The Consumption of Tobacco, Alcohol, and Coffee in Caucasian Male Twins: A Multivariate Genetic Analysis

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Despite the fact that epidemiologic studies demonstrate a consistent covariation between the use of tobacco, alcohol, and coffee, most previous behavioral genetic studies have determined the contribution of genetic and environmental influences as if the consumption of these substances occurred independently of each other. In this study, we used multivariate structural equation modeling to determine the genetic and environmental overlap in the observed correlations between tobacco smoking and alcohol and coffee drinking in 173 monozygotic and 183 dizygotic male twin pairs (M age = 59 years; range = 52–66 years) who participated in a follow-up cardiovascular examination of the National Heart, Lung, and Blood Institute's Twin Study. Consistent with hypothesized psychoneurogenetic predispositions for the joint use of these substances, the most parsimonious model fitting these data identified a common genetic latent factor underlying the observed associations between smoking, alcohol, and coffee use in this cohort. This factor, herein called *polysubstance use*, underscores the role of genetic influence on the clustering of these behaviors in the same individual.

Smoking, 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 & Matarazzo, 1984; Swanson, Lee, & Hopp, 1994). Coffee and alcohol consumption are also associated, especially when either substance is used heavily (Istvan & Matarazzo, 1984). These associations have led some to conclude that a common pathophysiologic process may underlie the use of all three substances (Istvan & Matarazzo, 1984; Kaprio & 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 & Matarazzo, 1984), personality models in which an underlying psychological trait or set of traits (e.g., antisocial behavior, depression, or neuroticism) predispose an individual to polysubstance use (Mangan & Golding, 1984), and neural/genetic models in which the various sub-

stances are seen to act and interact on common neural pathways and receptors (Collins, 1990a; Smith et al., 1992; 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 occurred independently of each other. Reviews of this literature indicate the presence of significant genetic variance for both tobacco and alcohol consumption (Hughes, 1986; Pedersen, 1981). Estimates of the proportion of variance attributable to genetic sources for tobacco use 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, Swan, Robinette, & Fabsitz, 1990, 1992; Heath & Martin, 1993; Swan, Carmelli, Rosenman, Fabsitz, & Christian, 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). Other studies have shown the heritability for coffee drinking in male twins to range from .46 to .88 (Carmelli et al., 1990; Kaprio, Koskenvuo, & Sarna, 1981; Partanen, Brunn, & Markkanen, 1966; Pedersen, 1981).

With few exceptions, previous twin studies of the use of these substances have not incorporated their covariance into the underlying genetic model. Our previous analyses (Carmelli et al., 1990; Swan et al., 1990) used a multiple regression approach to adjust the use of one substance for the use of the other in an attempt to deal with this issue. Genetic analyses were then conducted on both the unadjusted and adjusted levels of consumption, yielding evidence for residual genetic contribution to the use of each substance. However, the extent of genetic and environmental overlap between smoking, alcohol, and coffee consumption was not explored.

At present, the genetic and environmental contributions to the joint use of these substances are unknown. The question of genetic commonality in the use of these psychoactive substances takes on added interest in view of the fact that a liability for dependence is well established for alcohol and for tobacco (Collins, 1990b; Department of Health and Human Services [DHHS], 1988). We include coffee drinking in this analysis because caffeine is the most widely consumed psychotropic drug in the world, followed by alcohol and nicotine (Griffiths & Mumford, 1995). Recent studies indicate that caffeine also exhibits features of a psychoactive substance with a potential for dependence (Griffiths & Mumford, 1995; Hughes, Oliveto, Helzer, Higgins, & Bickel, 1992; Nehlig, Daval, & Debry, 1992; Strain, Mumford, Silverman, & Griffiths, 1994). These and other findings have led some authors to conclude that caffeine has a dependence potential under certain conditions (Heishman & Henningfield, 1992) and in certain individuals (Hughes et al., 1991, 1992; Strain et al., 1994).

METHODS

Participants

The National Heart, Lung, and Blood Institute (NHLBI) Twin Study of cardiovascular disease and risk factors was initiated in 1969 with 1,046 male participants (including 514 twin pairs) drawn from the National Academy of Sciences-National Research Council Twin Registry of white male World War II veterans (Feinleib et al., 1977). Twin zygosity was determined by analysis of genetic variants at 22 chro-

mosomal locations, yielding a probability of less than .001 for identical markers at all loci in dizygotic (DZ) twins. A second laboratory examination of this cohort was conducted in 1980–81, in which 76% of the original sample (792 individuals) participated. The average age of the participants in the second examination was 59 years (range = 52–66 years). Characteristics of participants and nonparticipants are described elsewhere (Fabsitz, Kalousdian, Carmelli, Robinette, & Christian, 1988).

Data concerning smoking, alcohol consumption, and coffee intake were obtained as part of a standardized medical interview conducted by two physicians who interviewed twin pairs independently (Swan et al., 1990). For this analysis, continuous measures of substance use were defined as follows: self-reported number of cigarettes ever smoked (past or present) in a typical smoking day; self-reported total number of alcoholic drinks (including beer, wine, and cocktails) per week in a typical week at the time of assessment; number of cups of coffee per day in a typical day at the time of assessment.

Our intent was to follow up the univariate genetic results from our previously published analysis of smoking in this sample (Swan et al., 1990). By doing so, we facilitate the comparison of the results from this analysis with the results from the univariate genetic analyses reported earlier. Smoking has been the subject of a massive public health effort aimed at reducing its prevalence since the appearance of the first Surgeon General's Report in 1964. By contrast, caffeine and alcohol use, although not without documented health consequences, have not received nearly as much attention from the public health field; total abstinence in the use of these substances is not advocated universally. To minimize the effects of smoking cessation on twin pair similarity in lifetime consumption of tobacco, we elected to use present or past reported amount ever smoked in a typical smoking day. This same definition of smoking was used in our previous analysis (Swan et al., 1990).

Information on tobacco, alcohol, and coffee consumption was available for 173 monozygotic (MZ) and 183 DZ twin pair participants in the second cardiovascular examination of this cohort. At the time of assessment, 32% of the sample were never smokers, 23% reported abstinence from alcohol, and 18% reported abstinence from coffee. Including nonusers, who were assigned values of zero, the average amount smoked was 18.7 cigarettes per day (SD = 18.0), the average amount of alcohol consumed was 10.3 alcoholic drinks per week (SD = 13.6), and that for coffee drinking was 3.2 cups of coffee per day (SD = 3.2). As a group, MZ twins smoked an average of 17.4 cigarettes per day (SD = 17.9), drank 10.3 alcoholic drinks per week (SD = 13.6), and drank 3.1 cups of coffee per day (SD = 3.1). Corresponding values for DZ twins were 19.9 cigarettes per day (SD = 18.1), 10.1 alcoholic drinks per week (SD = 13.7), and 3.3 cups of coffee per day (SD = 3.3). Mean levels of consumption did not differ significantly across zygosity. Because of skewness in the distribution of these variables, each was log transformed. In the entire sample, pairwise correlations between these consumption measures were: smoking–alcohol, r = .24, p < .001; smoking–coffee, r = .20, p < .001; and alcohol-coffee, r = .12, p < .001.

With respect to cigarette smoking, we note that the prevalence of ever-smoking in this cohort, 68%, is somewhat less than that for unrelated individuals in a similar birth cohort (80%; DHHS, 1989, p. 300). The average number of cigarettes smoked per day is similar to that for a comparably aged cohort (Stein, Lederman, & Shea, 1993). The

proportion of consumers of alcohol, 77%, is comparable to that for similarly aged un-related individuals (75%; Stein et al., 1993). The average number of drinks per week, 10.3, 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 (80%, Griffiths & Mumford, 1995; 82%, Klag et al., 1994). Assuming an av-erage of 100 mg of caffeine per cup of coffee (Consumers Union, 1994), the level of consumption on a daily basis (320 mg) also appears to be somewhat higher than the level noted for the general US population (235 mg/day; Griffiths & Mumford, 1995) and for a sample of males (230 mg/day; Klag et al., 1994).

Model-fitting Procedures

Multivariate structural equation modeling procedures (Neale & Cardon, 1992) were used to estimate the genetic and environmental contributions to individual dif-ferences in tobacco use, alcohol consumption, and coffee intake. These modeling procedures are extensions of the classical genetic twin model (Falconer, 1990), which draws information about genetic influences on a behavior by comparing the similarity of MZ twins (who are genetically identical) with that of DZ twins (who share on aver-age only half of their segregating genes). In the basic model, the comparison of the intraclass correlations for MZ twins with those of DZ twins is used to estimate the pro-portion of trait variation attributable to additive genetic (A) and environmental (E) factors. Environmental factors are further partitioned into those that are shared by members of a twin pair and contribute to twin similarities (common environmental factors [CE] such as shared family environment while growing up, extent of contact as adult twin brothers, etc.) and those that are specific to individual twins and contribute to twin differences (specific environmental factors [SE] such as work and marital in-fluences that are not shared as adults). A critical assumption of the twin model is that CE influences in MZ twins do not differ from those in DZ twins (Plomin, 1990). The fact that no significant differences in the distribution of smoking, alcohol, and coffee use were observed between MZ and DZ twins supports the tenability of the "equal en-vironments" assumption in this sample (Swan et al., 1990).

The multivariate genetic model estimates the same sources of variation as does the basic model (A, CE, and SE), extending the univariate case of estimating the components of variance to estimating the components of covariance between to-bacco, alcohol, and coffee intake. The objective is to determine the extent of genetic and/or environmental overlap, in addition to substance-specific genetic and/or environmental influences.

This approach involves a model comparison series in which several alternative models are fitted to the data to determine the statistical significance of overlapping and substance-specific A, CE, and SE effects. The general multivariate model from which we began the series of significance tests in this study is referred to as the "independent pathway model" (Kendler, Heath, Martin, & Eaves, 1987). In this model, depicted in Figure 1a, each of the three common factors (A, CE, and SE) has its own path to each of the three substances; thus, *independently* they account for the observed associations.

An alternative to the independent pathway model is the "common pathway model" (Kendler et al., 1987), which views, as in traditional factor analysis, each
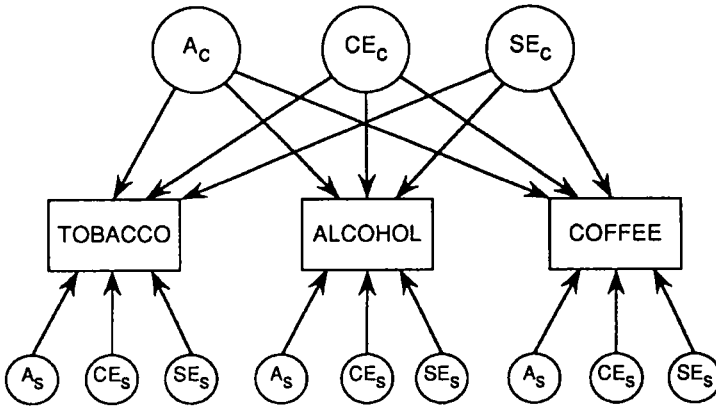
Figure 1a. The full independent pathway model for polysubstance use. Measured variables are contained in boxes; latent variables are shown in circles. *Note:* A_c: additive genetic influences for joint use; CE_c: common environmental influences for joint use; SE_c: specific environmental influences for joint use; A_s: additive genetic influences for use of a specific substance; CE_s: common environmental influences for use of a specific substance; SE_s: specific environmental influences for use of a specific substance. (Adapted from Kendler et al., 1987.)

measure of substance use as an index of a broad latent factor that underlies their joint use. In this model, depicted in Figure 1b, overlapping genetic and/or environmental effects are modeled jointly as a common latent factor rather than as individual factors. As shown in Figures 1a and 1b, both the independent and common pathway models accommodate genetic and environmental effects that do not over-
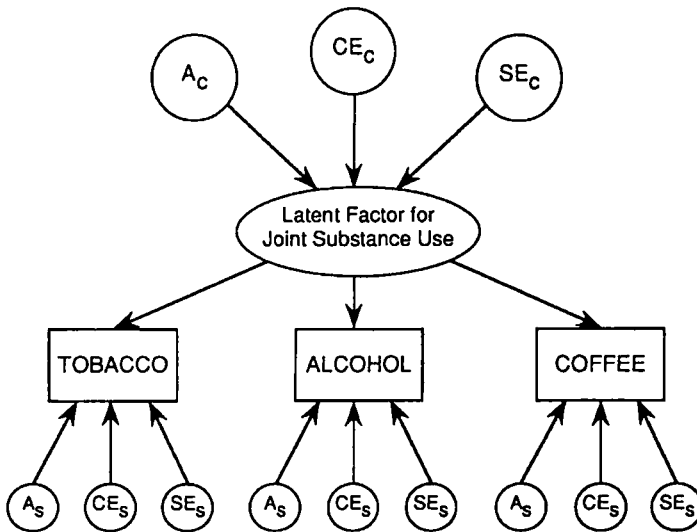

Figure 1b. The full common pathway model for polysubstance use. Measured variables are contained in boxes; latent variables are shown in circles.

lap (i.e., substance-specific effects). The reader should bear in mind that in situations where only one common factor (genetic or environmental) explains the observed associations, the independent and common pathway models are equivalent (Kendler et al., 1987).

In this study, alternative models were fitted to the observed within-twin-pair and cross-substance correlations using the LISREL program (Jöreskog & Sörbom, 1989). This program provides maximum-likelihood estimates of all model parameters and calculates for each model a chi-square goodness-of-fit measure. For tests of statistical significance of submodels involving different combinations of genetic and environmental effects, we systematically omit the corresponding parameters from the model and recalculate the chi-square statistic. Larger p values indicate a better fit to the data. An additional statistic for model evaluation is the Akaike Information Criterion (AIC = $\chi^2 - 2df$, Akaike, 1987), with smaller values (larger negative values) indicating greater parsimony. In this study, we used both the goodness-of-fit index and the parsimony criteria to arrive at the "best-fitting" model.

RESULTS

Table 1 shows the intrapair correlations for the use of each substance and the bivariate cross-substance correlations for the smoking, alcohol, and coffee measures. The upper part of Table 1 represents values for MZ twins, the lower part those for DZ twins. As expected, the intraclass correlations for MZ pairs are higher for each substance than the corresponding DZ intraclass correlations (e.g., for smoking, $r(MZ) = .55$, $r(DZ) = .32$), supporting the presence of genetic influences on each behavior. We also observe that the cross-substance correlations in MZ twins are generally higher than those in DZ twins (e.g., the smoking–alcohol correlation is .29 in MZ pairs and .08 in DZ pairs), in support of the hypothesis that genetic influences underlie joint consumption of tobacco, alcohol, and coffee.

The second part of our analyses consisted of structural modeling procedures fitted to the correlation matrices shown in Table 1. A listing of these models, their goodness-of-fit statistics, the AIC measure of parsimony, along with the likelihood-

Table 1.   Correlations Among Quantity of Smoking, Alcohol Consumption, and Coffee Intake in NHLBI Twins

|	Twin 1		
	Smoking	Alcohol	Coffee
MZ Twins (173 pairs)			
Twin 2: Smoking	.55	.29	.17
Alcohol	.26	.47	.08
Coffee	.01	.10	.34
DZ Twins (183 pairs)			
Twin 2: Smoking	.32	.08	.11
Alcohol	.16	.32	.14
Coffee	.05	−.00	.17

ratio statistic for the comparison of submodels with the full model, are presented in Table 2. The application of the full common pathway model with A, CE, and SE common and substance-specific influences to these data yielded a good initial fit, $\chi^2(28) = 22.64$, $p = .751$ (Model 1a, Table 2). A good fit also was achieved from the application of the full independent pathway model to these data, $\chi^2(24) = 19.28$, $p = .737$ (Model 1b). Thus, both models provide an excellent account of the observed twin covariances shown in Table 1 (recall that the larger the p value, the better the fit). Because of greater parsimony (indicated by a larger negative value of the AIC statistic), the common pathway model is preferred over the independent pathway model (AIC $= -33.36$ and -28.72, respectively). Because these two general models are not nested, we are unable to test the significance of the difference between the two AIC values.

Given that the common pathway model is preferred, we now turn to the testing of individual parameters or submodels. Model comparisons involved a series of statistical significance tests on selected parameters of the full common pathway model. We note initially that CE effects, common and substance-specific (Models 2, 5, 6), do not contribute significantly to goodness of fit when compared with the full common pathway model (Model 1a). Specific environmental influences (SE) also do not exert a detectable impact on the joint use of these substances but do have a substantial impact on residual variance of each substance (Models 3, 5). We notice that additive genetic effects (common and specific) cannot be dropped without significant loss in goodness of fit, as indicated by the significant p values in the comparison of Models 4 and 7 with Model 1a. These effects are important in accounting for a genetic overlap between smoking, alcohol, and coffee use (Model 4) and contribute to the residual variability in the use of each substance (Model 7).

Table 2. Model Comparison Tests of Additive Genetic (A), Common Environmental (CE), and Specific Environmental (SE) Sources of Variation-Covariation in Smoking, Alcohol Consumption, and Coffee Intake

Model	Goodness of Model Fit			Parsimony	Tests of Parameter Significance		
	χ^2	df	p	AIC	Change χ^2[a]	df	p
1a) Full common pathway	22.64	28	.751	−33.36			
1b) Full independent pathway	19.28	24	.737	−28.72			
Testing of Submodels of the Common Pathway Model							
2) No shared CE sources	22.64	29	.793	−35.36	0.00	1	ns
3) No shared SE sources	22.66	29	.792	−35.34	0.02	1	ns
4) No shared A sources	31.80	29	.329	−26.20	9.16	1	<.03
5) No shared CE & SE	22.66	30	.829	−37.34	0.02	2	ns
6) Model 5 & no CE trait-specific sources	24.83	33	.846	−41.17	2.17	3	ns
7) Model 5 & no A & CE trait-specific sources	87.60	36	.000	15.60	64.94	6	<.001

[a]"Change in χ^2" refers to the difference in χ^2 values for each model in comparison to that for model 1a.
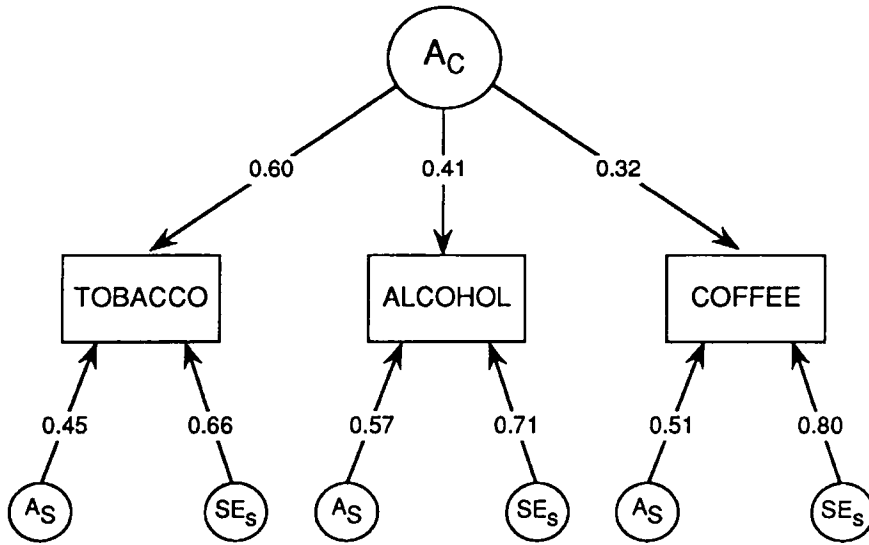
Model $\chi^2(33) = 24.83$, $p = .846$, AIC = -41.17

Figure 2. Path diagram of best-fitting model of tobacco, alcohol, and coffee use. Measured variables are contained in boxes; latent variables are shown in circles (A_c: additive genetic influences for joint use; A_s: additive genetic influences specific to the use of each substance; SE_s: environmental influences specific to the use of each substance). Parameter estimates listed adjacent to causal pathways reflect the relative impact of genes and the environment on variation and covariation among the observed measures. These parameter estimates represent standardized factor loadings which may be squared to reveal the proportional influence of the respective additive genetic (A), common environmental (CE), or specific environmental (SE) effect.

   In summary, the tests of parameter significance converge to a model that is equivalent to a common pathway genetic model. The best-fitting and most parsimonious model is Model 6, $\chi^2(33) = 24.83$, $p = .846$, AIC = -41.17. Parameter estimates from the best-fitting model are presented in Figure 2. In the best-fitting model of these data, variation in the latent common factor is determined by genetic influences (i.e., the observed association in joint consumption of tobacco, alcohol, and coffee is due to common genetic influences). However, the presence of significant substance-specific genetic influences implies that the observed twin correlations in smoking, alcohol, and coffee consumption also are determined by genetic influences acting independently from those that link all three behaviors.

   Table 3 presents the additive genetic and specific environmental proportions of variation for each measure and the latent factor as derived from parameter estimates in Figure 2. Smoking, alcohol, and coffee use all exhibit significant heritable variation, with additive genetic variance proportions (the sum of genetic variance attributable to both the common factor and the specific substance) ranging from 36% to 56%. These estimates provide evidence for the influence of common genes

Table 3.   Percent of Variation in Cigarette Smoking, Alcohol
Consumption, and Coffee Intake Attributable to Genetic and
Environmental Sources

| | Genetic Variance | | |
| | Common Factor for Joint Use | Substance-Specific | Environmental Variance |
Substance			
Tobacco	36%	20%	44%
Alcohol	17%	32%	50%
Coffee	10%	26%	64%

on the consumption of all three substances, particularly with respect to smoking, where 64%[1] of the heritable variation is shared with the alcohol and coffee measures. For alcohol and coffee consumption, 35%[2] and 28%[3] of the heritable effects are shared, respectively.

Correlations among the additive genetic influences (r_g) also may 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 heritabilities. 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. For example, a higher genetic correlation is seen between smoking and alcohol consumption ($r_g = .47$, calculated as $(.60 \times .41)/(\sqrt{.56} \times \sqrt{.49})$) than between smoking and coffee intake ($r_g = .43$); the smallest genetic correlation was estimated between alcohol and coffee consumption ($r_g = .31$). Because these are all significantly different from zero, they support the conclusion of genetic overlap in the etiology of these three behaviors.

DISCUSSION

Consistent with previous genetic analyses of this twin cohort (Carmelli et al., 1990; Swan et al., 1990), significant heritabilities were obtained for smoking (56%), alcohol consumption (50%), and coffee consumption (36%). Also consistent with a hypothesized common process underlying the use of all three substances, the most parsimonious, best-fitting model derived from our analyses suggests a common etiology for smoking, alcohol, and coffee use. Our finding of shared genetic effects agrees with a hypothesized common genetic pathway for the use of these substances. The finding of common genetic influence on smoking, alcohol, and coffee use has not, to our knowledge, been reported.

Our conclusion that a common factor underlies the joint use of alcohol, tobacco, and coffee is consistent with the findings from a recent population-based investigation of the co-occurrence of substance use among drug abusers (Kozlowski et al.,

[1] $0.64 = (.60)^2/((.45)^2 + (.60)^2)$
[2] $0.35 = (.41)^2/((.57)^2 + (.41)^2)$
[3] $0.28 = (.32)^2/((.51)^2 + (.31)^2)$

1993). These authors found that whereas the severity of alcoholism was directly related to the use of tobacco and caffeinated beverages, tobacco and caffeine consumption were not associated with the use of other drugs of abuse, such as heroin. The authors concluded, as do we, that joint use of nicotine, coffee, and alcohol may be governed by similar factors.

Although these findings suggest that the covariance in the use of these substances results from common genes, it is important to note that residual genetic variance specific to the use of each substance also was identified by this analysis. The findings reveal that much of the genetic variation in each behavior is substance-specific, accounting for 36%,[4] 65%,[5] and 72%[6] of the total heritabilities in smoking, alcohol, and coffee use, respectively. This pattern of results also is consistent with research in animal models showing that, although gene products responsible for the regulation of ethanol sensitivity also regulate sensitivity to nicotine (Collins, 1990c), there remain unique genetic components that regulate sensitivity to each substance separately (de Fiebre, Marks, & Collins, 1990).

The fact that no common environmental variance was observed to contribute to the hypothesized polysubstance use factor may be a result of the fact that these twins were middle-aged at the time of examination, which occurred approximately 25 to 30 years after the time they were in the armed forces during World War II. Had this analysis been conducted on data collected closer to the time when both twins were in the armed forces and experiencing a unique and very strong common environmental influence to use these substances, the results might well have been different. An interesting direction for future research would be to determine the extent to which a common environmental source of variance is identifiable in models derived from twins who are younger and, therefore, more likely to be closer in time to the effects of having been reared in a common environment.

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 participants in this study had a strong motivation to underreport their level of smoking, drinking, or coffee use, the use of a 7-day diary of consumption would have resulted in more accurate assessment of true levels and possibly even larger estimates of genetic variance. Second, the analysis used in this study relied on an assessment of coffee use as our 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 are confounded to some extent with measurement error. Fourth, this was an analysis of the joint use of tobacco, alcohol, and coffee over the entire range of consumption. Because the etiology of the abuse of these substances may be quite different from that for usual consumption, caution is urged in extrapolating these

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[4] $0.36 = (.45)^2/((.60)^2 + (.45)^2)$

[5] $0.65 = (.57)^2/((.41)^2 + (.57)^2)$

[6] $0.72 = (.51)^2/((.32)^2 + (.51)^2)$

results to heavy, addictive polysubstance use. Fifth, because there is some evidence to suggest that women are different from men with respect to substance use (Grunberg, Winders, & Wewers, 1991; Lex, 1991), it would be of great interest to repeat these analyses in a female twin cohort.

The NHLBI Twin Study is composed of twin pairs of which both members 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 this 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 this cohort demonstrated that heavy smokers and drinkers, in fact, were less likely to volunteer to participate in the study (Fabsitz et al., 1988). Again, we believe that the effect of this bias in the sample would lead to an underestimation of the observed genetic variance.

It is important to point out that unassessed variables that quite plausibly underlie the joint use of these substances include psychological and physiological reactions to stress and environmental pressure. One such reaction could be depression. Associations between depression and different facets of smoking (Hall, Munoz, Reus, & Sees, 1993; Hemenway, Solnick, & Colditz, 1993), alcohol use (Berger & Adesso, 1991; Greeley, Swift, & Heather, 1992; Hartka et al., 1991), and caffeine consumption (Leibenluft, Fiero, Bartko, Moul, & Rosenthal, 1993) have been established. 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, Heath, Neale, Kessler, & Eaves, 1993) and to smoking and depression (Kendler et al., 1993). To date, the genetic association between caffeine use and depression remains untested, as far as we know.

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