ORIGINAL ARTICLE

Genetic and Environmental Influences on Substance Initiation, Use, and Problem Use in Adolescents

Soo Hyun Rhee, PhD; John K. Hewitt, PhD; Susan E. Young, PhD; Robin P. Corley, PhD; Thomas J. Crowley, MD; Michael C. Stallings, PhD

Background: We conducted a sibling/twin/adoption study of substance initiation, use, and problem use, estimating the relative contribution of genetic and environmental influences on these phenotypes in adolescents.

Methods: The participants were 345 monozygotic twin pairs, 337 dizygotic twin pairs, 306 biological sibling pairs, and 74 adoptive sibling pairs assessed by the Colorado Center for the Genetics and Treatment of Antisocial Drug Dependence, Denver and Boulder. The initiation, use, and problem use of tobacco, alcohol, marijuana, and other illicit drugs were assessed. Tetrachoric correlations were computed for each group, and univariate model-fitting analyses were conducted.

Results: There were moderate to substantial genetic influences, with the exception of alcohol use and any drug use, and modest to moderate shared environmental influences on substance initiation, use, and problem use. For alcohol and any drug, heritability was higher and the magnitude of shared environmental influences was lower for problem use than for initiation or use. Environmental influences shared only by twin pairs had a significant effect on tobacco initiation, alcohol use, and any drug use. For tobacco use, tobacco problem use, and marijuana initiation, heritability was higher and the magnitude of shared environmental influences was lower in female than in male adolescents. There was no evidence for sex-specific genetic or shared environmental influences on any variable.

Conclusions: The moderate to substantial heritabilities found for adolescents in the present study are comparable to those found in twin studies of adult substance use and substance use disorders. The finding that problem use is more heritable than initiation and use is also consistent with the results of adult twin studies. The significance of environmental influences shared only by twin pairs on tobacco initiation, alcohol use, and any drug use suggests the influences of peers, accessibility of substances, and sibling interaction.

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From the Department of Psychology (Dr Rhee) and the Institute for Behavioral Genetics (Drs Rhee, Hewitt, Young, Corley, and Stallings), University of Colorado at Boulder; and the Division of Substance Dependence, Department of Psychiatry, University of Colorado Health Sciences Center, Denver (Dr Crowley).

EPIDEMIOLOGICAL studies[1] suggest that substance use disorders are common in adults, with lifetime prevalences of 35% in men and 18% in women. The prevalence of substance use disorders is lower in adolescents (ie, 12% in males and 10% in females[2]), but substance use during adolescence is common. According to a recent Monitoring the Future study report,[3] 80% of adolescents had used alcohol and 54% of adolescents had used an illicit drug by the end of the 12th grade. Also, early-onset substance use is a significant risk factor for the development of substance use disorders.[4,5] Although many published twin studies suggest the importance of genetic influences on substance use and substance use disorders in adults, little information regarding the cause of substance use and substance use disorders in adolescence is available. Therefore, the goal of the present study was to estimate the relative contribution of genetic and environmental influences on the risk for substance use disorders in adolescents in a combined sibling/twin/adoption study. We also examined whether the magnitude of genetic and environmental influences on the risk for substance use disorders is different for male and female adolescents. Specifically, we examined the initiation, use, and problem use for tobacco, alcohol, marijuana, and a composite variable, any drug (ie, tobacco, alcohol, marijuana, or other illicit drugs). Any drug was examined given previous evidence[6,7] of significant common genetic influences on the abuse of and dependence on different drugs.

Twin studies examine the cause of a trait by taking advantage of the fact that monozygotic (MZ) twin pairs have 100% genetic similarity, whereas dizygotic (DZ) twin pairs have 50% genetic similarity on average. By using this information and comparing the correlations of a trait in MZ and DZ twin pairs, 3 types of influences on the trait

are estimated: heritability (a^2), the magnitude of additive genetic influences; shared environmental influence (c^2), the magnitude of environmental influences that family members experience in common and make family members similar to one another; and nonshared environmental influence (e^2), the magnitude of environmental influences that family members experience uniquely and make family members different from one another. Adoption studies take advantage of the fact that the correlation of a trait between adoptive sibling pairs can only be due to shared environmental influences, and compare the correlations between adoptive and biological sibling pairs to estimate a^2, c^2, and e^2. Given that the present study includes sibling pairs and twin pairs, the magnitude of environmental influences that are shared only by twin pairs (t^2) also can be estimated. In a twin study, it is not possible to estimate c^2 and the magnitude of nonadditive genetic influences (d^2) simultaneously because both the estimation of c^2 and d^2 rely on the same information (ie, the difference between the MZ and DZ twin correlations). Given that the present study is a combined sibling/twin/adoption study, a model including shared environmental influences and nonadditive genetic influences can be tested.

As previously noted, consistent evidence for genetic influences on substance use and substance use disorders has been found in adults, although there are more published twin studies examining tobacco[8,9] and alcohol[10-12] than those examining illicit drugs.[13-15] In comparison, there are relatively few published twin studies examining substance use and substance use disorders in adolescents.[16-18]

Although the estimates of the relative magnitudes of additive genetic, shared environmental, and nonshared environmental influence vary among published studies, several general conclusions can be made from the twin studies examining substance use and substance use disorders. First, problem use, abuse, or dependence may be more heritable and less influenced by shared environment than the initiation or use of substances, including tobacco,[9,19] alcohol,[20,21] and illicit drugs.[15,22-24] Second, substance use and substance use disorders may be more heritable in adulthood than in adolescence.[18,25] This difference may be due to more variance in the accessibility of substances or stronger influences of peers and social factors in adolescence than in adulthood. Third, the reported heritability estimates for illicit drug use disorders are more variable (eg, 22%-31% in Pickens et al[26] and 60%-80% in Kendler et al[24]) than those for tobacco and alcohol. These variations may be due to greater cohort and regional differences in the accessibility of illicit drugs than in the accessibility of tobacco or alcohol. Also, heritability estimates in these studies may be imprecise because illicit substance use is less common than tobacco or alcohol use.

METHODS

PARTICIPANTS

The participants were 345 MZ twin pairs (159 male and 186 female pairs), 337 DZ twin pairs (113 male, 101 female, and 123 opposite sex pairs), 306 biological sibling pairs (139 male, 32 female, and 135 opposite sex pairs), and 74 adoptive sibling pairs (5 male, 11 female, and 58 opposite sex pairs) assessed by the Colorado Center for the Genetics and Treatment of Antisocial Drug Dependence, Denver and Boulder; these pairs were aged 12 to 19 years (mean, 15.85 years; SD, 2.08 years). Of the sample, 54.0% were male and 46.0% were female adolescents. The MZ and DZ twin pairs were recruited from 2 community-based twin samples, the Colorado Longitudinal Twin Sample and the Colorado Twin Registry. Two hundred eight of the biological sibling pairs were from the control families assessed by the Adolescent Substance Abuse Family Study, which recruits the families of patients in a treatment program for antisocial substance problems and the families of matched controls. Ninety-eight of the biological sibling pairs and all of the adoptive sibling pairs were assessed through the Colorado Adoption Project, which recruits adoptive families and control nonadoptive families. The ethnicity distribution for the combined sample is 82.1% non-Hispanic white, 10.9% Hispanic, 2.6% Asian, 2.4% African American, 1.6% Native American, and 0.3% unknown.

PROCEDURE

Written informed assent (from minor participants) or consent (from adult participants and guardians of minor participants) was obtained from all participants. Zygosity for same-sex twin pairs was determined by a 9-item assessment of physical characteristics[27] completed by the interviewers, and by comparing the twin pairs' genotype at a minimum of 11 highly informative short-tandem repeat polymorphisms. Twin pairs with similar physical characteristics and concordant markers were categorized as MZ twin pairs, and twin pairs with dissimilar physical characteristics and discordant markers were categorized as DZ twin pairs. Discrepancies between the zygosity determination by the interviewer rating and genotyping were reevaluated and resolved.

Substance initiation was assessed by responses on questions from the Monitoring the Future survey.[3] Data for substance initiation were available for 335 MZ twin pairs, 330 DZ twin pairs, 249 biological sibling pairs, and 46 adoptive sibling pairs. Substance use and problem use were assessed by the Composite International Diagnostic Interview—Substance Abuse Module (CIDI-SAM), a valid and reliable structured interview[28-31] that assesses symptoms and diagnoses of abuse and dependence for tobacco, alcohol, and 8 classes of illicit drugs (marijuana, opioids, sedatives/hypnotics, inhalants, amphetamines, cocaine, hallucinogens, and phencyclidine). The CIDI-SAM has been successfully used to assess substance use disorders in adolescents.[32,33] Interviewers were trained by 2 professional research assistants who attended training sessions conducted by the authors of the CIDI-SAM, and the interviewing team met biweekly to discuss issues regarding the standardization of assessment. Data for substance use and problem use were available for 345 MZ twin pairs, 337 DZ twin pairs, 306 biological sibling pairs, and 74 adoptive sibling pairs.

Substance initiation was defined as any lifetime use for all substances, and assessed via the questions "Have you ever smoked cigarettes?" or "On how many occasions have you had/used [name of substance] in/during your lifetime?" Substance use is defined by the CIDI-SAM as using almost daily for at least 30 days for tobacco, having 6 or more drinks during one's lifetime for alcohol, and using more than 5 times during one's lifetime for illicit drugs. Problem use was defined as the presence of at least one *DSM-IV*[34] dependence symptom for tobacco (given that tobacco abuse is not defined by the *DSM-IV*) and at least one abuse or dependence symptom for alcohol, marijuana, and other illicit drugs.

ANALYSES

Table 1 presents the prevalence of substance initiation, use, and problem use in the entire sample. There were no sex differences for the prevalence of substance initiation, use, and problem use except for problem use of alcohol ($\chi^2_1=6.14$, $P=.01$). More detailed results regarding the epidemiological features of

Table 1. Prevalence of Substance Initiation, Use, and Problem Use in the Combined Sample*

Type of Substance	Initiation	Use	Problem Use
Tobacco			
Overall	42.0	15.0	12.8
Males	42.7	15.7	12.8
Females	41.3	14.1	12.7
Alcohol			
Overall	64.4	37.5	18.9
Males	65.8	38.6	20.8
Females	62.6	36.2	16.6
Marijuana			
Overall	27.2	16.9	13.2
Males	27.2	17.2	13.7
Females	27.1	16.5	12.7
Other drugs			
Overall	17.3	5.1	4.0
Males	17.0	5.1	4.6
Females	17.6	5.1	3.4
Any drug†			
Overall	69.8	39.7	24.7
Males	71.3	41.2	26.3
Females	68.0	38.0	22.7

*Data are given as percentages.
†Tobacco, alcohol, marijuana, or other drugs.

Table 2. Correlation Between Age and Substance Initiation, Use, and Problem Use in the Combined Sample

Type of Substance	Initiation	Use	Problem Use
Tobacco			
Overall	0.43	0.31	0.30
Males	0.41	0.29	0.28
Females	0.46	0.34	0.33
Alcohol			
Overall	0.46	0.54	0.37
Males	0.43	0.52	0.39
Females	0.50	0.56	0.35
Marijuana			
Overall	0.41	0.34	0.30
Males	0.36	0.32	0.29
Females	0.46	0.36	0.31
Other drugs			
Overall	0.23	0.19	0.18
Males	0.21	0.20	0.19
Females	0.24	0.17	0.16
Any drug*			
Overall	0.44	0.55	0.43
Males	0.42	0.53	0.42
Females	0.46	0.57	0.44

*Tobacco, alcohol, marijuana, or other drugs.

substance use and substance use disorders in our sample are presented in Young et al.[35] Analyses were not conducted separately for illicit substances other than marijuana (ie, other drugs in Table 1), given the low prevalence of use (5.1%) and problem use (4.0%) of these substances.

We assumed a normal continuous liability distribution underlying our categorical assessments for all variables. Tetrachoric correlations were estimated for substance initiation, use, and problem use for MZ twin pairs, DZ twin pairs, biological sibling pairs, and adoptive sibling pairs using a statistical modeling package.[36] An examination of substance use or substance use disorders in adolescents must address the fact that the prevalence of substance use and substance use disorders increases with age (**Table 2**). We controlled for the effects of age and sex by estimating the age- and sex-specific threshold appropriate for each individual using the following formula: individual's threshold = estimated threshold + (the age difference in threshold × the individual's age) + (the sex difference in threshold × the individual's sex).

Univariate model-fitting analyses were conducted using a statistical modeling package, analyzing raw data. Again, the age- and sex-specific threshold appropriate for each individual was estimated. The ACDTE model is the full model, including additive genetic influences (A), environmental influences shared by all siblings (C), nonadditive genetic influences (D), environmental influences shared only by twins (T), and nonshared environmental influences (E). C and D can be distinguished in the present study because twin pairs and adoptive sibling pairs are included in the sample. C and T can be distinguished in the present study because twin pairs and nontwin sibling pairs are included in the sample. Additional models constraining the magnitude of one or more of these influences to 0 (ie, the ACTE, ACDE, ACE, ADE, CTE, CE, and AE models) also were fit to the observed data.

Three kinds of models were fit to the data to examine whether the magnitude of genetic and environmental influences is different in males and females. The most restricted model is the homogeneity model, which assumes that the same genetic and environmental influences affect males and females to the same extent and constrains the parameter estimates to be equal in males and females. The heterogeneity model assumes that the same genetic and environmental influences affect males and females, but that the magnitude of genetic and environmental influences differs for males and females, and the parameter estimates are free to vary in males and females. The full model is the general sex limitation model, which assumes that there are sex-specific genetic or shared environmental influences and genetic or shared environmental influences that are common across the sexes. In addition to allowing the parameter estimates to vary in males and females, the general sex limitation model tests for sex-specific genetic influences by allowing the genetic correlation between opposite sex twin pairs to be lower than 0.5 or the correlation between shared environmental influences between opposite sex twin pairs to be lower than 1. Sex-specific genetic and shared environmental influences cannot be included in the general sex limitation model at the same time because a model including both parameters is not identified. Therefore, a model including sex-specific genetic influences and a model including sex-specific shared environmental influences were tested separately.

The fit of each model was evaluated by comparing minus twice the log-likelihood of data of the model with minus twice the log-likelihood of data of the saturated model, which allows the correlation of each group free to vary. The differences in minus twice the log likelihood of data between nested models are distributed as χ^2. The fit of each model also was evaluated using the Akaike Information Criterion (AIC), a fit index that reflects the fit of the model and its parsimony.[37] Among competing models, the model with the lowest χ^2 relative to its *df* and the lowest AIC is considered the best-fitting model.

RESULTS

Table 3 presents the tetrachoric correlations and confidence intervals for substance initiation, use, and problem use for tobacco, alcohol, marijuana, and any drug in MZ twin pairs, DZ twin pairs, biological sibling pairs, and adoptive sibling pairs. With few exceptions, the MZ correlation was higher than the DZ correlation and the

Table 3. Tetrachoric Correlations for Substance Initiation, Use, and Problem Use*

Variable	MZ	DZ	BS	AS
		Tobacco		
Initiation				
Overall	0.90 (0.83 to 0.95)	0.71 (0.57 to 0.81)	0.55 (0.37 to 0.69)	0.36 (–0.16 to 0.75)
Males	0.89 (0.77 to 0.95)	0.68 (0.41 to 0.86)	0.35 (0.06 to 0.60)	†
Females	0.91 (0.80 to 0.97)	0.69 (0.40 to 0.87)	†	†
Opposite sex	NA	0.74 (0.52 to 0.87)	0.68 (0.45 to 0.83)	0.41 (–0.16 to 0.82)
Use				
Overall	0.86 (0.73 to 0.94)	0.56 (0.31 to 0.75)	0.38 (0.15 to 0.57)	0.08 (–0.28 to 0.42)
Males	0.69 (0.38 to 0.88)	0.79 (0.45 to 0.94)	0.43 (0.12 to 0.68)	†
Females	0.95 (0.84 to 1.00)	0.45 (–0.05 to 0.81)	0.53 (–0.21 to 0.93)	0.74 (–0.45 to 1.00)
Opposite sex	NA	0.31 (–0.21 to 0.71)	0.26 (–0.13 to 0.60)	–0.08 (–0.47 to 0.33)
Problem use				
Overall	0.87 (0.73 to 0.95)	0.51 (0.22 to 0.73)	0.44 (0.21 to 0.63)	0.13 (–0.24 to 0.47)
Males	0.71 (0.37 to 0.90)	0.75 (0.34 to 0.94)	0.55 (0.24 to 0.77)	†
Females	0.95 (0.82 to 0.99)	0.45 (–0.09 to 0.82)	0.27 (–0.60 to 0.89)	0.74 (–0.45 to 1.00)
Opposite sex	NA	0.20 (–0.37 to 0.67)	0.37 (–0.03 to 0.69)	–0.01 (–0.42 to 0.40)
		Alcohol		
Initiation				
Overall	0.70 (0.57 to 0.80)	0.43 (0.25 to 0.58)	0.64 (0.46 to 0.78)	0.45 (–0.32 to 0.90)
Males	0.77 (0.59 to 0.88)	0.47 (0.17 to 0.71)	0.62 (0.37 to 0.80)	†
Females	0.63 (0.41 to 0.78)	0.36 (0.02 to 0.63)	†	†
Opposite sex	NA	0.44 (0.15 to 0.68)	0.73 (0.43 to 0.90)	†
Use				
Overall	0.84 (0.73 to 0.91)	0.79 (0.66 to 0.88)	0.46 (0.28 to 0.62)	0.46 (0.09 to 0.74)
Males	0.89 (0.76 to 0.96)	0.83 (0.59 to 0.94)	0.42 (0.13 to 0.65)	†
Females	0.77 (0.56 to 0.89)	0.72 (0.40 to 0.90)	0.05 (–0.54 to 0.62)	0.35 (–0.55 to 0.91)
Opposite sex	NA	0.81 (0.60 to 0.92)	0.58 (0.32 to 0.77)	0.45 (0.02 to 0.77)
Problem use				
Overall	0.75 (0.58 to 0.87)	0.44 (0.19 to 0.64)	0.47 (0.26 to 0.64)	0.24 (–0.13 to 0.56)
Males	0.73 (0.45 to 0.90)	0.47 (0.04 to 0.78)	0.48 (0.17 to 0.71)	†
Females	0.77 (0.53 to 0.91)	0.14 (–0.40 to 0.61)	0.32 (–0.30 to 0.79)	0.37 (–0.62 to 0.93)
Opposite sex	NA	0.56 (0.18 to 0.81)	0.48 (0.16 to 0.72)	0.15 (–0.26 to 0.52)
		Marijuana		
Initiation				
Overall	0.90 (0.81 to 0.95)	0.65 (0.48 to 0.78)	0.63 (0.45 to 0.76)	0.08 (–0.36 to 0.50)
Males	0.81 (0.61 to 0.92)	0.74 (0.43 to 0.91)	0.60 (0.34 to 0.79)	†
Females	0.96 (0.88 to 1.00)	0.70 (0.36 to 0.90)	0.48 (–0.38 to 0.95)	†
Opposite sex	NA	0.55 (0.26 to 0.77)	0.68 (0.42 to 0.85)	–0.14 (–0.60 to 0.39)
Use				
Overall	0.88 (0.76 to 0.94)	0.69 (0.50 to 0.83)	0.60 (0.41 to 0.74)	0.20 (–0.17 to 0.54)
Males	0.86 (0.65 to 0.96)	0.66 (0.26 to 0.89)	0.55 (0.26 to 0.77)	†
Females	0.89 (0.72 to 0.96)	0.74 (0.33 to 0.93)	0.15 (–0.53 to 0.73)	0.28 (–0.69 to 0.93)
Opposite sex	NA	0.69 (0.37 to 0.88)	0.76 (0.50 to 0.90)	0.03 (–0.38 to 0.44)
Problem use				
Overall	0.64 (0.40 to 0.81)	0.63 (0.39 to 0.80)	0.60 (0.40 to 0.76)	0.13 (–0.27 to 0.50)
Males	0.81 (0.52 to 0.95)	0.38 (–0.17 to 0.78)	0.51 (0.18 to 0.75)	†
Females	0.46 (0.09 to 0.74)	0.86 (0.51 to 0.98)	0.25 (–0.46 to 0.79)	–0.22 (–0.91 to 0.82)
Opposite sex	NA	0.59 (0.19 to 0.84)	0.82 (0.54 to 0.96)	–0.03 (–0.47 to 0.42)
		Any Drug‡		
Initiation				
Overall	0.70 (0.57 to 0.81)	0.50 (0.33 to 0.64)	0.56 (0.35 to 0.73)	†
Males	0.74 (0.55 to 0.87)	0.43 (0.11 to 0.68)	0.52 (0.23 to 0.74)	†
Females	0.66 (0.45 to 0.81)	0.48 (0.17 to 0.72)	†	†
Opposite sex	NA	0.55 (0.26 to 0.76)	0.65 (0.31 to 0.86)	†
Use				
Overall	0.82 (0.71 to 0.90)	0.75 (0.60 to 0.85)	0.40 (0.21 to 0.56)	0.32 (–0.08 to 0.65)
Males	0.86 (0.70 to 0.94)	0.80 (0.55 to 0.93)	0.35 (0.06 to 0.59)	†
Females	0.78 (0.58 to 0.90)	0.68 (0.36 to 0.88)	0.15 (–0.46 to 0.68)	†
Opposite sex	NA	0.74 (0.50 to 0.88)	0.49 (0.22 to 0.70)	0.50 (0.07 to 0.80)
Problem use				
Overall	0.82 (0.69 to 0.90)	0.46 (0.24 to 0.65)	0.45 (0.26 to 0.61)	0.10 (–0.26 to 0.43)
Males	0.78 (0.55 to 0.91)	0.27 (–0.15 to 0.63)	0.38 (0.10 to 0.62)	†
Females	0.85 (0.67 to 0.94)	0.56 (0.13 to 0.84)	0.34 (–0.31 to 0.81)	0.05 (–1.0 to 0.97)
Opposite sex	NA	0.53 (0.19 to 0.78)	0.56 (0.26 to 0.77)	0.09 (–0.31 to 0.47)

Abbreviations: AS, adoptive sibling pairs; BS, biological sibling pairs; DZ, dizygotic twin pairs; MZ, monozygotic twin pairs; NA, data not applicable.
*Data in parentheses are 95% confidence intervals.
†A tetrachoric correlation could not be computed because of missing cells.
‡Tobacco, alcohol, marijuana, or other drugs.

Table 4. Univariate Model-Fitting Results: The Full Model (ACDTE General Sex Limitation Model) and the Best-Fitting Model

Variable	Model Fit				Parameter Estimates (95% Confidence Intervals)*		
	χ^2	*df*	*P*	AIC	a^2	c^2	d^2
Tobacco							
Initiation							
ACDTE general sex limitation*	4.91	2	.09	0.91	0.24 (0.00 to 0.70) 0.30 (0.00 to 0.70)	0.34 (0.11 to 0.60) 0.48 (0.13 to 0.81)	0.08 (0.00 to 0.53) 0.05 (0.00 to 0.50)
ACTE homogeneity	5.98	8	.65	−10.02	0.38 (0.13 to 0.66)	0.34 (0.13 to 0.52)	NA
Use							
ACDTE general sex limitation*	3.25	2	.20	−0.75	0.06 (0.00 to 0.61) 0.91 (0.00 to 0.99)	0.43 (0.05 to 0.68) 0.01 (0.00 to 0.46)	0.00 (0.00 to 0.40) 0.00 (0.00 to 0.98)
ACE/AE heterogeneity*	5.21	8	.73	−10.79	0.24 (0.00 to 0.71) 0.95 (0.84 to 0.99)	0.45 (0.06 to 0.70) NA	NA NA
Problem use							
ACDTE general sex limitation*	3.45	2	.18	−0.55	0.10 (0.00 to 0.75) 0.73 (0.00 to 0.99)	0.52 (0.06 to 0.77) 0.03 (0.00 to 0.45)	0.01 (0.00 to 0.51) 0.19 (0.00 to 0.98)
ACE/AE heterogeneity*	4.04	8	.85	−11.96	0.26 (0.00 to 0.73) 0.95 (0.82 to 0.99)	0.48 (0.08 to 0.74) NA	NA NA
Alcohol							
Initiation							
ACDTE general sex limitation*	5.11	2	.08	1.11	0.41 (0.00 to 0.79) 0.41 (0.00 to 0.73)	0.36 (0.04 to 0.69) 0.22 (0.00 to 0.61)	0.00 (0.00 to 0.52) 0.00 (0.00 to 0.58)
ACE homogeneity	7.57	9	.58	−10.43	0.39 (0.05 to 0.71)	0.32 (0.04 to 0.57)	NA
Use							
ACDTE general sex limitation*	3.69	2	.16	−0.31	0.10 (0.00 to 0.44) 0.07 (0.00 to 0.43)	0.42 (0.19 to 0.65) 0.39 (0.13 to 0.67)	0.00 (0.00 to 0.32) 0.00 (0.00 to 0.34)
CTE homogeneity	6.38	9	.70	−9.62	NA	0.45 (0.28 to 0.59)	NA
Problem use							
ACDTE general sex limitation*	3.44	2	.18	−0.56	0.25 (0.00 to 0.87) 0.26 (0.00 to 0.87)	0.33 (0.00 to 0.65) 0.17 (0.00 to 0.51)	0.16 (0.00 to 0.67) 0.34 (0.00 to 0.82)
AE homogeneity	5.90	10	.82	−14.10	0.78 (0.64 to 0.88)	NA	NA
Marijuana							
Initiation							
ACDTE general sex limitation*	6.19	2	.05	2.19	0.39 (0.00 to 0.80) 0.60 (0.00 to 0.94)	0.44 (0.08 to 0.74) 0.24 (0.02 to 0.69)	0.00 (0.00 to 0.43) 0.00 (0.00 to 0.68)
ACE heterogeneity*	6.40	7	.49	−7.60	0.39 (0.02 to 0.81) 0.72 (0.29 to 0.95)	0.44 (0.07 to 0.73) 0.24 (0.02 to 0.65)	NA NA
Use							
ACDTE general sex limitation*	10.43	2	<.01	6.43	0.41 (0.00 to 0.80) 0.43 (0.00 to 0.86)	0.40 (0.10 to 0.70) 0.27 (0.04 to 0.61)	0.00 (0.00 to 0.50) 0.00 (0.00 to 0.58)
ACE homogeneity	11.35	9	.25	−6.65	0.55 (0.30 to 0.81)	0.33 (0.10 to 0.53)	NA
Problem use							
ACDTE general sex limitation*	18.78	2	<.01	14.78	0.44 (0.00 to 0.83) 0.22 (0.00 to 0.67)	0.35 (0.05 to 0.71) 0.33 (0.04 to 0.67)	0.00 (0.00 to 0.63) 0.00 (0.00 to 0.40)
ACE homogeneity	20.29	9	.02	2.29	0.34 (0.00 to 0.67)	0.36 (0.10 to 0.60)	NA
Any Drug†							
Initiation							
ACDTE general sex limitation*	2.29	2	.32	−1.71	0.45 (0.00 to 0.79) 0.34 (0.00 to 0.74)	0.29 (0.02 to 0.64) 0.33 (0.01 to 0.70)	0.00 (0.00 to 0.58) 0.00 (0.00 to 0.53)
ACE homogeneity	2.65	9	.98	−15.35	0.39 (0.05 to 0.72)	0.32 (0.03 to 0.57)	NA
Use							
ACDTE general sex limitation*	6.03	2	.05	2.03	0.06 (0.00 to 0.50) 0.09 (0.00 to 0.57)	0.37 (0.10 to 0.60) 0.31 (0.09 to 0.63)	0.04 (0.00 to 0.37) 0.07 (0.00 to 0.45)
CTE homogeneity	8.23	9	.51	−9.77	NA	0.38 (0.22 to 0.54)	NA
Problem use							
ACDTE general sex limitation*	3.63	2	.16	−0.37	0.54 (0.00 to 0.89) 0.59 (0.00 to 0.94)	0.12 (0.00 to 0.47) 0.19 (0.00 to 0.64)	0.10 (0.00 to 0.75) 0.04 (0.00 to 0.76)
AE homogeneity	5.37	10	.87	−14.63	0.83 (0.72 to 0.91)	NA	NA

Abbreviations: A, additive genetic influences; AIC, Akaike Information Criterion; a^2, proportion of variance explained by additive genetic influences; C, shared environmental influences; c^2, proportion of variance explained by shared environmental influences; D, nonadditive genetic influences; d^2, proportion of variance explained by nonadditive genetic influences; E, nonshared environmental influences; e^2, proportion of variance explained by nonshared environmental influences; NA, data not applicable; *r*T, genetic correlation between opposite-sex twin pairs; environmental influences shared only by twin pairs; t^2, proportion of variance explained by environmental influences shared only by twin pairs.

*Parameter estimates (95% confidence intervals) are given for males (first) and females (second).

†Tobacco, alcohol, marijuana, or other drugs.

Parameter Estimates (95% Confidence Intervals)*			Comparison With Full Model		
t^2	e^2	r	χ^2	*df*	*P*
		Tobacco			
0.23 (0.00 to 0.49) 0.08 (0.00 to 0.44)	0.11 (0.05 to 0.23) 0.09 (0.03 to 0.19)	0.50 (0.00 to 0.50)	NA	NA	NA
0.18 (0.00 to 0.39)	0.10 (0.05 to 0.17)	NA	1.07	6	.98
0.25 (0.00 to 0.60) 0.03 (0.00 to 0.63)	0.26 (0.11 to 0.48) 0.05 (0.01 to 0.16)	0.50 (0.00 to 0.50)	NA	NA	NA
NA NA	0.31 (0.14 to 0.52) 0.05 (0.01 to 0.16)	NA	1.96	6	.92
0.12 (0.00 to 0.49) 0.00 (0.00 to 0.70)	0.25 (0.09 to 0.50) 0.05 (0.01 to 0.18)	0.50 (0.00 to 0.50)	NA	NA	NA
NA NA	0.26 (0.10 to 0.48) 0.05 (0.01 to 0.18)	NA	0.59	6	.99
		Alcohol			
0.00 (0.00 to 0.19) 0.00 (0.00 to 0.30)	0.23 (0.11 to 0.39) 0.37 (0.22 to 0.57)	0.50 (0.00 to 0.50)	NA	NA	NA
NA	0.29 (0.19 to 0.43)	NA	2.46	7	.93
0.37 (0.12 to 0.62) 0.31 (0.04 to 0.62)	0.11 (0.04 to 0.23) 0.23 (0.11 to 0.39)	0.50 (0.00 to 0.50)	NA	NA	NA
0.37 (0.20 to 0.54)	0.18 (0.12 to 0.27)	NA	2.69	7	.91
0.00 (0.00 to 0.38) 0.00 (0.00 to 0.41)	0.26 (0.10 to 0.50) 0.23 (0.09 to 0.47)	0.50 (0.00 to 0.50)	NA	NA	NA
NA	0.22 (0.12 to 0.36)	NA	2.46	8	.96
		Marijuana			
0.00 (0.00 to 0.38) 0.12 (0.00 to 0.57)	0.17 (0.07 to 0.34) 0.04 (0.01 to 0.12)	0.50 (0.00 to 0.50)	NA	NA	NA
NA NA	0.17 (0.07 to 0.34) 0.04 (0.01 to 0.12)	NA	0.21	5	.99
0.06 (0.00 to 0.36) 0.19 (0.00 to 0.63)	0.13 (0.04 to 0.31) 0.11 (0.03 to 0.25)	0.50 (0.00 to 0.50)	NA	NA	NA
NA	0.12 (0.05 to 0.22)	NA	0.92	7	.99
0.01 (0.00 to 0.33) 0.09 (0.00 to 0.57)	0.20 (0.06 to 0.46) 0.36 (0.18 to 0.61)	0.50 (0.00 to 0.50)	NA	NA	NA
NA	0.30 (0.16 to 0.48)	NA	1.51	7	.98
		Any Drug†			
0.00 (0.00 to 0.25) 0.00 (0.00 to 0.39)	0.26 (0.13 to 0.44) 0.33 (0.19 to 0.52)	0.50 (0.00 to 0.50)	NA	NA	NA
NA	0.29 (0.19 to 0.43)	NA	0.36	7	.99
0.39 (0.12 to 0.65) 0.31 (0.03 to 0.67)	0.14 (0.06 to 0.28) 0.22 (0.10 to 0.40)	0.50 (0.00 to 0.50)	NA	NA	NA
0.40 (0.23 to 0.58)	0.22 (0.15 to 0.30)	NA	2.20	7	.95
0.01 (0.00 to 0.32) 0.03 (0.00 to 0.52)	0.23 (0.09 to 0.44) 0.15 (0.06 to 0.31)	0.50 (0.00 to 0.50)	NA	NA	NA
NA	0.17 (0.09 to 0.28)	NA	1.74	8	.99

biological sibling pairs' correlation was higher than the adoptive sibling pairs' correlation, suggesting the importance of genetic influences. Also, with few exceptions, the DZ correlation was higher than the biological sibling pairs' correlation, suggesting the importance of environmental influences shared only by twin pairs.

Table 4 presents the results of the univariate model-fitting results. The fit of the full model (the ACDTE general sex limitation model), the fit of the best-fitting model by the AIC, the comparison between the fit of the full model and the best-fitting model, and the parameter estimates and confidence intervals are presented.

For several models, the fit of the best-fitting model by the AIC was close to the fit of the second best-fitting model, and some parameters from the best-fitting model could be dropped without a significant worsening of fit, as indicated by the χ^2 difference test. These include the ACTE homogeneity model for tobacco initiation, in which t^2 could be dropped; the ACE/AE heterogeneity model for tobacco use, in which a^2 for male adolescents could be dropped; the ACE/AE heterogeneity model for tobacco problem use, in which a^2 for male adolescents could be dropped; the ACE heterogeneity model for marijuana initiation, in which the parameter estimates could be constrained across the sexes; and the ACE homogeneity model for marijuana problem use, in which a^2 could be dropped.

In general, the model-fitting results suggest that the magnitude of genetic influences on substance initiation, use, and problem use is moderate to substantial, with the exception of alcohol use and any drug use. The magnitude of shared environmental influences is modest to moderate, with the magnitude being significant except for tobacco use in female adolescents, tobacco problem use in female adolescents, alcohol problem use, and any drug problem use, for which the AE model was the best-fitting model. The estimate of environmental influences shared only by twin pairs was significant for tobacco initiation, alcohol use, and any drug use, but not for the problem use of any substances. Heritability was higher and the magnitude of shared environmental influences was lower for problem use than for either initiation or use for alcohol and any drug.

In general, there were few sex differences in the magnitude of genetic and environmental influences on the risk for substance use disorders, and there was no evidence for sex-specific genetic or shared environmental influences. Notable exceptions were tobacco use and tobacco problem use, for which the magnitude of genetic influences was significantly higher in females and the magnitude of shared environmental influences was significantly higher in males. The ACE model fit best in males, and the AE model fit best in females. For marijuana initiation, the ACE heterogeneity model was the best-fitting model by the AIC and indicated a higher heritability in females and a higher magnitude of shared environmental influences in males.

COMMENT

Although the significance of genetic influences on substance use and substance use disorders has been established in many twin studies,[8-15] the present study makes a unique contribution to the literature in several ways. First, the present study is one of few studies examining the cause of risk for licit and illicit drug use disorders in adolescents. Second, to our knowledge, it is the first study to examine twin, biological sibling, and adoptive sibling pairs jointly and to estimate the magnitude of environmental influences shared only by twin pairs on the risk for substance use disorders. Studies examining only twin pairs cannot distinguish between environmental influences that are shared by all family members and environmental influences that are shared only by same-age twin pairs. Third, given that the present study is a combined sibling/twin/adoption study, we were able to test a model including shared environmental influences and nonadditive genetic influences. Fourth, the effects of age were controlled by estimating age-specific thresholds for each individual in the analyses, given that the prevalence of substance use and substance use disorders increases significantly with age.[35]

There were moderate to substantial genetic influences and modest to moderate shared environmental influences on substance initiation, use, and problem use. Notable exceptions were alcohol use ($a^2=0.00$ and $c^2=0.45$) and any drug use ($a^2=0.00$ and $c^2=0.38$). Given the wide confidence intervals around the parameter estimates, it is difficult to assess whether the magnitude of genetic influences is lower in adolescents than in adults by comparing the present study's results with those of twin studies examining adults. However, the moderate to substantial heritability estimates found in the present study are comparable to those found in twin studies[8-15] examining substance use and substance use disorders in adults.

For alcohol and any drug, the magnitude of genetic influences was higher and the magnitude of shared environmental influences was lower for problem use than for initiation or use. These results are consistent with the general conclusions from twin studies[9,21] comparing substance initiation or use with problem use, abuse, or dependence in adults. In contrast to the results from other studies examining marijuana,[15,24] the magnitude of genetic influences was higher for marijuana initiation ($a^2=0.39$ and 0.72 for males and females, respectively) and use ($a^2=0.55$) than for problem use ($a^2=0.34$).

The environmental influences shared only by twin pairs had a significant effect on tobacco initiation, alcohol use, and any drug use, but did not affect the problem use of any substances. These results suggest the possible importance of peer influences and the accessibility of substances on substance experimentation. They also suggest the possible importance of sibling interaction and are consistent with the results of a study[38] showing a significant relationship between twin closeness and concordance for smoking initiation, but lack of a significant relationship between twin closeness and concordance for nicotine or alcohol dependence. In contrast, they are inconsistent with the results of a study[39] showing a significant relationship between twin closeness and concordance for illicit drug abuse or dependence.

There were few sex differences in the magnitude of genetic and environmental influences on risk for substance use disorders. Tobacco use and tobacco problem use were exceptions, with the ACE model fitting best in male adolescents, the AE model fitting best in female adolescents, and heritability being significantly higher in female adolescents. McGue et al[18] also reported a higher heritability for female than male adolescents for tobacco use and dependence, but this difference was not statistically significant. Also, these findings are not consistent with studies[9,40] of tobacco use in adults, which conclude that tobacco use is highly heritable in men and women. Also, there was no evidence that the genetic or shared environmen-

tal influences on substance initiation, use, or problem use differ in male and female adolescents.

The results of the present study should be interpreted in light of the following limitations. First, despite our large sample (N = 1062 pairs), lack of power is a limitation, as evidenced by the wide confidence intervals around the parameter estimates. Second, multiple thresholds could not be examined when analyzing data for problem use, given the low prevalence of substance abuse and dependence symptoms in the sample. Third, differences in results for substance initiation vs substance use and problem use should be interpreted in light of the fact that a questionnaire was used to assess substance initiation while an interview was used to assess substance use and problem use. Fourth, twin studies make the equal environments assumption, or the assumption that the degree to which environmental influences on a trait are shared is similar for MZ and DZ twin pairs. Although the present study lacked data to test the equal environments assumption, several twin studies,[41,42] including twin studies[38,39,43] examining substance use disorders, have found support for the equal environments assumption.

In conclusion, the results of this study provide evidence for moderate to substantial genetic influences and modest to moderate shared environmental influences on substance initiation, use, and problem use in adolescents. There were few sex differences in the magnitude of genetic and environmental influences on the risk for substance use disorders, and the results suggest that the genetic and shared environmental influences on the risk for substance use disorders are similar for male and female adolescents. They provide evidence of significantly higher heritability for tobacco use and problem use in female than in male adolescents, but these results are inconsistent with those from previous studies. The significance of environmental influences shared only by twin pairs on tobacco initiation, alcohol use, and any drug use suggests the importance of future research investigating the influences of peers, accessibility of substances, and sibling interactions on substance initiation and use.

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Corresponding author: Soo Hyun Rhee, PhD, Institute for Behavioral Genetics, University of Colorado at Boulder, Campus Box 447, Boulder, CO 80309 (e-mail: soo.rhee@colorado.edu).

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