Heavy Consumption of Cigarettes, Alcohol and Coffee in Male Twins*

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ABSTRACT. *Objective:* To determine the relative contribution of environmental and genetic influences on the joint distribution of heavy smoking, heavy alcohol use and heavy coffee drinking. *Method:* Multivariate structural equation modeling in a large cohort of male twins (*N* = 2,220 monozygotic and 2,373 dizygotic twin pairs; mean age = 62.1 years) from the National Academy of Sciences-National Research Council's World War II Twin Registry. *Results:* The best-fitting model identified two independent (i.e., uncorrelated) sets of genetic and environmental latent factors, with one set underlying joint heavy smoking and heavy alcohol use and the other set underlying joint heavy smoking and heavy coffee drinking (χ^2 = 14.13, 22 df, p > .80). Heavy alcohol use and heavy coffee drinking were uncorrelated in this sample. While common genetic factors accounted for 35% to 78% of the total genetic variance in heavy substance use, a substantial amount of genetic variance remained specific to each of the three substances. *Conclusions:* Several hypotheses involving genetic and environmental factors are presented to account for the independent clustering of heavy smoking and heavy alcohol use and of heavy smoking and heavy coffee drinking. (*J. Stud. Alcohol* **58:** 182-190, 1997)

S MOKING, alcohol use and coffee consumption are consistently correlated across a wide variety of populations with moderately strong associations between tobacco and alcohol consumption and between coffee drinking and cigarette smoking (Istvan and Matarazzo, 1984; Swanson et al., 1994). Although the strength of these associations appears to increase with the level of consumption, the intercorrelation between heavy coffee drinking and alcohol use appears to be less consistent over a variety of studies (Istvan and Matarazzo, 1984). These associations have led some to conclude that common pathophysiologic processes may underlie the joint use of these substances (Istvan and Matarazzo, 1984; Kaprio and Koskenvuo, 1988).

Several models have been proposed to explain the clustering in the use of these substances. These include biobehavioral models in which the effects of one substance serve as cues for the use of others (Istvan and Matarazzo, 1984), personality models in which an underlying psychological trait or set of traits (e.g., antisocial behavior, depression or neuroticism) predisposes an individual to polysubstance use (Mangan and Golding, 1984) and neurochemical models in which the various substances are seen to act and interact on common neural pathways and receptors (Collins, 1990; Wise, 1988).

Most previous behavioral genetic studies have estimated the heritability (i.e., proportion of total variance attributable to genetic sources) in the use of these substances as if they

occur independently of each other. Reviews of this literature indicate the presence of significant genetic variance for both tobacco and alcohol consumption (Ball and Murray, 1994; Froehlich, 1995; Heath and Madden, 1995; Hughes, 1986; Pedersen, 1981; Pomerleau et al., 1993; Schuckit, 1994). Estimates of the proportion of variance attributable to genetic sources for cigarette smoking range from .28 to .84, with a mean of .53 (Hughes, 1986). Recent work done by our group and others supports the conclusion of genetic influence on tobacco use (Carmelli et al., 1990, 1992; Heath and Martin, 1993; Swan et al., 1990). Heritability estimates for alcohol use range from .28 to .51, with a mean of .42 (Carmelli et al., 1990; Hughes, 1986; Swan et al., 1990).

We include coffee drinking in the present analysis because caffeine is the most widely consumed psychotropic drug in the world, followed by alcohol and nicotine (Griffiths and Mumford, 1995). Recent studies indicate that caffeine also exhibits features of a psychoactive substance with a potential for dependence (Griffiths and Mumford, 1995; Hughes et al., 1991; Nehlig et al., 1992; Strain et al., 1994). These and other findings have led some authors to conclude that caffeine has a dependence potential under certain conditions (Heishman and Henningfield, 1992) and in certain individuals (Hughes et al., 1991, 1992; Strain et al., 1994). Other studies have shown the heritability for coffee drinking in male twins to range from .46 to .88 (Carmelli et al., 1990; Kaprio et al., 1981; Partanen et al., 1966; Pedersen, 1981).

A previous multivariate genetic analysis over the full range of consumption of all three substances identified a common latent factor underlying twin similarity in the joint use of tobacco, alcohol and coffee. This latent factor was explained entirely by additive genetic sources, suggesting that

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the observed associations between substances over the full range of use are genetically mediated (Swan et al., 1996). At present, the genetic and environmental contributions to the joint *heavy* use of these substances are unknown. Because the factors determining joint heavy use (e.g., impaired neuropsychological status, psychopathology, family history of heavy use; Meyer, 1994) may be different from those determining joint use over the entire range of consumption (e.g., social settings, work demands, everyday stress; Wills, 1990), we sought to determine the best-fitting multivariate genetic model for the joint distribution of heavy smoking and heavy alcohol use and coffee drinking. To do this we used a recently developed constrained multivariate structural equation model postulating two latent sets of polygenes instead of one to account for the clustering of heavy smoking with heavy alcohol use and of heavy smoking with heavy coffee drinking. The complete mathematical development of this model is presented in Cardon et al., in press.

Method

Subjects

The NAS-NRC Twin Registry consists of white male twins born between 1917 and 1927 who both served in the military, primarily in World War II. Beginning in 1965, an initial questionnaire was mailed to 27,502 men; of the 20,946 respondents, 13,486 have been classified by zygosity. A second questionnaire was mailed to individuals in the Registry during 1967-79 in a collaborative study with investigators of the Twin Registry of the Karolinska Institute in Stockholm (Cederlof et al., 1971). The objectives of the questionnaire were to evaluate respiratory and coronary symptoms, to obtain a history of tobacco, alcohol and coffee consumption and diet, and to collect information on other social and environmental factors that might be related to tobacco use or coronary and respiratory disease experience. The methods used to construct the NAS-NRC Twin Registry are described elsewhere (Jablon et al., 1967).

Complete data for the smoking, alcohol and coffee consumption indices in the second questionnaire were available for 2,220 monozygotic (MZ) and 2,373 dizygotic (DZ) twin pairs. The measures are defined as: *smoking,* self-reported number of cigarettes smoked currently (i.e., 1967-69) per day; *alcohol,* self-reported total number of drinks (including beer, wine and cocktails) per month at the time of evaluation; and *coffee,* number of cups of coffee consumed per typical day at the time of assessment. For the analysis of heavy polysubstance use, we define heavy consumption of each substance as the upper 20% of the respective distributions after excluding never users of each substance. For smoking, this translated as more than 30 cigarettes per day; for heavy alcohol use, as more than 67 drinks per month; and, for heavy coffee consumption, as more than five cups per day.

Although we present concordance rates for heavy substance use, our analyses in this report use a more efficient statistic, the tetrachoric correlation, that uses all the information available in the joint distribution of these variables (Mather and Jinks, 1982). The tetrachoric correlation assumes that, underlying the division of twins into heavy and nonheavy users, there exists a latent distribution that is the liability or vulnerability to heavy substance use. The threshold of this liability is such that individuals with liability above the threshold will become heavy users while those with a liability below the threshold will be regular users. The tetrachoric correlation represents the correlation in twins for an underlying liability to become heavy smokers, heavy users of alcohol and heavy coffee drinkers. Since the model further assumes a multifactorial etiology involving multiple genetic and environmental risk factors of small to moderate effects, the distribution of the liability to heavy substance use is assumed to be approximately normal.

Multivariate structural equation modeling procedures (Neale and Cardon, 1992) were used to estimate the genetic and environmental contributions to the variation and covariation described in Table 2. We used a multivariate genetic model recently developed to account for the specific pattern of correlations observed in heavy smoking, heavy alcohol use and heavy coffee drinking (i.e., higher correlations between heavy smoking and heavy alcohol use and heavy smoking and heavy coffee drinking than between heavy alcohol use and heavy coffee drinking; Cardon et al., in press).

A path diagram of the model is presented in Figure 1, in which observed variables are in boxes and latent variables are in ovals. The diagram shows two groupings of substance use (latent factors), heavy smoking–heavy alcohol use and heavy smoking–heavy coffee drinking, corresponding to the observed correlational structure. The weaker association between heavy alcohol use and heavy coffee drinking is explained by the second-order correlation, ρ, between the two factors (shown as a double-headed arrow). The extent to which all three substances share a common source of covariance also will be reflected in the factor correlation. For example, a shared genetic etiology for heavy smoking, heavy alcohol use and heavy coffee drinking would be manifest as a significant estimate of the genetic factor correlation, ρ, whereas independent etiologies for the two clusters would result in a zero correlation. In application to twin data, all the parameters in Figure 1 are specified for each of three components of variation: additive genetic (A); environmental effects shared by, or "common" to, twins (CE); and environmental effects not shared by twins (SE). The substance-specific effects additionally account for genetic and environmental effects specific to each measure of substance use.

The full model was fitted to the tetrachoric correlations for substance use given in Table 2. The 18 free parameters in the model were estimated from the data by weighted least squares using the Mx computer program (Neale, 1991). This program provides maximum-likelihood estimates of all model parameters and calculates for each model a χ^2 goodness-of-fit measure. Larger p values indicate a better fit to the data. For tests of statistical significance of submodels
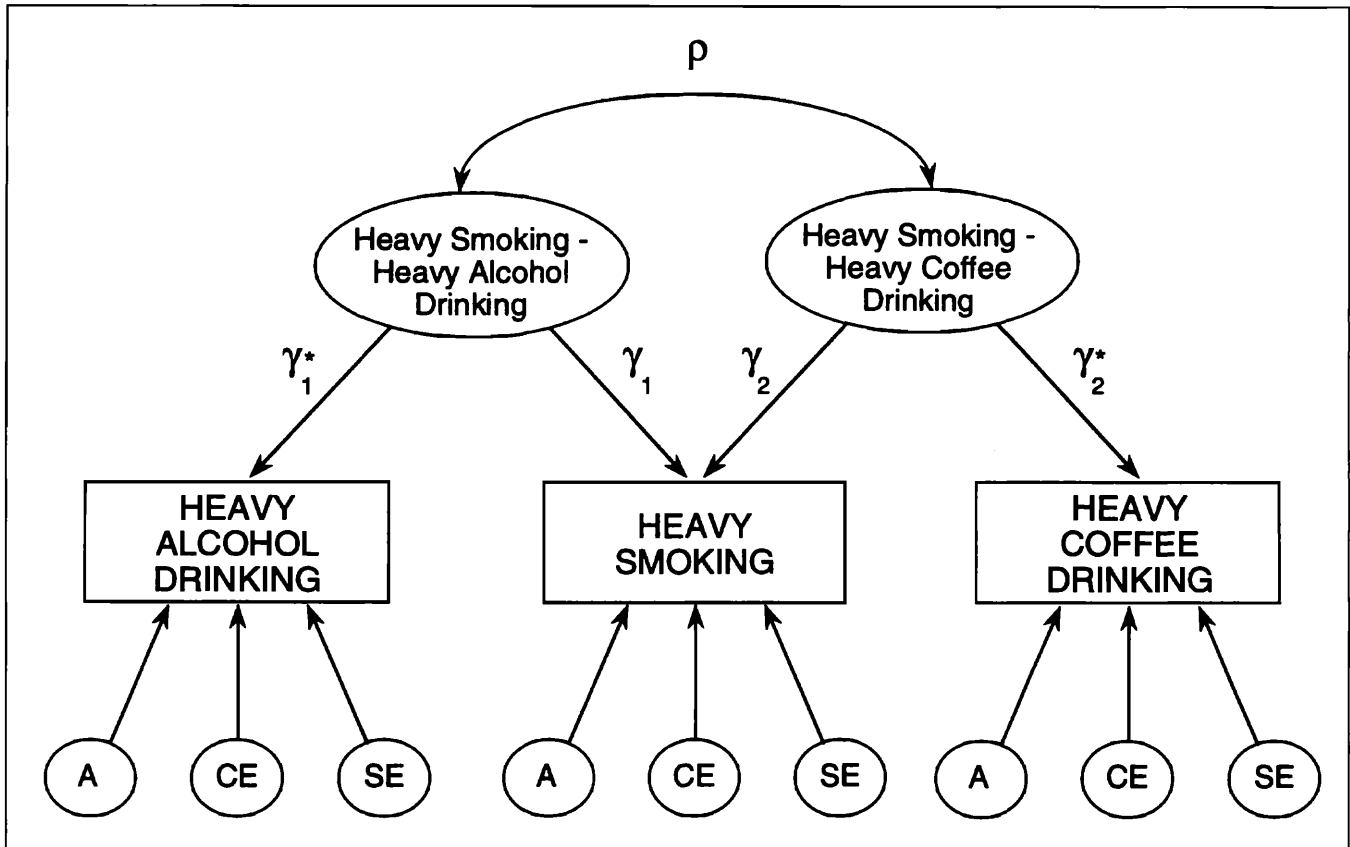
FIGURE 1.   Two-factor model of heavy smoking, heavy alcohol use and heavy coffee drinking. Circled variables "Heavy Smoking-Heavy Alcohol Drinking" and "Heavy Smoking-Heavy Coffee Drinking" represent unmeasured (latent) clusters of heavy smoking and heavy alcohol use and heavy smoking and heavy coffee drinking. Latent variables A, CE and SE represent substance-specific factors contributing to variation in heavy alcohol use, heavy smoking and heavy coffee drinking. Model parameters $\gamma_1{}^*$ and $\gamma_2{}^*$ are constrained for model identification.

involving different combinations of genetic and environmental effects, we systematically omit the corresponding parameters from the model and recalculate the χ^2 statistic. If the change in χ^2 values is significant, then the omitted parameter must be retained in the final model. Smaller p values are indicative of significant loss of fit.

The specific parameters evaluated for significance included the higher-order factor correlation (ρ), shared influences for each cluster (γ_1 for heavy alcohol-heavy smoking correlations and γ_2 for heavy smoking-heavy coffee use correlations) and substance-specific effects for each covariance component: additive genetic, shared environmental and nonshared environmental.

Results

Over the entire sample, subjects smoked an average of 18.6 ± 16.1 cigarettes per day, consumed 9.5 ± 13.3 alcoholic drinks per month and had 3.7 ± 2.4 cups of coffee per day. As a group MZ twins smoked an average of 18.0 ± 16.0 cigarettes per day, reported 9.3 ± 12.7 alcoholic drinks per month and consumed 3.6 ± 2.4 cups of coffee per day. Corresponding values for DZ twins were: 19.0 ± 16.2 cigarettes

per day, 9.8 ± 13.5 alcoholic drinks per month and 3.8 ± 2.5 cups of coffee per day. Phenotypic Pearson correlations for the entire sample over the entire range of consumption are: smoking-alcohol, $r = .22$ $(p < .001)$; smoking-coffee, $r = .28$ $(p < .001)$; and alcohol-coffee, $r = .14$ $(p < .001)$.

Prevalences and twin concordance rates for the three substances and their joint occurrence are presented in Table 1. About 20% of the NAS-NRC twins of either zygosity exceeded at least one of these thresholds, and 4% (81 MZ and 105 DZ twins) exceeded all three criteria for heavy polysubstance use. The probandwise concordance rates given in the table reveal higher concordances for MZ twins than for DZ twins for combined heavy use, indicating heritable etiologies for the use of these substances.

Across the entire sample, the tetrachoric correlation between heavy smoking and heavy alcohol use was .29 $(p < .001)$, and that between heavy smoking and heavy coffee drinking was also .29 $(p < .001)$. The correlation between heavy alcohol use and heavy coffee drinking was $-.04$ $(p < .01)$. Tetrachoric correlations by zygosity are presented in Table 2. Cross-twin correlations, shown in boldface, provide the information for estimation of genetic and

TABLE 1. Prevalences and concordance rates for heavy smoking, heavy alcohol use and heavy coffee drinking among male monozygotic (MZ; 2220 pairs) and dizygotic (DZ; 2373 pairs) twins

Categories of heavy substance use	Total number of affected individuals		N pairs, both affected (C)		N pairs, one affected (D)		Prevalence (2C + D)/2N		Proband concordance 2C/(2C + D)		Pairwise concordance C/(C + D)	
	MZ	DZ	MZ	DZ	MZ	DZ	MZ	DZ	MZ	DZ	MZ	DZ
Smoking	821	971	166	139	489	693	18.5	20.5	40.4	28.6	25.3	19.0
Alcohol	912	1020	203	178	506	664	20.5	21.5	44.5	34.9	28.6	21.1
Coffee	1027	227	238	226	551	775	23.1	25.8	46.4	36.8	30.2	22.6
Smoking–Alcohol	266	323	29	19	208	285	6.0	6.8	21.8	11.8	12.2	6.3
Alcohol–Coffee	189	244	13	11	163	222	4.3	5.1	13.8	9.0	7.4	4.7
Smoking–Coffee	311	376	40	23	231	330	7.0	7.9	25.7	12.2	14.8	6.5
Smoking–Alcohol–Coffee	81	105	3	2	75	101	1.8	2.2	7.4	3.8	3.7	1.9

environmental influences. Again, MZ twins are more similar than are DZ twins for the liability of heavy use of each substance (italic diagonal elements) and their combined use (off-diagonal elements). In addition, MZ twins reveal greater correlations than DZ twins only for the heavy smoking–heavy alcohol and heavy smoking–heavy coffee relationships. For the joint heavy use of alcohol and coffee, all correlations are close to zero.

The full two-factor model applied to the tetrachoric correlations in Table 3 provided a very good explanation of the data (goodness of fit $\chi^2 = 13.74$, 15 df, $p > .60$; Model 1).

Model-fitting results revealed that shared environmental influences did not contribute significantly to a correlation between the two factors or on the two factors individually, on the joint heavy use of cigarettes, alcohol and coffee, or on the individual heavy use of cigarettes or coffee (Models 2-5, 7-8, as compared with Model 1, indicated nonsignificant loss of fit). Significant common environmental effects were observed for the specific heavy use of alcohol only ($\chi^2 = 4.02$,1 df, $p < .025$; the difference between Model 6 and Model 1).

Further testing revealed that, while nonshared environmental influences did not contribute to a significant correlation between the heavy smoking-heavy alcohol and heavy smoking-heavy coffee groupings ($\chi^2 = .42$, NS; Model 9 vs Model 1), nonshared environmental effects on the two individual groupings were significantly different from zero (test of heavy smoking–heavy alcohol use: $\chi^2 = 12.36$, $p \le .01$; test of heavy smoking–heavy coffee drinking: $\chi^2 = 5.93$, 1

df, $p \le .025$; Models 10 and 11 vs Model 9, respectively). This suggests that nonshared environment does affect joint heavy substance use but the environmental factors influencing joint heavy consumption of alcohol and heavy smoking are not the same as those influencing heavy joint smoking and heavy coffee use.

The final test series indicated no effect for additive genetic influences on the genetic correlation between heavy smoking–heavy alcohol and heavy smoking–heavy coffee factors ($\chi^2 = 1.08$, 1 df, NS; Model 12 vs Model 1), whereas genetic influences on each of the substance use clusters were highly significant (heavy alcohol/heavy smoking: $\chi^2 = 42.79$, 1 df, $p \le .0001$; heavy smoking/heavy coffee: $\chi^2 = 80.08$, 1 df, $p \le .0001$; Models 13 and 14 vs Model 1, respectively). Substance-specific genetic effects could also not be omitted from the model without significant loss of fit (see Models 15-18 tested against Model 1).

The best fitting model for these data included genetic and nonshared (e.g., residual) environmental effects overlapping heavy smoking and the heavy use of alcohol and heavy smoking and heavy coffee drinking, the respective substance-specific genetic influences and the shared environmental influences on heavy alcohol use ($\chi^2 = 14.13$, 22 df, $p > .80$). Standardized parameter estimates and summary statistics for this model are presented in Table 4 and Figure 2. For heavy polysubstance use, the best fitting model shows no common genetic or environmental effects among all three substances ($\rho_g = \rho_e = 0.00$; Figure 2). Rather, genetic and environmental effects that are unique to each of the two

TABLE 2. Correlations among twins [MZ (DZ)] for heavy alcohol use, heavy smoking and heavy coffee drinking[a]

Category of heavy substance use	Twin 1			Twin 2		
	Alcohol use	Smoking	Coffee drinking	Alcohol use	Smoking	Coffee drinking
Twin 1						
Alcohol use						
Smoking	.31 (.27)					
Coffee drinking	.00 (−.04)	.31 (.33)				
Twin 2						
Alcohol use	.53 (.35)	.18 (.02)	−.04 (.05)			
Smoking	.21 (.11)	.50 (.24)	.22 (.12)	.28 (.32)		
Coffee drinking	.02 (−.02)	.24 (.09)	.51 (.28)	−.05 (.01)	.32 (.24)	

[a]Threshold criteria for heavy use: smoking, >30 cigarettes/day; alcohol, >67 drinks/month; coffee, >5 cups of coffee/day

TABLE 3.   Model comparison tests of shared environmental (CE), nonshared environmental (SE) and additive genetic (A) sources of variation-covariation in heavy smoking, heavy alcohol use and heavy coffee drinking

		Goodness of model fit			Tests of parameter significance		
Model		χ^2	df	p	change χ^2	df	p
1	Full 2-factor model	13.74	15	>.60			

Tests for common environmental (CE) effects on specific and joint heavy substance use

2	No factor correlation	13.97	16	>.60	0.23	1	NS
3	2 and no smoking–alcohol factor	13.97	17	>.60	0.00	1	NS
4	2 and no smoking–coffee factor	13.97	17	>.60	0.00	1	NS
5	No effect for joint use of all three substances	13.97	18	>.70	0.23	3	NS
6	No alcohol-specific	17.76	16	>.30	4.02	1	<.05
7	No smoking-specific	13.97	16	>.60	0.00	1	NS
8	No coffee-specific	14.22	16	>.50	0.48	1	NS

Tests for nonshared environmental (SE) effects on common factors for joint heavy use

9	No factor correlation	14.16	16	>.50	0.42	1	NS
10	9 and no smoking–alcohol factor	26.52	17	>.05	12.36	1	<.01
11	9 and no smoking–coffee factor	20.09	17	>.20	5.93	1	<.03

Tests for genetic (A) effects on common factors for joint heavy use

12	No factor correlation	14.82	16	>.40	1.08	1	NS
13	12 and no smoking–alcohol factor	56.53	17	<.01	42.79	1	<.0001
14	12 and no smoking–coffee factor	93.82	17	<.01	80.08	1	<.0001

Tests for genetic (A) effects on specific heavy substance use

15	No alcohol-specific	18.97	16	>.25	5.23	1	<.05
16	No smoking-specific	26.13	16	>.05	12.39	1	<.01
17	No coffee-specific	21.02	16	>.05	7.28	1	<.01
18	All substance-specific effects	105.28	19	<.01	91.54	3	<.0001
19	Best-fitting model	14.13	22	>.80			

clusters of heavy smoking and heavy alcohol use and heavy smoking and heavy coffee drinking are essential to the overall fit.

Table 4 presents the additive genetic and specific environmental proportions of variation for the three observed measures and the latent phenotypes as derived from parameter estimates in Figure 2. Heavy smoking, heavy alcohol use and heavy coffee drinking exhibit significant heritable variation, with percent of variation (heritabilities, h^2) of 38% to 51%. The heavy smoking–heavy alcohol genetic factor accounted

TABLE 4.   Percent of variation in heavy smoking, heavy alcohol use and heavy coffee drinking attributable to genetic and environmental sources in best-fitting model[a]

	Genetic variance in heavy use				Environmental variance in heavy use				
Substance	Proportion of total variance	Common factor for alcohol use and smoking	Common factor for smoking and coffee drinking	Substance-specific	Proportion of total variance Common	Specific	Common factor for alcohol drinking and smoking	Common factor for smoking and coffee drinking	Substance-specific
Alcohol	38	45[b]	–	55	15[c]	47	26[d]	–	74
Smoking	49	35	43	22	0	51	24	16	60
Coffee	51	–	41	59	0	49	–	16	84

[a]Model χ^2 = 14.13, 22 df, p > .80.
[b]Percent of total genetic variance.
[c]All shared twin environmental influences are substance-specific.
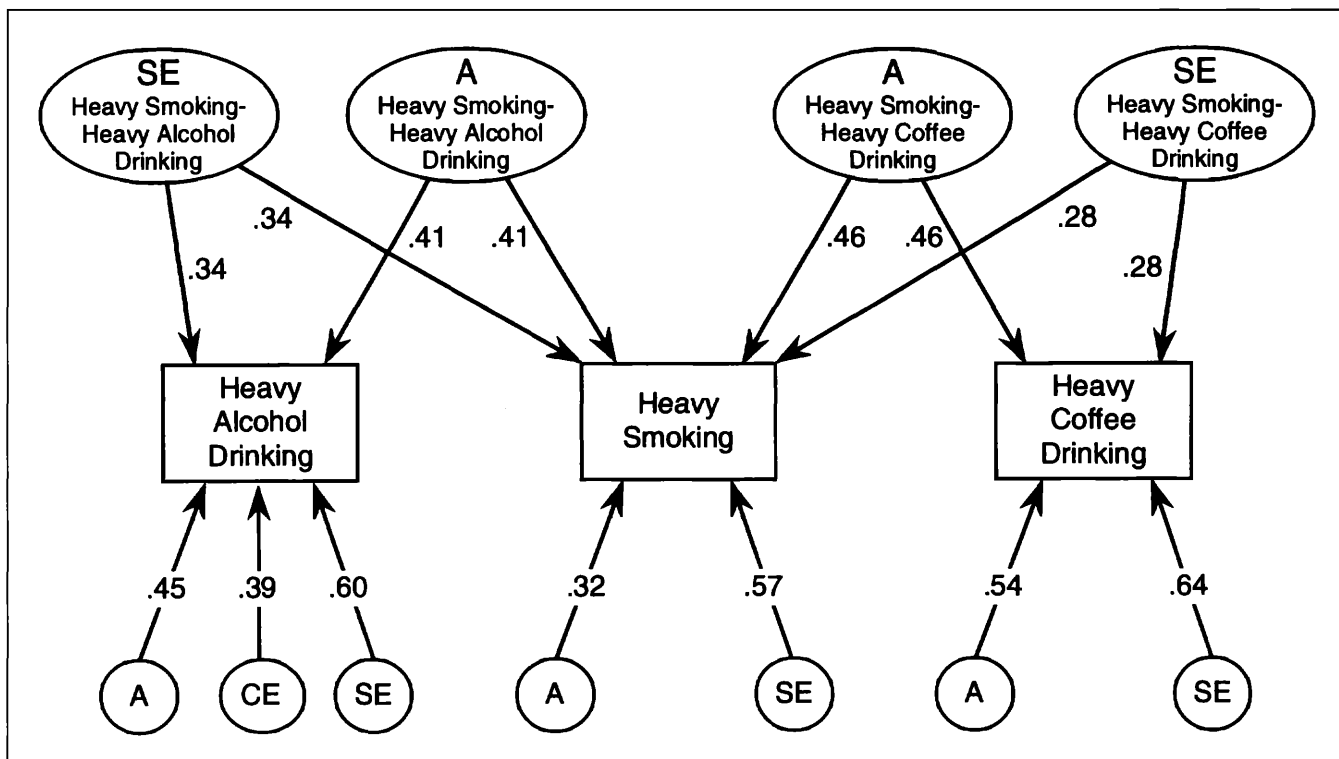[d]Percent of total specific environmental variance.

FIGURE 2.   Parameter estimates from best-fitting model of heavy smoking and heavy alcohol and heavy coffee drinking, $\chi^2 = 14.13, 22$ df, $p > .80$. Parameter estimates that were not significantly different from zero are omitted from the diagram.

for 35% of the heritable variance in heavy smoking and 45% of the heritable variance in heavy alcohol use. The heavy smoking–heavy coffee genetic factor accounted for approximately equal amounts of the heritable variance in heavy smoking (43%) and heavy coffee drinking (41%). Substance-specific genetic influences contributed 22% of the total heritable variance in heavy smoking, 55% in heavy alcohol use and 59% in heavy coffee drinking.

The remaining percentage of the total variance in the use of each substance was attributable to environmental sources and ranged from 49% for heavy coffee drinking to 62% for heavy alcohol use. The joint heavy smoking–heavy alcohol environmental factor accounted for 24% in heavy smoking and 26% of the nonshared environmental variance in heavy alcohol use. A similar pattern was observed for the joint environmental factor for heavy smoking and heavy coffee drinking, with approximately equal amounts of "environmentality" accounted for in heavy smoking and heavy coffee drinking. Substance-specific environmental influences (calculated as percentages of total specific environmentality) were similar for heavy use of all three substances: smoking (60%), alcohol (74%) and coffee (84%).

Correlations among the additive genetic influences (r_g) may also be derived directly from parameter estimates in Figure 2, as the product of the common genetic paths (A) divided by the product of the square roots of the individual her-

itabilities. These values can be viewed as estimates of the genetic correlation between the two substances. As expected, the genetic correlations mirror the pattern of observed correlations showing relatively high but similar genetic correlations between heavy smoking and heavy alcohol use $(r_g = .40$, calculated as $[.41 \times .41]/[\sqrt{.49} \times \sqrt{.38}])$ and between heavy smoking and heavy coffee drinking $(r_g = .43)$. In contrast, the environmental correlations, r_e, between the clusters of heavy substance use were approximately one-half to one-third the size of the genetic correlations $(r_e = .24$ for heavy smoking and heavy alcohol use; $r_e = .15$ for heavy smoking and heavy coffee drinking), suggesting that joint heavy use in these two pairings is determined primarily by common genetic etiology.

Discussion

With respect to cigarette smoking, we note that the prevalence of ever smoking in this cohort, 80%, is identical to that for unrelated individuals similar in birth cohort (80%, DHHS, 1989, p. 300). The average number of cigarettes smoked per day (18.6) is also similar to that for a comparably aged cohort (18.3, Stein et al., 1993). At the time of assessment, 52% of the sample was still smoking. This prevalence is about 10% higher than that reported by the Health Interview Survey (DHHS, 1989) of noninstitutionalized white males in the United States at about the same time.

The proportion of consumers of alcohol (84%) is comparable to that for similarly aged unrelated individuals (75%, Stein et al., 1993). The average number of drinks per week (9.5) appears to be higher than that for the general population (5.1, Stein et al., 1993). The prevalence of coffee drinking, 82%, is comparable to that for the general population (82%, Klag et al., 1994; 80%, Griffiths and Mumford, 1995). Assuming an average of 100 mg of caffeine per cup of coffee and that coffee consumption accounts for about 75% of total caffeine intake (Consumers Union, 1994), the level of consumption on a daily basis (370 [100 × 3.7] mg caffeine from coffee and an estimated 500 mg from all sources of caffeine) also appears to be substantially higher than the level noted for the general U.S. population (235 mg/day, Griffiths and Mumford, 1995) and for a sample of men (230 mg/day, Klag et al., 1994).

In a previous multivariate genetic analysis of the joint use of tobacco, alcohol and coffee over the entire range of consumption in the National Heart, Lung, and Blood Institute Twin Study, we obtained evidence for a common genetic factor underlying the use of all three substances (Swan et al., 1996). The present analysis identified two *independent* sets of polygenes underlying the joint heavy use of cigarettes and alcohol and of cigarettes and coffee. Despite differences in sample size, methodology and results, conclusions from our previous article are similar to several of those drawn here. Heritabilities for the use of the three substances over the full distribution of consumption ranged from 36% to 56% and those for heavy consumption ranged from 38% to 51%. Best fitting models in both analyses included a common genetic factor or factors accounting for 28% to 64% of total genetic variance in the full range of consumption and for 41% to 78% of total genetic variance in heavy consumption. In both analyses common genetic factor(s) accounted for the most genetic variance in smoking (64% and 78%, respectively) and for the least genetic variance in coffee drinking (28% and 41%, respectively). From these analyses, we conclude that future behavior genetic studies of the use of these substances will need to account for their common genetic etiologies. In other words, the issue of genetic influence on substance use is only partially addressed in the absence of multivariate approaches to genetic analyses that take advantage of data from measures of concurrent use of other psychoactive substances.

Several lines of research can be invoked to explain the genetic and environmental correlations underlying the joint heavy use of cigarettes and alcohol and of cigarettes and coffee. On the environmental side, stress is known to increase the use of both alcohol and tobacco (Wills, 1990), and the use of both substances individually to manage the effects of stress is well known (NIAAA, 1994; Pomerleau and Pomerleau, 1984). The combined effects of nicotine and alcohol on the mesolimbic dopamine system, the structure and function of which may be genetically mediated, may enhance the ability of both substances to lessen biobehavioral responses to stress (Balfour, 1991, 1993).

The environmental overlap in the joint occurrence of heavy smoking and heavy coffee drinking would seem less likely to be related to stress, especially in view of caffeine's known anxiogenic potential and ability to disrupt sleep latency (Nehlig et al., 1992). A more likely explanation lies with the need to respond to an environmental demand with heightened cognitive abilities. The combined use of both nicotine and caffeine could produce a synergistic effect on receptor systems involving acetylcholine, norepinephrine and serotonin. The net result would be enhanced alertness, vigilance and concentration (Balfour, 1991, 1993; Nehlig et al., 1992).

While our discussion thus far has focused on neurochemical and environmental explanations for the apparent clustering of the two joint-use factors, the exact nature of what and how the two clusters for joint heavy substance use may be genetically influenced is currently speculative. Schuckit (1994), writing in the context of alcohol research, makes a convincing case that, while the mode of transmission of individual differences in receptor functioning may well be polygenic and multifactorial, other risk factors for substance use also possibly influenced by genetic factors include: (1) certain personality types (e.g., antisocial personality, reward dependence); (2) heightened stress reactivity; and (3) comorbidity with other psychiatric disorders such as depression (NIAAA, 1994). Associations between depression and different facets of smoking (Hall et al., 1993; Hemenway et al., 1993), alcohol use (Berger and Adesso, 1991; Greeley et al., 1992; Hartka et al., 1991) and caffeine consumption (Leibenluft et al., 1993) have been reported. The potential importance of depression as an explanatory variable to the observed genetic associations is underscored by the recent series of bivariate genetic analyses from Kendler and colleagues identifying genetic commonality to alcoholism and depression (Kendler et al., 1993a) and to smoking and depression (Kendler et al., 1993b). To date, the genetic association between coffee drinking and depression remains untested, as far as we know.

Other explanations can be invoked to explain the pattern of covariation seen in this study. Swanson et al. (1994) suggest a possible drug-drug interaction in which nicotine increases the rate of caffeine metabolism, resulting in the need to drink more caffeine to maintain the desired levels. Thus, heavy smoking could lead to heavy coffee drinking. It seems similarly likely that alcohol metabolism might also be altered when used concurrently with nicotine. There is also, of course, the possibility that the use of one substance such as nicotine has become a conditioned cue to use other substances as well, as originally proposed by Istvan and Matarazzo (1984).

Although an overlap in the genetic effects underlying the use of these substances was indicated in the present study, it is important to note that genetic variance specific to the use of each substance was also identified. The findings reveal that some of the variation in the use of each substance is specific, accounting for 22% of the total heritabilities in heavy smok-

ing, 55% in heavy alcohol use and 59% in heavy coffee drinking. This pattern of results is also consistent with research in animal models that shows, for example, that, although gene products responsible for the regulation of ethanol sensitivity also regulate sensitivity to nicotine (Collins, 1990), there remain unique genetic components that regulate sensitivity to each substance separately (De Fiebre et al., 1990).

In reviewing these results, the reader should bear in mind several limitations to generalizability. First, these findings are based entirely on self-report. Although we have no data to suggest that heavy users in this study had a strong motivation to underreport their level of smoking, alcohol use or coffee drinking, the use of a 7-day diary of consumption might have resulted in a more accurate assessment of true levels. Second, the analysis used in the present study relied on an assessment of coffee use as a proxy for caffeine intake. Because there are several other dietary sources of caffeine (e.g., soda, tea, chocolate, over-the-counter stimulants) that we did not assess, we may have underestimated the true level of caffeine intake in these participants. Third, although specific environmental/cultural influences are noted for each of the three substances, the nature of these influences was not assessed in this study. Moreover, these environmental influences could be confounded with measurement error. Fourth, because there is some evidence to suggest that women are different from men with respect to substance use (Grunberg et al., 1991; Lex, 1991), it would be of great interest to repeat these analyses in a female twin cohort.

Two basic assumptions of the twin model, if not met, could lead to biased estimates of heritability. The first is that all of the variance that contributes to the similarity within pairs is due to genetic similarity and/or shared environmental influences. Since twins spend more time together and are more often in similar situations (e.g., the same school) it is reasonable to assume that they share more environmental influences than do nontwin siblings; shared environmental influences are assumed to be the same for MZ and DZ twins. Only under this assumption is it possible to attribute underlying genetic causality to the observed twin similarity of a measured characteristic. If common environmental influences are not the same for MZ and DZ twins, then estimates of heritability will be biased. The second assumption is that genetic influences act in an additive manner. If dominance is involved or if polygenic influences interact with one another, then the estimate of heritability used in the present study will be biased upward.

The NAS-NRC Twin Registry is composed of twins, both of whom served in the U.S. armed forces during World War II. These men are not a random sample of adult U.S. men. To be included in the present study, twins had to pass an induction examination, survive military service, survive to middle age and be willing to participate in a longitudinal health study. This sampling process therefore may have resulted in the selection of a relatively healthy cohort. Previous research on a subset of this cohort demonstrated that heavy smokers and

drinkers were in fact less likely to volunteer to participate (Fabsitz et al., 1988). We believe that the effect of this bias in the sample would lead to an underestimation of the observed genetic variance.

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