

RESEARCH REPORT

Lifetime tobacco, alcohol and other substance use in adolescent Minnesota twins: univariate and multivariate behavioral genetic analyses

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Abstract

Aims. We sought to estimate the contribution of genetic and environmental factors to adolescent tobacco, alcohol and other substance use. **Design, setting and participants.** The sample consisted of 327 monozygotic and 174 like-sex dizygotic twin pairs born in Minnesota and aged 17–18 years at time of assessment. Biometrical methods were used to estimate the contribution of additive genetic, shared and non-shared environmental factors to adolescent substance use. **Measurements.** As part of a day-long psychological assessment, adolescent twins completed a computerized substance use interview to determine whether they had ever used tobacco, alcohol or other illicit drugs. **Findings.** The heritability for the liabilities to tobacco, alcohol and other drug use was estimated to be 59%, 60% and 33% among males, and 11%, 10% and 11% among females. However, the gender difference was not statistically significant. Estimates of shared environmental effect were substantial and insignificantly higher among females (71%, 68% and 36%, respectively) than among males (18%, 23% and 23%, respectively). The covariation among the three substance use phenotypes could be accounted for by a common underlying substance use factor. Estimates of the contributions of genetic, shared environmental and non-shared environmental factors to variance in this factor were 23% 63% and 14%, respectively. **Conclusions.** These findings add to the growing behavioral genetic literature indicating that adolescent initiation of substance use, a powerful predictor of adult substance use diagnosis, is influenced primarily by environmental rather than genetic factors.

Introduction

Problems associated with substance use have been of interest to researchers not only because extreme patterns of substance use are psychiatric disorders in their own right, but also because even moderate levels of substance use may represent an epidemiological risk factor for a wide array of health problems (Segal & Stewart, 1996). Investigation of genetic influences on substance use can provide insights into its origins

and thus may be of help in designing effective prevention and intervention measures.

Alcohol use

There is substantial twin study literature on substance use and abuse in adulthood, and this literature consistently implicates the importance of genetic factors during this developmental period. For alcohol dependence and alcohol abuse,

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adult twin studies tend to find moderate genetic effects among males but modest ones among females; shared environmental factors (i.e. those environmental factors that are shared by reared together relatives and thus a source of their behavioral similarity) may also influence alcoholism risk in adulthood (McGue, 1994, 1995). Genetic factors have also been consistently found to contribute to individual differences in the quantity and frequency of alcohol drinking among adults (heritability estimates, i.e. the proportion of variance associated with genetic factors, have generally fallen in the 0.40–0.60 range), although the evidence for shared environmental effects has been less consistent (Heath, 1995).

The finding of significant heritable influences on adult alcohol use and abuse may not generalize to adolescence, where the importance of peer and contextual factors may attenuate genetic effects. The evidence regarding genetic and environmental influences on adolescent alcohol use is, however, both limited and inconsistent. In a sample of socio-economically advantaged late-adolescent twin pairs, Loehlin (1972) reported similar monozygotic (MZ) and dizygotic (DZ) twin correlations for alcohol use, suggesting little genetic influence; but significantly greater MZ than DZ correlation for excessive alcohol use, suggesting the existence of a genetic effect. In a retrospective study of adolescent alcohol use in a large Australian twin sample, Heath & Martin (1988) reported a substantial genetic influence on drinking status for both males and females. In a separate study of Australian adolescent twins, a genetic influence on alcohol use was found in males but not females (Hopper *et al.*, 1992). In a Dutch study, however, the MZ correlation for alcohol use was higher than the DZ correlation in female twins but not in male twins (Koopmans *et al.*, 1993). Another report from the same project suggested that the relative strength of genetic and environmental influences could change even within adolescence. Additive genetic factors and shared environmental factors were estimated to account, respectively, for 34% and 58% of the variance in alcohol use liability among 15–16-year-olds, but 43% and 37% among those 17 and older (Koopmans & Boomsma, 1996). Although the existing research literature is not entirely consistent, it does suggest that age and gender may be important moderators of the strength of genetic and

environmental influences on alcohol use and abuse.

Tobacco use

Twin studies of tobacco use in adult populations have generally found evidence for the existence of genetic influences, with heritability estimates often, but not always, being higher for men than women. As with alcohol use among adults, the evidence for shared environmental effects on tobacco use is inconsistent (Heath & Madden, 1995). For example, shared environmental effects were significant among Swedish (Medlund *et al.*, 1977) and Finnish (Kaprio *et al.*, as cited in Heath & Madden, 1995) adult twins, but non-significant among Danish twins (Raaschou-Nielson, 1960) and the United States National Academy of Sciences-National Research Council Twin Registry adult twins (Carmelli *et al.*, 1992). Moreover, among Australian twins (Hannah, Hopper & Mathews, 1985; Heath & Martin, 1993) and twins in the Virginia Twin Register in the United States (Heath *et al.*, 1993), shared environmental effects were significant in females but not in males. This inconsistent pattern of findings concerning the importance of shared environmental influences on tobacco use may be due to a failure to distinguish smoking initiation from smoking persistence. Heath & Madden (1995) reported that, while genetic factors appear to influence both smoking phenotypes, shared environmental factors appeared to be substantial only for smoking initiation.

Only two twin studies of tobacco use in adolescence have been published. Among adolescent Dutch twins, 59% of the variance in liability to initiate smoking was estimated to be due to shared environmental influences and 31% to additive genetic effects (Boomsma *et al.*, 1994). Hopper *et al.* (1992) reported a higher odds ratio for smoking initiation (indicating greater similarity) among MZ as compared to DZ adolescent Australian twins, but their non-parametric analysis did not allow for quantification of the strength of genetic and environmental influences.

Other drug use

Twin studies on the use of other drugs by adults have been relatively rare (Pickens & Sviki, 1991;

Comings, 1996). In a study of MZ twins reared apart, heritability of substance abuse/dependence was estimated as 0.46 (Grove *et al.*, 1990). Pickens *et al.*, (1991) reported that for any drug use disorder (other than alcohol or tobacco), the MZ concordance rate was significantly higher than the DZ concordance rate among male twins, but not among female twins. Genetic and shared environmental effects were estimated to account for 0.31 and 0.51 of the liability variance in males and 0.22 and 0.07 in females, respectively. In a large study of male twin veterans, Tsuang *et al.* (1996) also reported significantly greater MZ than DZ twin concordance for drug use disorder, with genetic factors accounting for 34% and shared environmental factors 28% of the total liability variance. Finally, in a recent report of a twin study on non-alcohol, non-tobacco substance use, Gynther *et al.* (1995) reported that either the genetic or the shared environmental component of variance, but not both, could be removed from a model of twin resemblance without a statistically significant decrement in fit. Both genetic and shared environmental factors were estimated to account for slightly less than one-fourth of variance in drug use liability.

Only one twin study has investigated the heritability of illicit drug use in an adolescent sample. In a large sample of adolescent twins from Virginia, Maes *et al.* (1998) reported that genetic factors accounted for 45% and shared environmental factors for 47% of the variance in liability to having ever used an illicit drug other than alcohol or tobacco.

Covariance among substance use phenotypes

As consumptive behaviors are interrelated (e.g. Istvan & Matarazzo, 1984), it is interesting to investigate genetic and environmental contributions to not only the variance of the various substance use phenotypes, but also to the covariance among them. Swan *et al.* (1996) posited the existence of a single latent factor underlying tobacco, alcohol and coffee use. This common pathway model provided an adequate fit to their data on adult male twins, with a substantial proportion of the genetic effect on each phenotype being accounted for by the common factor. Swan *et al.* (1997) also postulated a model with two latent variables, namely, Heavy-Smoking-Heavy-Alcohol-Drinking and Heavy-Smoking-Heavy-Coffee-Drinking. Their results suggest a

set of genetic and environmental factors underlying joint heavy use of tobacco and alcohol. In a Dutch twin sample, Koopmans *et al.* (1997) found that the relationship between alcohol use and tobacco use was mediated largely by shared environmental factors in adolescents aged 12 to 16 years but genetic factors in young adults aged 17–25 years. As to substance use problems, Jang, Livesley, and Vernon (1995) postulated a less restrictive model of liabilities to alcohol and drug problems. Their results suggested that the covariation of alcohol and drug problems was largely due to a non-shared environmental factor common to both domains. On the other hand, common genetic mechanisms in alcohol and drug disorder have also been suggested (Pickens *et al.*, 1995; Johnson *et al.*, 1996).

Summary and overview of the present study

In summary, while adult studies are consistent in implicating genetic factors in substance use phenotypes, adolescent studies have not always found evidence of significant heritability. Some of this inconsistency may owe to low statistical power and limitations in assessment methodology (for example, retrospective versus contemporaneous). Alternatively, the inconsistent evidence for genetic influences on adolescent substance use may be due to weaker heritable effects at that age than in adulthood. Early substance use initiation may primarily reflect the influence of peer group, and social context. If so, we might expect that heritable influences on substance use would be weaker, and shared environmental effects stronger, in adolescence than in adulthood.

Our review of the literature also suggests that gender may moderate the heritability of substance use phenotypes in adolescence (heritability being stronger in males than females), and that there might be a common genetic liability underlying use of multiple substances. In order to explore questions concerning these issues, we undertook an investigation of the inheritance of contemporaneously assessed substance use phenotypes in an epidemiological sample of like-sex, reared-together adolescent twins. Specifically, the following questions were addressed: (1) to what extent do genetic and shared environmental factors contribute to variance in substance use liability in adolescence, (2) is the strength of genetic and environmental influences moderated by gender and (3) can the covariance among

substance use phenotypes be accounted for by a single common factor?

Methods

Participants

The sample is comprised of volunteer twin pairs participating in the Minnesota Twin Family Study, a longitudinal study of adolescent twins and their families. The twin participants in the present study were born in the state of Minnesota and aged 17–18 years at intake assessment. Twins were ascertained from birth records. The study was able to locate approximately 90% of twin births, with less than 20% of the located twins who met study eligibility requirement (that is, living within one day's drive of Minneapolis, Minnesota and having no physical or mental handicap that would preclude assessment) refusing to complete the intake assessment. In a comparison of participating and non-participating families on a brief assessment completed by telephone or through the mail, we found no significant differences in parents' self-reported treatment for alcoholism, drug abuse or depression, although parents from participating families were somewhat better educated than non-participating parents (less than 0.5 years on average). More detailed information on the design of the Minnesota Twin Family Study can be found in Iacono, Lykken & McGue (1996) and McGue, Lykken & Iacono (1996).

The sample in the present study included 179 MZ male, 97 DZ male, 148 MZ female and 77 DZ female twin pairs. The excess of MZ relative to like-sex DZ twins in the present sample reflects, in part, the population distribution of the two types of twins for the birth years sampled (Hur, McGue & Iacono, 1995).

Zygosity was determined from four sources of information. These included a zygosity questionnaire completed by the parents of the twins, an experimenter diagnosis of zygosity based on the evaluation of the physical similarity of the twins by an experienced staff member and a diagnosis of zygosity based on ponderal index, cephalic index and fingerprint ridge count. In the case of discrepancy among the first three methods, blood was drawn from both members of the pair and zygosity was determined through analysis of 12 blood group antigens and protein polymorphisms. In an analysis of 50 twin pairs, we found that a consensus among the questionnaire, ex-

perimenter diagnosis and physical similarity methods was always confirmed by serological analysis.

Measures

As part of a day-long in-person intake assessment, a computerized substance use and abuse questionnaire was self-administered to the adolescent twins, without the presence of any interviewer. The phenotypes analyzed here were: life-time tobacco use and life-time alcohol use (the latter without parental permission), both dichotomized as ever versus never used; life-time drug use, dichotomized such that a participant would have a positive score if he or she had ever used marijuana, or ever used stimulants, tranquilizers, Quaaludes, cadrones, inhalants, non-prescription (NoDoz, Sominex, etc.), cocaine, psychedelics or opiates to get high. No quantity or frequency threshold was given to the participants when they were asked whether they had ever used each of the substances. Thus, we are in effect investigating the nature of adolescent life-time use versus abstinence.

Statistical analysis

Twin data were analyzed using standard biometrical methods, the details of which can be found in Neale & Cardon (1992). Prior to model fitting, MZ and DZ prevalences and tetrachoric correlations of the substance use phenotypes were examined within genders.

Calculation of tetrachoric correlations assumes that there is a continuously and normally distributed latent construct, namely liability, underlying the dichotomous observed trait, with a threshold distinguishing users from non-users (Heath *et al.*, 1989; Falconer & Mackay, 1996). Comparison of MZ and DZ correlations is informative partly in that it may provide evidence for non-additive genetic effects. That is, an MZ correlation greater than twice the DZ correlation implies a non-additive genetic effect.

In the absence of non-additive genetic factors, biometrical genetics assumes that the variance in a quantitative phenotype (P) can be decomposed into three components, namely, one associated with additive genetic factors (A), one associated with the environmental factors that are shared by reared-together relatives (C) and one associated with the environmental factors that are not

shared by reared-together relatives (E). Symbolically, this can be expressed as:

$$V_P = V_A + V_C + V_E,$$

where V_P , V_A , V_C and V_E , represent the total variance in the phenotype, and the variance components due to additive genetic, shared environmental and non-shared environmental factors, respectively. Dividing both sides of the equation by the total phenotypic variance gives

$$1 = \frac{V_A}{V_P} + \frac{V_C}{V_P} + \frac{V_E}{V_P}.$$

Usually, it is defined that $a^2 = \frac{V_A}{V_P}$, which is often called heritability or narrow-sense heritability; $c^2 = \frac{V_C}{V_P}$, and $e^2 = \frac{V_E}{V_P}$.

In a classical twin study where like-sex, reared-together MZ and DZ twins are involved, the biometrical model gives;

$$r_{MZ} = a^2 + c^2$$

$$r_{DZ} = 0.5a^2 + c^2$$

$$1 = a^2 + c^2 + e^2$$

where r_{MZ} and r_{DZ} represent the phenotypic correlation between MZ and DZ twins, respectively. Thus, under the assumptions of the biometric model, a twin study allows us to estimate the three components of phenotypic variance.

In univariate genetic analysis, the model fitting procedure was based on two-way contingency tables (twin 1 \times twin 2). More specifically, the computer program Mx (Neale, 1997) was used to fit various genetic models to the observed contingency tables. The data were modeled in terms of the three parameters, A, C and E. After gender-specific models had been fitted, gender-invariant models were also fitted. In order to test the significance of individual parameters, likelihood ratio tests comparing a more constrained model with a less constrained model were performed. Confidence intervals (95%) for the parameters were calculated using a likelihood-based method (Neale & Miller, 1997).

As there were three potentially interrelated phenotypes, multivariate analysis was also performed. In multivariate genetic analysis, a common pathway model (Kendler *et al.*, 1987; Neale & Cardon, 1992) of tobacco, alcohol and drug

use was posited. In this model, it is hypothesized that the covariation among the substance use phenotypes is determined by a single latent variable which has phenotypic paths to the three substance use phenotypes. Genetic and environmental factors influence this latent variable, and the specific phenotypes as well. The path diagram for the initial specification of the common pathway model is shown in Fig. 1.

In fitting this multivariate model, 6×6 tetrachoric correlation matrices (3 traits for twin 1 and 3 for twin 2) and 15×15 asymptotic covariance matrices for these tetrachoric correlations ($6 \times 5/2 = 15$ subdiagonal elements in each correlation matrix) were computed separately for MZ male, DZ male, MZ female and DZ female twin pairs, using the computer program PRELIS 2 (Jöreskog & Sörbom, 1996b). These matrices were then used as input to LISREL 8 (Jöreskog & Sörbom, 1996a) for gender-specific and gender-invariant model fitting.

To assess model fit, Akaike Information Criterion (AIC; Akaike, 1983) was considered. AIC is defined as $\chi^2 - (2 \times \text{df})$ and is a measure of both fit and parsimony. Since a fully saturated model has a χ^2 of 0 with 0 degrees of freedom, a negative AIC reflects a good fit (Neale *et al.*, 1989). In both univariate and multivariate analyses, best-fitting models were defined by that model that had the smallest (negative) AIC.

Results

Table 1 gives the prevalences and tetrachoric correlations of the substance use phenotypes by gender and zygosity. None of the prevalence differences between MZ and DZ twins was significant. All the MZ correlations were less than twice the corresponding DZ correlations, so there was no evidence for non-additive genetic effects. Based on these preliminary analyses, the baseline model for univariate model fitting was a model containing an additive genetic effect (A), a shared environmental effect (C) and a non-shared environmental effect (E), which is often referred to as the ACE model. Subsequently, AE, CE and E models were also fitted to the data.

Table 2 gives the variance component estimates in the univariate models. For each of the three substance use phenotypes, according to the gender specific ACE models, heritability estimates were substantial for males but modest for

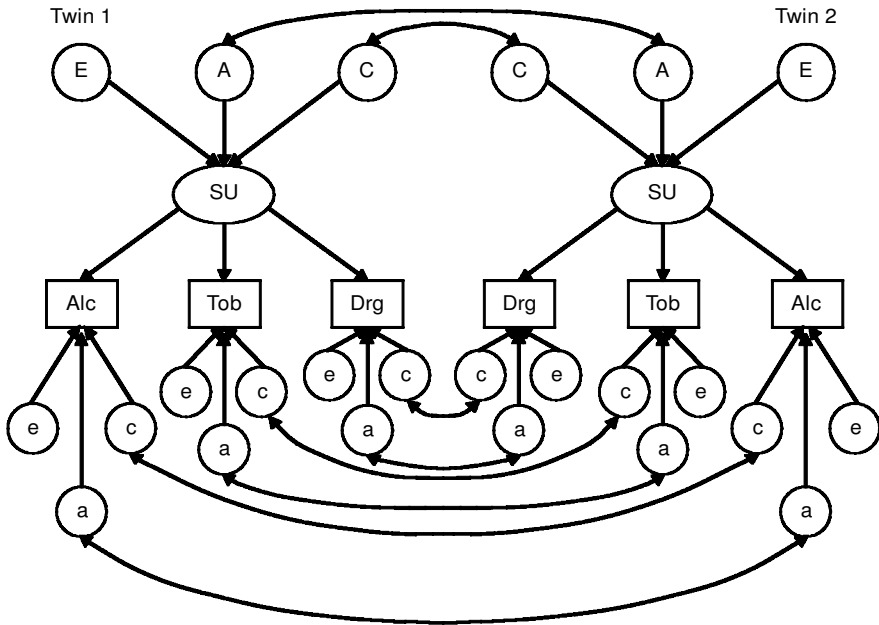


Figure 1. The initial specification of the common pathway model. “SU” is the phenotypic factor underlying the liabilities to tobacco, alcohol and other drug use; “Tob”, “Alc” and “Drg” stand for the liabilities to tobacco use, alcohol use and drug use, respectively; “A”, “C”, “E” and “a”, “c”, “e” represent the additive genetic, shared environmental and non-shared environmental factors at the general and specific level, respectively.

females. Alternatively, for all three phenotypes, the shared environmental component was large for females but small for males. Despite the large difference in estimates from the gender-specific models, however, for each phenotype an ACE model that constrained parameter estimates to be equal in the two genders (the gender-invariant model) fitted the data well and did not result in a significant decrement in fit as compared to the unconstrained model.

Under the gender-invariant ACE model, heritability estimates were moderate for both tobacco ($a^2 = 0.36$) and alcohol ($a^2 = 0.35$) use, and somewhat lower for drug use ($a^2 = 0.23$). Estimates of shared environmental effects were substantial for both tobacco ($c^2 = 0.44$) and alcohol ($c^2 = 0.46$) use, but also somewhat lower for drug use ($c^2 = 0.29$), leaving non-shared environmental effects to account for nearly half the variance in drug use ($e^2 = 0.48$), but less than a quarter of the variance in both tobacco ($e^2 = 0.21$) and alcohol ($e^2 = 0.19$) use.

The gender-invariant ACE, AE and CE models were all fitted to the data and the best-fitting

model identified using the AIC. The best-fitting model was the ACE model for tobacco use and alcohol use and the CE model for other drug use.

The multivariate genetic analyses were based on the tetrachoric correlation matrices given in Table 3. The first step in these analyses was the fitting of gender-specific common-pathway models. The baseline model included additive genetic, shared and non-shared environmental effects on the common liability factor as well as on each of the specific liabilities. From Table 4 it can be seen that in terms of having a relatively low AIC, but not by p -value, the general model gave a relatively good fit to both the male and female data. In the modification process, the A or C effects, or both, were removed from the general and specific levels simultaneously. In both males and females removing all genetic effects resulted in more parsimonious fits, as indicated by AIC.

The second step in the multivariate model fitting involved fitting gender-invariant common pathway models. This step started with fitting a

Table 1. Prevalence and tetrachoric correlation of ever having used tobacco, alcohol, or other drugs in twins aged 17–18

Phenotype	Number of pairs		Prevalence (%)			Tetrachoric correlation	
	MZ	DZ	MZ	DZ	Total	MZ	DZ
Male							
Tobacco	176	96	55.1	58.3	56.3	0.78	0.49
Alcohol	179	97	73.5	79.4	75.5	0.84	0.57
Drugs	178	97	45.2	50.5	47.1	0.56	0.40
Female							
Tobacco	148	77	49.7	59.7	52.9	0.83	0.76
Alcohol	148	77	68.9	74.7	70.9	0.79	0.72
Drugs	148	76	51.7	59.9	54.5	0.47	0.41

gender-invariant model that included all general and specific genetic, shared and non-shared environmental effects. Table 4 gives the fit statistics for the gender-invariant as well as the gender-specific multivariate models. As was the case with the univariate models, the gender-invariant models fit the data better than the gender-specific models, so the discussion will focus on the former rather than the latter.

The variance component estimates in the multivariate ACE models are summarized in Table 5. In the gender-invariant multivariate ACE model, it was estimated that 23% of the variance in the common substance use latent factor was accounted for by genetic effects, 63% by shared environmental effects and 14% by non-shared environmental effects. The genetic component of the common factor was estimated to account for 22% of the liability variance for tobacco use, 19% for alcohol use, but only 6% for other drug use. The specific genetic contributions to the substance use phenotypes were 2%, 0% and 30% for tobacco use, alcohol use and other drug use, respectively. The general and specific shared environmental effects accounted for 59% and 0%, 53% and 11% and 18% and 4% of the variance in tobacco use, alcohol use and other drug use, respectively. The general and specific shared environmental effects accounted for 59% and 0%, 53% and 11% and 4% of the variance in tobacco use, alcohol use and other drug use, respectively. As to the non-shared environmental effects, the most notable estimate was for the specific non-shared environmental effect for drug use, which accounted for 37% of the total variance. Figure 2 gives the parameter estimates in the gender-invariant multivariate ACE model.

For the gender-invariant multivariate model, removing all additive genetic effects simultaneously resulted in a non-significant increase in χ^2 ($\Delta\chi^2 = 5.13$, $df = 4$, $p = 0.27$), whereas deletion of the shared environmental components did result in a significant increase in χ^2 ($\Delta\chi^2 = 28.93$, $df = 4$, $p < 0.001$).

Discussion

Both MZ and DZ adolescent twins showed significant resemblance in substance use. Univariate behavioral genetic analyses of the substance use phenotypes suggested genetic factors might play a more important role in male adolescents than in female adolescents. The univariate gender-specific ACE models showed that the additive genetic factors accounted for an estimated 59%, 60% and 33% of the variance in liability to tobacco, alcohol and other drug use in males, but only 11%, 10% and 11% in females. This observed difference is consistent with a study of Australian adolescents that reported heritability of alcohol use liability of 0.47 in males and 0.35 in females (Heath & Martin, 1988). Despite their magnitude, the differences in heritability estimates in the present sample were not statistically significant, as constraining parameter estimates to be equal did not result in a significant increase in χ^2 . The common heritability estimates were 0.36, 0.35 and 0.23, respectively. This non-significance of the differences is probably due, in part, to the low statistical power associated with the analysis of categorical data (Neale, Eaves & Kendler, 1994). Although we fail to confirm gender differences in heritability, our findings are certainly suggestive

Table 2. Variance component estimates in the univariate ACE, AE, and CE models

Model	Estimate			χ^2	df	p-value	AIC
	a^2	c^2	e^2				
Male							
Tobacco							
ACE	0.59 (0.05,0.87)	0.18 (0.00,0.66)	0.23 (0.13,0.37)	1.51	3	0.68	-4.50
AE	0.78	—	0.22	1.92	4	0.75	-6.08
CE	—	0.68	0.32	6.16	4	0.19	-1.84
Alcohol							
ACE	0.60 (0.04,0.92)	0.23 (0.00,0.74)	0.17 (0.08,0.30)	6.76	3	0.08	0.76
AE	0.84	—	0.16	7.26	4	0.12	-0.74
CE	—	0.75	0.25	11.22	4	0.02	3.22
Drugs							
ACE	0.33 (0.00,0.72)	0.23 (0.00,0.63)	0.44 (0.28,0.64)	1.98	3	0.58	-4.02
AE	0.58	—	0.42	2.57	4	0.63	-5.43
CE	—	0.50	0.50	2.97	4	0.56	-5.03
Female							
Tobacco							
ACE	0.11 (0.00,0.63)	0.71 (0.21,0.88)	0.18 (0.09,0.31)	5.21	3	0.16	-0.79
AE	0.84	—	0.16	12.13	4	0.02	4.13
CE	—	0.80	0.20	5.45	4	0.24	-2.55
Alcohol							
ACE	0.10 (0.00,0.74)	0.68 (0.07,0.86)	0.22 (0.11,0.38)	3.47	3	0.32	-2.53
AE	0.80	—	0.20	8.11	4	0.09	0.11
CE	—	0.76	0.24	3.62	4	0.40	-4.38
Drugs							
ACE	0.11 (0.00,0.65)	0.36 (0.00,0.61)	0.53 (0.34,0.73)	3.42	3	0.33	-2.58
AE	0.50	—	0.50	4.46	4	0.35	-3.54
CE	—	0.45	0.55	3.50	4	0.48	-4.50
Gender invariant							
Tobacco							
ACE	0.36 (0.00,0.77)	0.44 (0.05,0.75)	0.21 (0.13,0.30)	9.80	8	0.28	-6.20
AE	0.81	—	0.19	14.62	9	0.10	-3.39
CE	—	0.74	0.26	13.74	9	0.13	-4.26
Alcohol							
ACE	0.35 (0.00,0.82)	0.46 (0.01,0.79)	0.19 (0.12,0.29)	11.60	8	0.17	-4.40
AE	0.82	—	0.18	15.56	9	0.08	-2.45
CE	—	0.76	0.24	14.84	9	0.10	-3.16
Drugs							
ACE	0.23 (0.00,0.64)	0.29 (0.00,0.58)	0.48 (0.35,0.63)	5.83	8	0.67	-10.18
AE	0.54	—	0.46	7.40	9	0.60	-10.60
CE	—	0.48	0.52	6.66	9	0.67	-11.34

The letters A, C and E refer to the components included in the model, with A representing the additive genetic, C representing the shared environmental and E representing the non-shared environmental component. a^2 , c^2 and e^2 represent the variance components associated with additive genetic, shared environmental, and non-shared environmental factors, respectively. The 95% confidence limits in the ACE models are given in the parentheses below the estimates.

Table 3. Tetrachoric correlations among the substance use phenotypes

	Twin 1 tobacco	Twin 1 alcohol	Twin 1 drugs	Twin 2 tobacco	Twin 2 alcohol	Twin 2 drugs
Male						
Twin 1 tobacco	1.00	0.91	0.70	0.50	0.27	0.59
Twin 1 alcohol	0.85	1.00	0.57	0.42	0.56	0.25
Twin 1 drugs	0.39	0.29	1.00	0.33	0.01	0.41
Twin 2 tobacco	0.78	0.75	0.31	1.00	0.44	0.52
Twin 2 alcohol	0.73	0.84	0.35	0.82	1.00	0.36
Twin 2 drugs	0.25	0.37	0.55	0.30	0.39	1.00
Female						
Twin 1 tobacco	1.00	0.75	0.24	0.75	0.54	0.53
Twin 1 alcohol	0.89	1.00	0.39	0.52	0.71	0.50
Twin 1 drugs	0.45	0.44	1.00	0.10	0.34	0.41
Twin 2 tobacco	0.83	0.73	0.27	1.00	0.79	0.56
Twin 2 alcohol	0.75	0.79	0.23	0.89	1.00	0.45
Twin 2 drugs	0.28	0.32	0.47	0.33	0.38	1.00

In each matrix, the elements below the main diagonal are MZ correlations and those above the main diagonal are DZ correlations.

Table 4. Fit statistic for gender-specific and -invariant common pathway model fitting

Model	χ^2	df	p_{χ^2}	AIC	$\Delta\chi^2$	Δdf	$p_{\Delta\chi^2}$
Male							
ACE	40.60	19	0.003	2.60	—	—	—
AE	49.02	23	0.001	3.02	8.42	4	0.08
CE	46.81	23	0.002	0.81	6.21	4	0.18
E	620.76	27	0.000	566.76	580.16	8	0.000
Female							
ACE	10.52	19	0.94	-27.48	—	—	—
AE	32.06	23	0.10	-13.94	21.54	4	0.000
CE	10.98	23	0.98	-35.02	0.46	4	0.98
E	428.94	27	0.000	374.94	418.42	8	0.000
Gender-invariant							
ACE	58.69	49	0.02	-39.31	—	—	—
AE	87.62	53	0.002	-18.38	28.93	4	0.000
CE	63.82	53	0.15	-42.18	5.13	4	0.27
E	1061.36	57	0.000	947.36	1002.67	8	0.000

The variance components were the same at the general and specific levels. All the models were compared to the corresponding ACE model and the results given as $\Delta\chi^2$. The test statistics comparing the gender-invariant models to the corresponding gender-specific models were $\chi_{11}^2 = 7.57, p = 0.75, \chi_7^2 = 6.54, p = 0.48, \chi_7^2 = 6.02, p = 0.54$ and $\chi_3^2 = 11.66, p = 0.01$, for the ACE, AE, CE and E models, respectively.

of weaker genetic effects in females than males and, when taken together with similar findings from other studies, indicate that gender moderation of substance use heritability is deserving of additional research.

Most notable is our finding that shared environmental factors seem to exert a strong influence on adolescent substance use, especially in female adolescents. The univariate gender-invariant ACE models showed that the shared environmental factors accounted for 44%, 46%

and 29% of the variance in liability to tobacco, alcohol and other drug use. In the female sample estimates of the shared environmental component were even higher, exceeding two-thirds for tobacco and alcohol use. These substantial estimates replicate findings from other adolescent twin studies. Estimates of shared environmental effects from the Dutch studies of adolescent twins were 58% to 88% for alcohol use in 15–16-year-olds, 37% for alcohol use in adolescents 17 years or older (Koopmans & Boomsma,

Table 5. Variance component estimates in the common pathway model

Phenotype	β	a^2_{general}	a^2_{specific}	c^2_{general}	c^2_{specific}	e^2_{general}	e^2_{specific}
Male							
Tobacco	0.97 (0.91,1.0)	0.41 (0.00,0.84)	0.00 (0.00,0.12)	0.41 (0.02,0.80)	0.00 (0.00,0.09)	0.12 (0.04,0.21)	0.06 (0.00,0.21)
Alcohol	0.91 (0.85,0.99)	0.36 (0.00,0.74)	0.00 (0.00,0.18)	0.36 (0.02,0.73)	0.15 (0.00,0.27)	0.11 (0.03,0.18)	0.01 (0.00,0.16)
Drugs	0.57 (0.47,0.67)	0.14 (0.00,0.29)	0.33 (0.00,0.50)	0.14 (0.01,0.32)	0.00 (0.00,0.34)	0.04 (0.01,0.08)	0.35 (0.14,0.55)
SU factor	—	0.44 (0.00,0.87)	—	0.44 (0.02,0.86)	—	0.13 (0.04,0.22)	—
Female							
Tobacco	0.94 (0.84,1.0)	0.04 (0.00,0.41)	0.06 (0.00,0.25)	0.67 (0.35,0.88)	0.04 (0.00,0.25)	0.17 (0.06,0.27)	0.01 (0.00,0.18)
Alcohol	0.95 (0.85,1.0)	0.05 (0.00,0.41)	0.05 (0.00,0.23)	0.69 (0.36,0.87)	0.00 (0.00,0.20)	0.17 (0.07,0.28)	0.04 (0.00,0.21)
Drugs	0.47 (0.33,0.60)	0.01 (0.00,0.10)	0.00 (0.00,0.54)	0.17 (0.06,0.29)	0.34 (0.00,0.52)	0.04 (0.01,0.08)	0.44 (0.20,0.65)
SU factor	—	0.05 (0.00,0.44)	—	0.76 (0.42,0.89)	—	0.19 (0.07,0.29)	—
Gender-invariant							
Tobacco	0.97 (0.90,1.0)	0.22 (0.00,0.49)	0.02 (0.00,0.14)	0.59 (0.36,0.82)	0.00 (0.00,0.11)	0.13 (0.07,0.20)	0.04 (0.00,0.15)
Alcohol	0.92 (0.87,0.99)	0.20 (0.00,0.43)	0.00 (0.00,0.18)	0.53 (0.31,0.78)	0.11 (0.00,0.21)	0.12 (0.06,0.18)	0.04 (0.00,0.15)
Drugs	0.53 (0.45,0.61)	0.07 (0.00,0.15)	0.30 (0.00,0.48)	0.18 (0.09,0.29)	0.04 (0.00,0.36)	0.04 (0.02,0.07)	0.37 (0.22,0.53)
SU factor	—	0.23 (0.00,0.51)	—	0.63 (0.37,0.87)	—	0.14 (0.07,0.21)	—

SU factor: the common factor underlying tobacco, alcohol and drug use; β : factor loadings. “General” subscript gives variance contribution from the common factor, “specific” subscript gives variance contribution from the specific factors (see Fig. 1). The 95% confidence limits are given in the parentheses below the estimates.

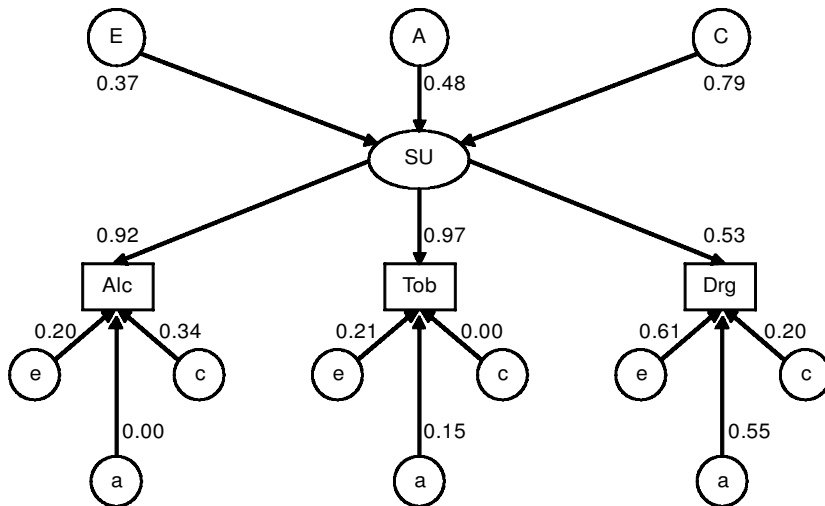


Figure 2. The parameter estimates in the gender-invariant common pathway model. The path diagram is drawn for only one member of a twin pair. The corresponding estimates are equal for both members. “SU” is the phenotypic factor underlying the liabilities to tobacco, alcohol and other drug use; “Tob”, “Alc” and “Drg” stand for the liabilities to tobacco use, alcohol use and other drug use; “A”, “C” and “E”, and “a”, “c”, “e” represent the additive genetic, shared environmental and non-shared environmental factors at the general and specific level, respectively.

1996) and 59% for tobacco use in both adolescent age groups (Boomsma *et al.*, 1994). In the Virginia adolescent twin study, estimates of shared environmental influences were 54% for alcohol use, 47% for drug use, but only 18% for tobacco use (Maes *et al.*, 1998).

By investigating life-time use of substances in a sample of 17–18-year-olds we are, in effect, investigating the origins of early adolescent substance use, a powerful predictor of adult substance use diagnosis (e.g. Grant & Dawson, 1997). Our findings thus imply that the early initiation of adolescent substance use is primarily environmentally, rather than genetically, mediated. The environmental factors that contribute to adolescent substance use might include school experience, neighborhood atmosphere and peer group characteristics, as well as parental attitude toward adolescent substance use. It is important to also recognize that the origins of life-time use versus abstinence may be quite different from the origins of continued substance use. Our findings are consistent with both those of Heath *et al.* (1991a, 1991b), who reported that drinking abstinence was non-heritable in adults, even though alcohol use frequency and quantity were moderately heritable; and Heath & Madden (1995), who found strong shared environmental effects on adolescent initiation of smoking.

Our univariate analyses suggested moderate genetic influences on each of the three substance use phenotypes; univariate heritability estimates were 36%, 35% and 23% for tobacco, alcohol and drug use, respectively. Somewhat unexpectedly, our multivariate analyses did not confirm a statistically significant genetic effect, as genetic factors could be deleted from these models without significantly incrementing the χ^2 test statistic. The apparent discrepancy between the univariate and multivariate results may reflect the lack of power associated with the simultaneous analysis of multiple dichotomized phenotypes in a moderately sized twin sample (Neale *et al.*, 1994). Our univariate results are consistent with findings from other twin studies that suggest that genetic factors do contribute to individual differences in substance use, even though the strength of that influence may be weaker in adolescence than in adulthood.

The common pathway model was posited to address the possibility that a single phenotypic factor underlies liabilities to tobacco, alcohol and other drug use during adolescence. This model

gave an excellent fit to the female data and a marginally acceptable fit to the male data. The latent phenotypic factor can be termed adolescent substance use liability. According to the gender-invariant ACE model, genetic factors were estimated to account for 23% of the variance in this latent factor, shared environmental factors 63% and non-shared environmental factors 14%.

The present results are in accord with Swan *et al.* (1996), who found that a common pathway model fitted their data on tobacco, alcohol and coffee use of adult male twins, and with Swan *et al.* (1997) who found that there was a latent factor representing joint heavy use of alcohol and tobacco, suggesting that the factors influencing tobacco and alcohol use overlap regardless of age. More significantly, these results partly corroborate the findings from the Dutch studies, where a high genetic correlation between tobacco and alcohol use was found in 12–16-year-olds, and a high shared-environmental correlation was found for 17–25-year-olds (Koopmans *et al.*, 1997). As the common latent factor accounted for 94%, 85% and 28% of the variance in liabilities to tobacco, alcohol and drug use, it can be inferred that adolescents' use of alcohol and tobacco use are substantially influenced by the same genetic and environmental factors, whereas other drug use primarily reflected substance-specific effects. It should be noted that, like the individual substance use phenotypes, the latent factor had a higher heritability in males than in females.

There are several limitations in this study. First, as mentioned above, the size of the present sample may not have sufficient power to test for gender differences in heritability. Secondly, opposite-sex twin pairs were not included. Thus it was impossible to investigate whether the same set of genes or environmental factors was influencing substance use in both genders. Thirdly, the sample consisted predominantly of Caucasian American adolescents. Thus the generalizability of the present findings might be limited to American whites only. Fourthly, the interpretation of our findings depends upon the validity of the twin study method. In particular, the twin study method assumes no assortative mating for the phenotype in question. As the existence of assortative mating could lead to overestimation of shared environmental effects and underestimation of heritable effects (Neale

& Cardon, 1992), our finding of strong shared environmental effects and weak heritable effects may be due, in part, to a failure to meet this critical assumption. Finally, we investigated lifetime use of tobacco, alcohol or other drugs in an adolescent sample. In all likelihood, some of the life-time abstinent twins in our sample will initiate substance use as adults. Consequently, our investigation focuses on adolescent initiation of substance use. We hasten to emphasize, however, that there is substantial epidemiological evidence that early substance use initiation is a powerful predictor of adult substance use disorders (e.g. Grant & Dawson, 1997).

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