs that included twins, extended family studies, and adoption-based studies. Hughes [8] summarized twin studies in which heritability estimates for tobacco use ranged from 0.28 to 0.84, with a mean of 0.53; heritability estimates for alcohol use ranged from 0.28 to 0.51, with a mean of 0.42. Other studies show that the heritabilities for coffee drinking in male twins range from 0.46 [12,15] to 0.88 [16].

It has been recognized that estimates of heritability of appetitive behaviors, based on twin studies, are confounded by multiple nongenetic sources of variance that underlie twin similarities or dissimilarities. Among these are age, sex, socioeconomic and marital status, and frequency of contact [6,11,13].

Another source of confounding variance lies in the fact that smoking, alcohol use, and caffeine consumption are correlated. Istvan and Matarazzo [9], in their review of the available evidence, conclude that there is a consistent moderate association between tobacco and alcohol consumption and between coffee drinking and cigarette smoking. Caffeine and alcohol consumption are also associated, but this may be true only when either substance is used heavily. These associations lead some to conclude that there may be a common pathophysiologic process underlying the use of all three substances that needs to be considered as part of any genetic analysis [9,14].

However, before we attempt to model the joint genetic and environmental influences underlying the co-occurrence of appetitive behaviors, it is important to examine the magnitude of these associations and their direct effect on the heritability estimates of each behavior separately. The approach we use in the current study is to compare raw heritability estimates with heritability estimates that were adjusted for the confounding of socioeconomic variables as well as the joint covariances among the three substance use variables (ie, tobacco, alcohol, and coffee).

MATERIALS AND METHODS

Subjects and Measures

The sample of the current study consists of the NAS-NRC Twin Registry. The methods used to construct this twin panel have been described elsewhere [7]. Multiple births of white males occurring in the continental United States during 1917 to 1927 were identified by searching birth certificates. About 93% of all such births estimated from national statistics to have occurred during those years were found [10]. Among them were 15,924 twin pairs with both members having records in the Master Index File of the Veterans Administration (VAMI), indicating that both twins had served in the military. Because of the years of birth selected, military service was generally during World War II, although some reentered or remained in service during the Korean period. All members of the registry were screened for entry into the armed forces during World War II. Pairs in which one or both members had childhood diseases with lasting sequelae or experienced early onset of chronic diseases such as diabetes mellitus or essential hypertension, which would render them unfit for military service, are not represented.

An initial questionnaire (Q1) was used to verify the man's eligibility for the sample, to obtain the brother's address, to determine the similarity of the two brothers for use in zygosity classification, and to obtain the man's medical history since separation from service. The mailings started in 1965 and the questionnaire has been mailed to 27,052 men; replies have been received from 20,946 (76%).

Of all the pairs in the panel, 13,486 have been classified by zygosity, most by self-reports or self-reports confirmed by fingerprint and anthropometric similarity scores. An epidemiologic questionnaire (Q2) was mailed during 1972-73 in a collaborative study with investigators responsible for the Twin Registry of the Karolinska Institute in Stockholm [3]. The English-language questionnaire was essentially a translation of the one used in Sweden and later adopted in the Finnish Twin Registry. The objectives were to evaluate respiratory and coronary symptoms, to obtain a history of tobacco, alcohol consumption, diet, urban residence, and to collect information on other social and environmental factors that might be related to tobacco use, exposure to air pollution, or coronary and respiratory disease experience. The sample consisted of the 7,372 twin pairs in which both members replied to the medical history questionnaire (Q1), and the rate of reply was 75.4%. When those not reached in the mailing or those found to be deceased are excluded, the rate of reply is increased to 83.9%. Replies from both members were obtained for 4,380 twin pairs which define the sample for the current study.

Smoking was defined as the self-reported number of cigarettes ever smoked per day; ascertaining only current cigarette smoking consumption, as has been done in several earlier studies, is unsatisfactory in intrapair comparisons if the smoking durations are different within the pairs. We therefore selected the daily average cigarette consumption for all the subjects that had been smoking, past and present. *Alcohol* consumption was determined from self-reported total number of drinks per week in a typical week at the time of assessment and included beer, wine, and cocktails. For each type of beverage, the reported consumption in glasses or bottles per month was converted into grams of absolute alcohol and summed to give an individual average consumption per month. Mean consumption of cups of *coffee* per day was used as a caffeine dose variable. A socioeconomic score was constructed using education and military rank. The occupational adjustment score included items related to changes in employment, occupation, the type of employment (subordinate vs supervisory position) and the frequency of overtime work or additional employment.

Statistical Methods

Analyses were directed at estimating the heritable components of smoking, alcohol, and coffee use, both before and after taking into account the effects of other substance use, age, socioeconomic status, and occupational adjustment. Unadjusted and adjusted estimates were calculated and compared to evaluate the contributions of these variables to the amount of genetic variance in each of the appetitive behaviors. In this approach, the adjustments for smoking on consumption of alcohol and/or coffee and vice versa were accounted for at the individual level, whereas the heritability analysis was conducted on twins as pairs following these adjustments. Using this approach, individual differences in the joint behavior of smoking, alcohol, and coffee consumption were reflected in the heritability estimates of the adjusted variables.

To determine the extent to which covariates were related to smoking and alcohol use, both univariate and multivariate analyses were performed. A linear regression was developed using each appetitive behavior as the dependent variable and related characteristics such as other substance use, age, and socioeconomic status as independent variables. Separate models for MZ and DZ twins were developed under the assumption that these covariates contribute differentially to twin similarity in the two zygosities.

The derived multivariate models had two purposes: first, to determine the amount of variance explained by associated variables in the two groups of twins, and, second, to use the derived models for adjustment of the raw values for their contribution to the between-pair variability. The actual adjustments were carried out on twins as individuals. For example, amount ever smoked was regressed on use of alcohol and coffee, age, and occupational adjustment (see Table 2). Intraclass correlations and heritability estimates were calculated for the residual values and compared with the corresponding estimates calculated for the unadjusted raw values [1,2]. We used both intraclass correlation heritability estimates [5] and an analysis of variance model [4] to test for the presence of genetic variance. Since estimates of heritability tend to be biased if either the means or total variances of MZ and DZ twins differ, we tested these assumptions using the corresponding T′ and F′ tests of Christian et al [4].

Raw measures of smoking, alcohol, and coffee consumption showed significant differences in total variances; in some cases, we also observed differences in means as well as deviations from normality. When a log transformation was employed on the observed raw values, these differences disappeared.

RESULTS

Bivariate Associations Between Smoking, Coffee, and Alcohol Use, and Covariates

Table 1 presents the correlation matrix of the bivariate associations between smoking, alcohol, coffee use, and demographic variables treating twins as individuals. As

Table 1 - Correlations among appetitive behaviors and sociodemographic variables

	Smoking	Coffee	Age	Occupational adjustment	Socioeconomic status
Alcohol	0.224	(0.021)	(−0.018)	(0.013)	0.081
Smoking		0.332	−0.047	−0.048	−0.035
Coffee			(−0.015)	−0.036	(−0.015)
Age				(0.012)	(−0.034)
Occupational adjustment					0.049

Values in parentheses are not significantly different from zero.

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expected, alcohol use and coffee consumption were positively related to cigarette smoking. Daily coffee consumption was unrelated to the amount of alcohol consumed monthly. Age was negatively related to the number of cigarettes ever smoked per day but not to total amount of alcohol or to number of cups of coffee consumed daily. Socioeconomic status was positively associated with alcohol consumption and negatively related to the number of cigarettes ever smoked per day. Occupational adjustment was negatively associated with the number of cigarettes per day and to the number of cups of coffee per day. Given these relationships we developed separate models for adjustment for each of the appetitive behaviors. Table 2 presents these models in detail.

Table 2 - Models for adjustment[a]

$$\text{Cigsday} = \alpha + \beta_1\text{alcohol} + \beta_2\text{coffee} + \beta_3\text{age} + \beta_4\text{occadj} \quad (1)$$

$$\text{Alcohol} = \alpha + \beta_1\text{cigsday} + \beta_2\text{coffee} + \beta_3\text{age} + \beta_4\text{soced} \quad (2)$$

$$\text{Coffee} = \alpha + \beta_1\text{cigsday} + \beta_2\text{alcohol} + \beta_3\text{occadj} \quad (3)$$

[a] Adjustment was done within zygosity group. Adjusted values are Student-t residuals from equations (1) – (3).

Heritability Analyses

Smoking. Estimates of heritability based on intraclass correlations and the estimate of genetic variance for the raw and log transformed smoking variable are presented in Table 3. Heritability estimates for cigarette smoking are moderate, with the additive genetic component accounting for 53% of the total variance. After adjustment for covariates, this genetic component of variance was reduced to 35% of the total variance. Estimates of heritability were highly significant both before and after adjustment.

Table 3 - Heritability analyses of cigarette smoking (number of cigarettes per day)

Variable	Intraclass correlation MZ (N=2390)	Intraclass correlation DZ (N=2571)	Test for equality of Mean	Test for equality of Variance	Heritability estimate	P
			T′	F′		
Cigarettes	0.43	0.18	−2.11*	1.09**	0.44[a]	0.0001
Log-cigarettes	0.44	0.20	−1.33	1.03	0.53[b]	0.0001
Adjusted cigarettes	0.32	0.14	−0.37	1.01	0.35[b]	0.0001

* $P < 0.05$; ** $P < 0.01$.
[a] Among-components estimate.
[b] Within-pair estimate.

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Alcohol. The heritability estimate of the log transformed alcohol variable was moderate and significant, with 36% of the total variance attributable to an additive genetic effect (Table 4). Adjusting the amount of alcohol consumed for smoking and related covariates lowered this estimate to 29%. Although reduced in magnitude, the adjusted estimate remained statistically significant.

Table 4 - Heritability analyses of alcohol consumption (amount in ounces of ethanol per month)

Variable	Intraclass correlation MZ (N=2390)	Intraclass correlation DZ (N=2571)	Test for equality of Mean	Test for equality of Variance	Heritability estimate	P
			T′	F′		
Alcohol	0.40	0.24	−0.54	1.06*	0.28[a]	0.0001
Log-alcohol	0.51	0.33	1.08	1.01	0.36[b]	0.0001
Adjusted alcohol	0.32	0.19	−0.40	1.01	0.29[b]	0.0001

* $P < 0.05$.
[a] Among-components estimate.
[b] Within-pair estimate.

Coffee. As seen in Table 5, average coffee consumption was significantly higher in DZ as compared to MZ twins. However, this difference was accounted for by the log transformation or adjustment for covariates. The unadjusted heritability estimate of coffee consumption was 45% and highly significant. Adjusting coffee for smoking lowered this estimate to 36%.

Table 5 - Heritability analyses of coffee consumption (number of cup per day)

Variable	Intraclass correlation MZ (N=2390)	Intraclass correlation DZ (N=2571)	Test for equality of Mean	Test for equality of Variance	Heritability estimate	P
			T′	F′		
Coffee	0.44	0.22	−2.04*	1.05+	0.40[a]	0.0001
Log-coffee	0.40	0.18	−1.58	1.01	0.45[b]	0.0001
Adjusted coffee	0.37	0.18	0.40	1.00	0.36[b]	0.0001

* $P < 0.05$; + $P = 0.10$.
[a] Among-components estimate.
[b] Within-pair estimate.

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DISCUSSION

In this analysis we have demonstrated an epidemiological approach to the investigation of twin similarity in smoking, alcohol, and coffee consumption. Our approach takes into account confounding and shared covariance between appetitive behaviors as well as selected demographic variables and their differential impact on MZ and DZ similarity. Because this approach treats the heritability analysis of substance use as essentially a multivariate problem (as opposed to its traditional treatment as a univariate problem), it provides a method to account for the confounding of estimates of heritability of smoking, alcohol, and coffee use when treated separately.

Our results showed unadjusted heritability estimates for smoking and alcohol to be consistent with previously published research. For smoking, the estimate obtained in the present study was 0.53, which is identical to the average cited by Hughes [8]. For alcohol use, the unadjusted heritability estimate was 0.36, somewhat lower than the mean value of 0.42 reported by Hughes [8]. As a result of the adjustment procedure, the within-pair heritability estimate for smoking decreased to 35%, while that for alcohol decreased to 29%.

Although the adjustment process resulted in heritability estimates that were lower than the unadjusted estimates, all estimates remained significant. The apparent robustness of the genetic component in smoking, alcohol, and coffee consumption, even after the adjustment for covariates, supports the general conclusion that each of the substance use behaviors is, in part, genetically determined. Genetic analyses of cardiovascular risk factors have shown a similar robustness under conditions of adjustment for environmental covariates for HDL and LDL cholesterol, triglycerides, and relative weight, and for some of the measures of Type A behavior [2] but not for systolic and diastolic blood pressure [1].

Other investigators [6] have argued for a multivariate genetic path model approach that allows the estimation of the separate and joint genetic and environmental effects that underlie the covariation of symptoms or behaviors in twin pairs. This approach, which we believe could further contribute to the understanding of substance use behaviors, is different from that addressed in the present analysis. We strongly believe that it is important, prior to fitting a series of causal models that test how genes and environment interact, to explore the effects of confounding variables. This in turn may aid in a better specification of models as well as allow for the testing of the underlying assumptions.

Finally, there are several limitations to this study that the reader should bear in mind. First, this is a heritability analysis of substance use, not of addiction. Second, our analysis included male twins only that were somewhat older than samples upon which previous heritability analyses have been conducted. It would be interesting to see whether the effects of adjustment generalize to younger males and to females. Most important, it is impossible from the present analysis to discern cause and effect. It is, at this point, equally plausible to suggest that differences in smoking, alcohol, or coffee consumption behavior cause or result from twin similarity or dissimilarity on the variables used in this analysis. Several aspects of the data also limit inferences regarding the differential impact of the twins' contact on twin

similarities of appetitive behaviors. For example, while we may have superficial knowledge of the extent of the interaction between twins, we have no knowledge of the type and quality of the interaction. Moreover, we do not know whether any early environmental differences existed between MZ and DZ twins, or whether there were differences in parental behavior that could account for present differences. The appropriate methodology to address these issues would be to fit a series of multivariate genetic causal models and to extend these types of investigations to other samples and populations.

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