Association between Alcohol Use and Smoking in Adolescent and Young Adult Twins: A Bivariate Genetic Analysis

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The association between alcohol use and smoking was examined in a large population-based sample of Dutch twins consisting of three age groups; young adolescent twins aged 12–14 years (n = 650 twin pairs), 15–16-years-old adolescent twins (n = 705 twin pairs), and young adult twins aged 17–25 years (n = 1266 twin pairs). For all three age groups, alcohol use and smoking were correlated (r = 0.5–0.6). Adolescents and young adults who smoked were more likely to drink alcohol than nonsmokers. The relation between alcohol use and smoking was also found within a twin pair; alcohol use in one twin was correlated with smoking in the cotwin. This finding suggested that familial factors contribute to the association between alcohol and tobacco use. With a bivariate genetic model, it was examined to what extent the comorbidity was due to genetic and environmental factors that predispose to both alcohol use and smoking. The genetic analyses showed that the underlying factors that influence alcohol and tobacco use and cause their association were different for adolescent and young adult twins. Initiation of alcohol use and smoking in adolescents (aged 12–16 years) was substantially influenced by the same shared environmental features. Alcohol and tobacco use in young adults were associated due to the same genetic risk factors.

Key Words: Alcohol Use, Smoking, Comorbidity, Twin Study, Bivariate Genetic Model.

A LCOHOL USE and smoking are associated—individuals who smoke are more likely to drink alcohol than nonsmokers.[1,2] Conversely, drinkers smoke more than abstainers. The link between drinking and smoking is found in both sexes and is consistent across different age groups and different nationalities.[1] The relationship between alcohol use and smoking is dose related in that heavy drinkers are heavy smokers and vice versa. Among alcoholics, over 90% were found to be smoking cigarettes and a substantial proportion of these alcoholics were heavy smokers.[2] In adolescents and young adults, the same association between drinking and smoking as in adults is found.[1,2] Not only are adolescents and young adults who drink more likely to smoke and vice versa, there is also a relationship between heavy drinking and heavy smoking in this age group. In an epidemiologic study of around 1000 young

adults, dependent and nondependent smokers had an elevated risk for alcohol dependence compared with nonsmokers.[3] In a clinical sample of adolescents with alcohol or other drug problems (n = 166), 75% were daily smokers and 61% smoked half a pack of cigarettes or more per day, rates that are much higher than that of the general adolescent population.[4]

It is well known that chronic abuse of alcohol and smoking have negative health consequences[5] and that both are associated with increased mortality risks.[6,7] Furthermore, there is evidence that the combination of alcohol and tobacco use increases the risk for some diseases such as cancer of the mouth and throat.[2] Cigarette smoking also has health consequences in adolescents. It was found that smoking had negative effects on the level and growth of lung function in adolescents, with girls being more vulnerable than boys to the effects of smoking on the growth of lung function.[8] For prevention, it is important to gain insight into the factors that determine the initiation of alcohol use and smoking and the co-occurrence of these two behaviors during adolescence. Adolescence is a period of major transitions in which many adolescents start to experiment with both alcohol and cigarettes. Not much is known about the mechanisms underlying the association between smoking and drinking.[2,9] The comorbidity can be caused by genetic and/or environmental factors that predispose to both smoking and drinking. Environmental factors can be shared between family members (e.g., religious affiliation) or can be specific for an individual (e.g., stressful life events).

With a twin design, it is possible to disentangle the genetic and environmental contributions to the association between alcohol use and smoking. The rationale of the twin method is that monozygotic (MZ) and dizygotic (DZ) twins only differ in the extent to which they share their genes; MZ twins are genetically identical, whereas DZ twins have on average 50% of their genes in common. In the bivariate case, the correlation between trait A in one twin and trait B in the cotwin provides information about the underlying factors that contribute to the phenotypic association within a person. If genetic factors contribute to the association between alcohol use and smoking, the cross-trait correlation in DZ twins is expected to be about half the cross-correlation in MZ twins. If the cross-correlations are about

equal for MZ and DZ twins then the association between alcohol use and smoking can be attributed to correlated shared environmental factors. If the association between alcohol use and smoking is induced by correlated unique environmental factors, the cross-trait cross-twin correlation is expected to be zero while the two traits are correlated within a person.[10]

Univariate twin and adoption studies have shown that individual differences in normal drinking behavior in adults are substantially influenced by genetic factors.[11] Genetic factors also contribute substantially to individual differences in various aspects of smoking behavior in adults.[12] Findings from twin studies of adolescent alcohol and tobacco use suggest that there are only small to moderate genetic influences on both drinking and smoking and that shared environmental influences are more important.[13-17] Although univariate results show that both smoking and drinking are influenced by genetic factors, the question is whether the comorbidity results from the same genes influencing both traits. For adults, there is indeed evidence from twin studies to suggest that correlated genetic factors contribute to the association between alcohol use and smoking.[18,19] Sher et al.[20] found among young adults evidence for a common vulnerability to alcohol use disorder and tobacco dependence. However, Sher et al. could not distinguish between a common genetic predisposition or common environmental influences to both dependencies. To our knowledge there are no published twin studies of the association between alcohol use and smoking during adolescence. The causes of comorbidity might be different for adolescents who experiment with alcohol and tobacco than for adults who may be regular smokers and drinkers.

In this paper, we explore the association between alcohol use and smoking in a population based sample of Dutch adolescent and young adult twins. Previously, we showed that 59% of the individual differences in smoking initiation could be attributed to environmental influences shared by twins and that genetic factors accounted for 31% of the total variance.[13] For alcohol use in adolescents aged 15–16 years, shared environmental factors (between 58 and 88%) were more important than genetic influences (ranging from 0 to 34%), whereas for young adults (aged 17 years and older), 43% of the variance in alcohol use could be attributed to genetic factors and 37% to shared environment.[16] Thus, we found that both individual differences in both alcohol and tobacco use among youngsters could be attributed to moderate genetic influences and to substantial shared environmental influences. These findings raise the question to what extent the same genetic and the same environmental factors influence alcohol use and smoking in adolescents and young adults.

METHODS

Subjects and Measures

This study is part of an ongoing twin-family study of health-related behavior.[13,16,21,22] Questionnaires on health and lifestyle were mailed in 1991 and 1993 to adolescent twins and their parents. Twin families were recruited by asking all city councils in The Netherlands for addresses of twins aged 13–22 years. An initial positive response was received from 252 city councils that supplied 3859 addresses; 177 addresses were available from other sources. After contacting these 4036 families by letter, 2375 twin families indicated that they were willing to complete a questionnaire on health and lifestyle and 1700 families returned these questionnaires in 1991. Data from three families were entered twice by mistake, leaving a total of 1697 families. In 1993, a second questionnaire was mailed to the 4036 families that had been contacted before and to 1987 new families. Additional addresses of new twin families were obtained from city councils that had reacted positively to our request, but were not able to furnish addresses in time for the first wave of data collection. The new addresses included several of the larger cities in the Netherlands. At the second measurement occasion, we obtained questionnaires from 1974 families; 959 families participated for the second time; 877 families came from the new addresses; 138 families were contacted before in 1991 but had not responded at the time. In total, we have studied 2712 families measured at two different occasions, with 959 families participating twice. Results are reported for the 1697 families that participated in 1991 and for the additional 1015 families that participated for the first time in 1993.

Age of the twins was between 12 and 25 years. The mean age of the twins at the first measurement occasion was 17.7 years (SD = 2.3), 4% of this sample was younger than 14 years and 7% was 21 years or older. The mean age of the twins that participated for the first time in 1993 was 16.0 years (SD = 2.7). In this group, 29% of the sample was younger than 14 years and 7% was 21 years or older.

Zygosity of the twins was determined by questionnaire items about physical similarity and frequency of confusion of the twins by family and strangers.[23,24] The classification of zygosity was based on a discriminant analysis, relating the questionnaire items to zygosity based on bloodgroup polymorphisms and DNA fingerprinting in a group of 131 same-sex adolescent twin pairs who participated in a study of cardiovascular risk factors.[25] In that sample, zygosity was correctly classified by questionnaire in 95% of the cases. A subsample of 96 same-sex twins, aged 16 years at the time, participated both in our study and in a longitudinal study of brain development.[26] For these same-sex twins, zygosity was based on blood polymorphisms. The agreement between zygosity based on the questionnaire and zygosity based on blood polymorphisms was 92%. Compared with the classification based on blood polymorphisms, there were 8 MZ twin pairs who were mistakenly assigned as DZ twins by the questionnaire. The total sample was divided into five groups by sex and zygosity; monozygotic males (MZM) and females (MZF), dizygotic males (DZM), and females (DZF) and dizygotic opposite sex twins (DOS).

The questionnaire contained questions about alcohol and tobacco use, sport activities, health, socioeconomic status, religion, and a number of personality factors. In the first questionnaire we asked the twins whether they used or had used alcohol. The question could be answered with "No, seldom or never," "Yes, but not any more" and "Yes." Less than 2% of the sample of twins answered "yes, but not any more." Therefore, the last two answers were collapsed into one category, leaving a dichotomous variable for alcohol use. Those who answered "No, seldom or never" but indicated that the quantity of alcohol they consumed in a week was one or more glasses, were considered alcohol users. Smoking was assessed with the question, "Have you ever smoked?" which could be answered with "No" or "Yes." In the second questionnaire, we asked, "Have you ever used alcohol?" and "Have you ever smoked?" The response categories were "No," "A few times just to try," and "Yes." Those who answered, "A few times just to try," were not considered as alcohol users or smokers. Thus, the variables under study are never used alcohol versus ever used alcohol and never smoked versus ever smoked. The data were analyzed for the 1697 twins that completed the first questionnaire and for the additional 1015 twin pairs that participated for the first time in 1993 at the second measurement occasion. In total, there were 2612 twin pairs available for analyses with complete data for both smoking and alcohol use.
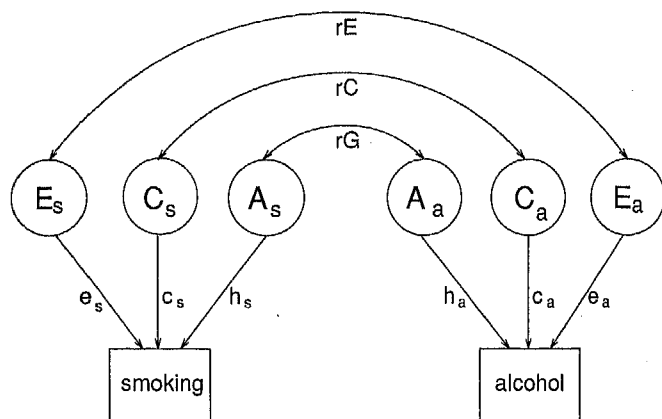
Fig. 1. Path diagram of the bivariate genetic model. Circles represent the latent variables and squares the observed variables. A_s and A_a represent the additive genetic influences on smoking and alcohol use, respectively, C_s and C_a the shared environmental effects, and E_s and E_a the unique environmental influences. The influence of the latent factors on smoking and alcohol use is given by path coefficients h, c, and e, with the subscripts s and a standing for smoking and alcohol use, respectively. The path coefficients equal the standardized regression coefficients and must be squared to equal the proportion of variance accounted for in the observed variable. The phenotypic correlation between alcohol use and smoking is decomposed into that due to the correlation between the genetic factors (rG), the correlation between the shared environmental effects (rC) and the correlation between the unique environmental factors (rE). The phenotypic correlation can be expressed as $rP = h_s\, rGh_a + c_s\, rCc_a + e_s\, rEe_a$.

Statistical Analysis

Quantifying the genetic and environmental factors that contribute to a dichotomous variable is possible by assuming that the variable has an underlying continuous distribution.[27] This underlying continuous variable has been termed the liability. The liability can be due to multiple genetic and environmental influences, giving a normal distribution in liability. A threshold divides the distribution into two classes, e.g., smokers and nonsmokers. The correlation in liability, between two family members for example, is called the tetrachoric correlation. We used PRELIS2[28] to estimate the tetrachoric correlations between twins. For each pair of variables (e.g., drinking in twin 1 and drinking in twin 2; smoking in twin 1 and drinking in twin 2), a two-by-two contingency table was obtained from which the maximum likelihood estimate of the tetrachoric correlation was computed by PRELIS2, under the assumption that the two variables have a bivariate normal distribution. Putting these correlations together results in a four-by-four correlation matrix, giving the correlations between alcohol use and smoking of first and second born twins. The matrix of tetrachoric correlations was computed for each zygosity group. For opposite-sex twins correlations between males and females were computed. The correlation matrices and their asymptotic weight matrices were used for genetic analyses.

A general bivariate genetic model was fitted to the data to test for the genetic and environmental contributions to the variance and covariance of alcohol use and smoking.[10,29] Figure 1 represents the path diagram of the full bivariate model. The variation in alcohol use and smoking is decomposed into genetic effects, environmental effects shared by siblings growing up in the same family, and individual specific environmental effects. The phenotypic correlation between alcohol use and smoking can be decomposed into three parts: a correlation between the genetic factors that influence alcohol use and smoking (rG); a correlation between the shared environmental influences on alcohol use and smoking (rC); and correlated individual specific environmental influences for alcohol use and smoking (rE). Under the full model, the genetic and the two environmental correlations were estimated. Several submodels were fitted to the data by constraining one or more correlations between the latent factors to zero. For example, the hypothesis that the correlation between alcohol use is induced by correlated environmental factors was tested by constraining

the genetic correlation (rG) to zero. The hypothesis that alcohol use and smoking are correlated due to correlated genetic factors can be tested by constraining both the shared environmental correlation (rC) and the unique environmental correlation (rE) to zero. Sex differences were assessed by estimating different parameters for males and females and by estimating in opposite-sex twins the correlation between the shared environmental factors that influence males and the shared environmental factors that influence females. If this correlation is less than unity, this implies that different environmental factors influence alcohol use and smoking in males and females, at least to some extent. The bivariate genetic models were fitted to the data by weighted least squares using Mx.[30] The weight matrices, which are required for weighted least squares estimation, were computed with PRELIS2 and consisted of the asymptotic covariance matrix of the observed correlations. For each model an overall χ^2 test of the goodness-of-fit of the model was obtained. The goodness-of-fit of each submodel was compared with the fit of the full model by likelihood ratio χ^2 tests, with degrees of freedom equal to the number of parameters that are fixed to zero. For each parameter estimate Mx computed likelihood based confidence intervals.[31]

RESULTS

Most adolescents take up the habits of drinking and smoking between ages 15 and 16. Figure 2 shows that the percentage of adolescent boys and girls who have used alcohol increased after the age of 14 and stabilized after the age of 17. The percentage of adolescents who reported that they had ever smoked is shown in Figure 3. The number of smokers increased from around 15% at age 15–16 to around 35% after the age of 17. Based on these age differences in the prevalence of alcohol use and smoking, the sample was divided into three age groups: 12- to 14-year-old twins (n = 650 twin pairs); 15- to 16-year-old twins (n = 705); and 17- to 25-year-old twins (n = 1266; mean age 19.44, SD = 1.56).

Table 1 shows the percentages of alcohol users and smokers for males and females in these three age groups. Alcohol use is more common in males than in females. Between the ages of 15 and 16 years, 46% of the males and 38% of the females stated that they had used alcohol. After the age of 17 years, around 78% of the males and 55% of the females had used alcohol. For all three age groups, the sex differences in alcohol use were highly significant [χ^2 (1) = 5.87, p = 0.02 for 12–14 years olds; χ^2 (1) = 9.02, p = 0.003 for 15–16 years olds; χ^2 (1) = 142.39, p < 0.001 for 17–25 year olds]. For smoking, there were fewer differences between males and females. In the youngest group, 9% of the males and females had ever smoked. In the 15- to 16-year-old group, more females (21%) than males (17%) stated that they had smoked, but this difference was not significant [χ^2 (1) = 3.10, p = 0.08]. In the oldest group, more males (38%) than females (32%) had smoked [χ^2 (1) = 9.93, p = 0.002].

The association between alcohol use and smoking is shown in Table 2. For all three age groups, alcohol use and smoking were highly associated. The odds ratios were significant and ranged from 4.28 in young adult females to 8.89 in young adolescent boys. The relation between alcohol use and smoking can also be expressed as the tetra-
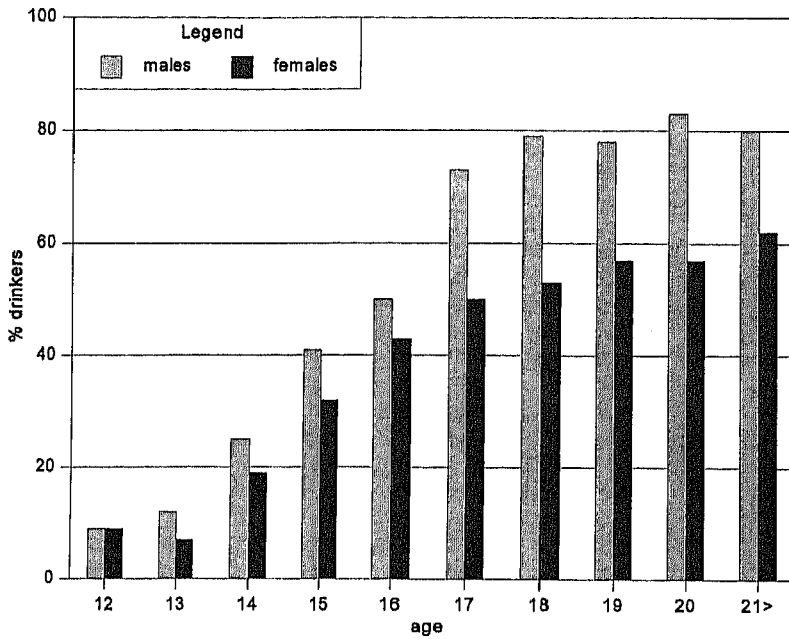
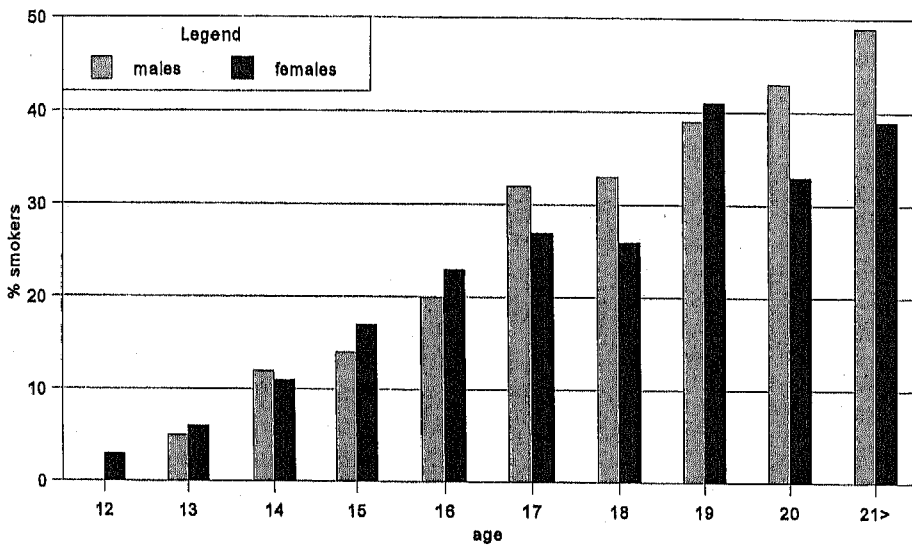Fig. 2. Percentage alcohol users as a function of age.

Fig. 3. Percentage smokers as a function of age.

Table 1. Percentage Alcohol Use and Smoking for Males and Females in Three Different Age Groups

Age (yr)	Males			Females		
	n	Alcohol use	Smoking	n	Alcohol use	Smoking
12–14	573	19.0	8.9	727	14.0	8.8
15–16	667	45.6	16.8	743	37.7	20.5
17–25	1154	77.7	38.2	1378	55.1	32.2

n, number of individuals, based on pairwise deletion.

choric correlation, i.e., the correlation in liability. This correlation was between 0.5 and 0.6 for all three age groups (Table 2). The question was addressed whether this phenotypic correlation between alcohol use and smoking could be attributed to correlated genetic factors and/or correlated environmental factors.

Table 3, 4, and 5 give for each age group the matrices of tetrachoric correlations between alcohol use and smoking

of the first and second born twin. As explained in the introduction, the cross-correlations between the liability in alcohol use in one twin and liability in smoking in the cotwin (or vice versa) can give a first indication of the underlying factors that explain the observed correlation between alcohol use and smoking. For 12- to 14-year-old twins (Table 3) and 15- to 16-year-old twins (Table 4), there was not much difference between the cross-correlations for

Table 2. Magnitude of the Association between Alcohol Use and Smoking for Three Different Age Groups

Age (yr)	Males			Females		
	OR	95% CI	r (SE)	OR	95% CI	r (SE)
12–14	8.89	4.83–16.37	0.61 (0.07)	6.63	3.83–11.46	0.54 (0.07)
15–16	6.15	3.77–10.02	0.55 (0.06)	4.78	3.27–6.99	0.52 (0.05)
17–25	5.68	3.85–8.37	0.53 (0.04)	4.28	3.31–5.52	0.50 (0.04)

OR, odds ratio; CI, confidence interval; r, tetrachoric correlation; SE, standard error.

Table 3. Tetrachoric Correlations for Alcohol Use and Smoking for Each Zygosity Group in 12- to 14-year-old twins

		Males				Females			
		Alcohol		Smoking		Alcohol		Smoking	
		Twin 1	Twin 2	Twin 1	Twin 2	Twin 1	Twin 2	Twin 1	Twin 2
MZ		n = 112 pairs				n = 159 pairs			
Alcohol	Twin 1	1.00				1.00			
	Twin 2	**0.79**	1.00			**0.93**	1.00		
Smoking	Twin 1	0.60	0.51	1.00		0.24	0.34	1.00	
	Twin 2	0.83	0.68	**0.95**	1.00	0.53	0.69	**0.66**	1.00
DZ		n = 88 pairs				n = 118 pairs			
Alcohol	Twin 1	1.00				1.00			
	Twin 2	**0.73**	1.00			**0.75**	1.00		
Smoking	Twin 1	0.57	0.62	1.00		0.55	0.52	1.00	
	Twin 2	0.45	0.60	**0.95**	1.00	0.61	0.54	**0.88**	1.00
DOS		n = 173 pairs							
Alcohol	Male	1.00							
	Female	**0.45**	1.00						
Smoking	Male	0.60	0.32	1.00					
	Female	0.37	0.61	**0.71**	1.00				

Twin pair correlations for alcohol use and for smoking are given in boldface.

Table 4. Tetrachoric Correlations for Alcohol Use and Smoking for Each Zygosity Group in 15- to 16-year-old Twins

		Males				Females			
		Alcohol		Smoking		Alcohol		Smoking	
		Twin 1	Twin 2	Twin 1	Twin 2	Twin 1	Twin 2	Twin 1	Twin 2
MZ		n = 127 pairs				n = 162 pairs			
Alcohol	Twin 1	1.00				1.00			
	Twin 2	**0.74**	1.00			**0.93**	1.00		
Smoking	Twin 1	0.56	0.16	1.00		0.33	0.41	1.00	
	Twin 2	0.56	0.45	**0.75**	1.00	0.35	0.64	**0.92**	1.00
DZ		n = 103 pairs				n = 106 pairs			
Alcohol	Twin 1	1.00				1.00			
	Twin 2	**0.86**	1.00			**0.82**	1.00		
Smoking	Twin 1	0.67	0.39	1.00		0.53	0.28	1.00	
	Twin 2	0.26	0.57	**0.65**	1.00	0.50	0.39	**0.79**	1.00
DOS		n = 207 pairs							
Alcohol	Male	1.00							
	Female	**0.61**	1.00						
Smoking	Male	0.57	0.36	1.00					
	Female	0.24	0.61	**0.32**	1.00				

Twin pair correlations for alcohol use and for smoking are given in boldface.

MZ and DZ twins. For 17- to 25-year-old twins (Table 5) the DZ cross-correlations were on average lower than the MZ cross-correlations. Thus, for the youngest twins it is expected that the association between alcohol use and smoking is explained by correlated shared environmental factors, whereas for the oldest twins correlated genetic factors are expected. The pattern of twin pair correlations within a trait gives a first impression of the factors that

contribute to the familial resemblances. For 12- to 14-year-old twins and 15- to 16-year-old twins, there were only small differences between the MZ and DZ twin pair correlations for alcohol use and for smoking (Table 3 and 4). This finding suggests that for these two age groups shared environmental factors are the most important influences on both alcohol use and smoking. For 17- to 25-year-old twins the pattern of twin pair correlations suggests that both

Table 5. Tetrachoric Correlations for Alcohol Use and Smoking for Each Zygosity Group in 17- to 25-year-old Twins

		Males				Females			
		Alcohol		Smoking		Alcohol		Smoking	
		Twin 1	Twin 2	Twin 1	Twin 2	Twin 1	Twin 2	Twin 1	Twin 2
MZ		n = 197 pairs				n = 266 pairs			
Alcohol	Twin 1	1.00				1.00			
	Twin 2	**0.78**	1.00			**0.81**	1.00		
Smoking	Twin 1	0.45	0.43	1.00		0.47	0.42	1.00	
	Twin 2	0.39	0.47	**0.83**	1.00	0.44	0.50	**0.88**	1.00
DZ		n = 202 pairs				n = 245 pairs			
Alcohol	Twin 1	1.00				1.00			
	Twin 2	**0.58**	1.00			**0.61**	1.00		
Smoking	Twin 1	0.57	0.33	1.00		0.43	0.30	1.00	
	Twin 2	0.24	0.56	**0.57**	1.00	0.24	0.44	**0.77**	1.00
DOS		n = 356 pairs							
Alcohol	Male	1.00							
	Female	**0.38**	1.00						
Smoking	Male	0.56	0.32	1.00					
	Female	0.21	0.56	**0.51**	1.00				

Twin pair correlations for alcohol use and for smoking are given in boldface.

Table 6. Model Fitting Results for 12- to 14-year-old twins

Model	df	χ^2	p	Δdf	$\Delta\chi^2$	p
1. Full sex-dependent model	14	19.84	0.14			
2. rE = 0 for males and females	16	23.25	0.11	2	3.41	NS
3. rC = 0 for males and females	16	77.94	0.00	2	58.10	< 0.01
4. rG = 0 for males and females	16	20.35	0.21	2	0.51	NS
5. rG = 0 and rE = 0 for m&f	18	23.51	0.17	4	3.67	NS
6. Model 5 with rc_{mf} = 1	20	27.67	0.12	2	4.16	NS
7. Model 5 without sex differences	25	44.18	0.01	7	24.34	< 0.01

rc_{mf}, correlation between shared environmental factors in opposite-sex twins.

genetic and shared environmental influences contribute to the familial resemblances in alcohol use and smoking (Table 5).

Genetic Analyses

For each age group, bivariate genetic models were fitted to the data to test whether correlated genetic factors and/or correlated environmental factors contributed to the observed phenotypic correlation between alcohol use and smoking. The models allowed for sex differences by estimating different factor loadings for males and females and by estimating the correlation between the shared environmental factors in opposite-sex twins. Under the full model genetic, shared environmental and unique environmental correlations were estimated. For each latent factor, the correlation was first fixed to zero for males and females separately. Model fitting results report the fixation of a correlation in both sexes unless the conclusion about the significance of a correlation was different for males and females.

Table 6 summarizes the model fitting results for the 12- to 14-year-old twins. Without a significant deterioration in the goodness-of-fit, the unique environmental correlation (model 2) and the genetic correlation (model 4) could be set to zero. By constraining the shared environmental correlation to zero (model 3), the χ^2 increased significantly

($\Delta\chi^2$ (2) = 58.10, p < 0.01). Thus, a model that explained the correlation between alcohol use and smoking by correlated shared environmental factors gave the best description of the data (model 5). The correlation between the shared environmental factors in opposite-sex twins could be set to unity (model 6), indicating that the same environmental factors influence smoking and drinking in males and females. However, a model that constrained the magnitude of the factor loadings to be equal for males and females gave a significantly worse fit, indicating that males and females differ in the extent to which they are influenced by genetic and shared environmental factors. The estimates of the genetic and environmental variances for alcohol use and smoking in 12- to 14-year-old males and females are given in Table 7. For both alcohol use and smoking, there is not much evidence for genetic variance. The confidence intervals showed that only the estimate of the heritability for alcohol in females (48%) was significantly different from zero. Shared environmental influences accounted for 78% and 48% of the total variance of alcohol use in males and females, and for 97 and 84% of the total variance of smoking in males and females. The correlation between the shared environmental factors that influenced alcohol use and the shared environmental factors that determined smoking was estimated at 0.88 in males and 0.86 in females (Table 7). For smoking in males, the unique environmental

Table 7. Parameter Estimates for Alcohol Use and Smoking with 95% Confidence Intervals in Italics

		12–14 years		15–16 years		17–25 years	
		Male	Female	Male	Female	Male	Female
Alcohol	h^2	0.01	0.48	0.01	0.10	0.48	0.75
		0.00–0.24	*0.19–0.74*	*0.00–0.21*	*0.00–0.32*	*0.27–0.91*	*0.46–0.92*
	c^2	0.78	0.48	0.84	0.86	0.32	0.10
		0.59–0.92	*0.23–0.74*	*0.68–0.94*	*0.65–0.99*	*0.00–0.52*	*0.00–0.36*
Smoking	h^2	0.03	0.01	0.00	0.27	0.66	0.33
		0.00–0.17	*0.00–0.36*	*0.00–0.45*	*0.00–0.62*	*0.43–0.86*	*0.21–0.54*
	c^2	0.97	0.84	0.71	0.67	0.19	0.57
		0.83–1.00	*0.61–0.95*	*0.34–0.87*	*0.33–0.96*	*0.04–0.39*	*0.38–0.69*
	rG	—	—	—	—	0.91	0.98
						0.63–1.00	*0.73–1.00*
	rC	0.88	0.86	0.52	0.67	—	—
		0.77–1.00	*0.67–1.00*	*0.37–0.77*	*0.49–0.98*		
	rE	—	—	0.97	1.00	—	—
				0.47–1.00	*0.14–1.00*		

h^2, proportion of total variance due to additive genetic factors; c^2, proportion of total variance due to shared environmental factors; total variance, $h^2 + c^2 + e^2$ = 1; the proportion of total variance due to unique environmental factors is e^2, $1 - (h^2 + c^2)$; rG, genetic correlation; rC, shared environmental correlation; rE, unique environmental correlation.

Table 8. Model Fitting Results for 15- to 16-year-old twins

Model	df	χ^2	p	Δdf	$\Delta\chi^2$	p
1. Full sex-dependent model	14	22.85	0.06			
2. rE = 0 for males	15	31.09	0.01	1	8.20	< 0.01
3. rE = 0 for females	15	24.60	0.06	1	1.75	NS
4. rE = 0 for males and females	16	33.25	0.01	2	10.40	< 0.01
5. rC = 0 for males and females	16	35.97	0.00	2	13.12	< 0.01
6. rG = 0 for males and females	16	25.41	0.06	2	2.56	NS
7. rG = 0 for males rG = 0 and rE = 0 for females	17	29.63	0.03	1	4.22	0.04
8. Model 6 with rc_{mf} = 1	18	33.83	0.01	2	8.42	< 0.05
9. Model 6 without sex-differences	24	56.91	0.00	7	27.28	< 0.01

rc_{mf}, correlation between shared environmental factors in opposite-sex twins.

variance was estimated at zero. The unique environmental variance not only consists of individual specific influences but also includes variance due to measurement errors. Thus, the unique environmental variance is expected to be greater than zero. The low estimate of the unique environmental variance is probably due to the high concordance for not smoking in same-sex male twins (r = 0.95; SE = 0.05 for both MZ and DZ twins). Because of the low rate of smoking in this age group, there were only a few discordant pairs in which one twin was a smoker and the other was not. In sum, the association between alcohol use and smoking in 12- to 14-year-old adolescents is to a large extent due to the same shared environmental influences, both in males and females.

The model fitting results for 15- to 16-year-old twins are shown in Table 8. The unique environmental correlation could be fixed to zero in females (model 3) but not in males (model 2). When the unique environmental correlation was constrained to be zero in both males and females (model 4), the goodness of fit was significantly worse than that of the full model. The shared environmental correlation was also significant, the model that fixed it to zero (model 5) was rejected by the likelihood-ratio test. Without a significant deterioration in the goodness of fit, the genetic correlation could be set to zero (model 6). Model 6, in which

the correlation between alcohol use and smoking was explained by correlated shared environmental factors and correlated unique environmental factors, was the best fitting model. The model in which both the genetic and the unique environmental correlations were constrained to be zero for females (model 7) fitted the data less well. The sex differences were significant (model 8 and model 9). The correlation between the shared environmental influences in opposite-sex twins was estimated at 0.34 for alcohol use and 0.69 for smoking. This finding suggests that environmental effects on males are (to some extent) different from the environmental influences on females. Table 7 shows the parameter estimates for alcohol use and smoking in 15- to 16-year-old twins. Shared environmental influences were the most important factor, explaining 84 and 86% of the individual differences of alcohol use in males and females and 71 and 67% of the total variance in smoking in males and females. The confidence intervals showed that the lower bounds of the heritability estimates were all zero. The upper range of the confidence intervals suggested only small genetic influences, except for smoking in females. The association between alcohol use and smoking in 15- to 16-year-old twins was explained by correlated shared environmental factors in males and females, and by correlated unique environmental factors in males (Table 7). Although

Table 9. Model Fitting Results for Twins Aged 17 Years and Older

Model	df	χ^2	p	Δdf	$\Delta \chi^2$	p
1. Full sex-dependent model	14	4.25	0.99			
2. rE = 0 for males and females	16	7.44	0.96	2	3.19	NS
3. rC = 0 for males and females	16	7.07	0.97	2	2.82	NS
4. rG = 0 for males and females	16	12.53	0.71	2	8.28	0.02
5. rC = 0 and rE = 0 for m&f	18	9.50	0.95	4	5.25	NS
6. Model 5 with rc_{mf} = 1	20	13.23	0.88	2	3.73	NS
7. Model 5 without sex-differences	25	24.91	0.48	7	15.41	0.03

rc_{mf}, correlation between shared environmental factors in opposite-sex twins.

the unique environmental correlation for females is estimated at unity, the unique environmental factors explain only 6 and 4% of the total variance of smoking and drinking, respectively, and thus does not contribute much to the phenotypic correlation between alcohol use and smoking in females.

Table 9 gives the model fitting results for the 17- to 25-year-old twins. The full model gave an excellent fit to the data. In this age group, both the unique environmental correlation (model 2) and the shared environmental correlation (model 3) could be fixed to zero, while the genetic correlation was significant (model 4). The best fitting model was a model that explained the correlation between alcohol use and smoking by correlated genetic factors (model 5). The correlation between the shared environmental factors in opposite-sex twins could be set to unity without a significant loss of fit (model 6). The sex differences in the magnitude of the genetic and environmental influences were significant (model 7). For the 17- to 25-year-old twins the genetic factors were more important compared with the two younger age groups for both alcohol use and smoking (Table 7). The heritability for alcohol use was 48% in males and 75% in females and the heritability for smoking was 66% in males and 33% in females. Shared environmental factors contributed 32 and 10% to the variance of alcohol use in males and females and 19 and 57% to the variance in smoking. The confidence intervals showed that the estimates of the shared environmental influences on alcohol use were not significantly different from zero. There was an almost perfect correlation between genes that affect alcohol use and genes that affect smoking for both males and females.

DISCUSSION

The causes of the association between alcohol use and smoking in Dutch adolescents and young adults were analyzed. The question was addressed to what extent genetic and environmental factors contribute to the comorbidity of alcohol use and smoking. The twin sample was divided into three groups; young adolescent twins aged 12–14 years, 15- to 16-year-old adolescent twins, and young adults aged 17–25 years. For all three age groups, alcohol use and smoking were highly associated (r = 0.5–0.6). Adolescents and young adults who smoked were much more likely to drink alcohol than nonsmokers. The correlation between

alcohol use and smoking was also found across twins; the liability to alcohol use in one twin was correlated with the liability to smoking in the cotwin. This suggests that familial factors are important. Genetic analyses showed that the underlying factors that cause the relationship between alcohol and tobacco use were different in adolescents and young adults.

Initiation of alcohol and tobacco use in adolescents aged 12–16 years are both substantially influenced by shared environmental factors. Not much evidence was observed for the influence of genetic factors. The estimates of the heritabilities ranged between 0 and 10%, with the exception of alcohol use in 12- to 14-year-old females (48%) and smoking in 15- to 16-year-old females (27%). A retrospective study on age of onset of teenage drinking in adult Australian twins aged 20–30 years showed that early versus late onset of drinking was more influenced by genetic factors in females, but by shared environmental influences in males.[14]

Alcohol use and smoking in young adults are largely due to genetic influences and to a less extent to shared environmental effects. For smoking in young adult females, more moderate genetic influences and substantial shared environmental effects were found. Findings from surveys of adult twins consistently show a significant genetic contribution to abstinence of alcohol use and smoking initiation in males and females.[11,12]

Although there is some evidence for genetic influences on alcohol use and smoking in adolescent females, shared environmental factors are most important in the risk of initiation of alcohol and tobacco use in both males and females. The genetic analyses for the adolescent twins showed that the association between drinking and smoking could be explained by shared environmental factors that predispose to both behaviors. For young adult twins, we found that the same genetic factors increase the risk of alcohol use and smoking in both males and females. The findings suggest that once an individual is exposed to the effects of alcohol or nicotine, genetic factors come into play and only those individuals with a certain set of genes will persist in using the substances.[32]

Which shared environmental features might be involved in the association between alcohol use and smoking? Probably most important is the influence of peers. Numerous studies have found that peer influence is one of the most important determinants of the initiation of both cigarette

smoking and alcohol use.[33-40] The peers who encourage the initiation of alcohol use are most likely the same peers who are involved in the onset of smoking. For example, in a prospective study of 2159 nonsmoking secondary school-children aged 11–13, it was shown that the uptake of smoking was associated with having a boyfriend or a girlfriend who drank.[34]

Another aspect that comes to mind when we think of environmental features that are shared between twins is the influence of parents. Positive family relationships and parental monitoring were found to be protective factors for the onset of smoking and drinking.[39,41] However, parenting behavior is not merely an environmental factor. It is possible that parenting behavior is influenced by genetic factors and that these genetic factors are associated with the genetic vulnerability for substance (ab)use. For example, Kendler et al.[42,43] found, in a population based sample of female adult twins, that both the association between depression and alcoholism, and the association between depression and smoking could be explained by common genetic risk factors. In this way, parents at high genetic risk for depression not only are more likely to show negative parenting behavior, they can also transmit their genetic predisposition for substance abuse to their children.

The association between alcohol use and smoking in young adults is due to the same genetic risk factors. A significant genetic correlation between smoking and drinking was also found in a study of older adult male twins.[18] A preliminary analysis of smoking and alcohol problems in two cohorts of Australian female twins (aged 18–25 and 25–89 years) suggested that the same genetic factors predispose to both disorders.[19] Additional evidence that there is a genetic link between smoking and drinking comes from animal studies. It has been demonstrated that there is common genetic control of sensitivities to ethanol and nicotine.[44] Mouse lines that were selectively bred for differential sensitivity to ethanol also differed in sensitivity to nicotine. Other evidence that the same mechanisms are involved in alcohol use and smoking comes from animal studies of cross-tolerance. Chronic treatment with nicotine in mice resulted in the cross-tolerance to some of the effects of ethanol and chronic ethanol-treated animals were cross-tolerant to some of the effects of nicotine.[2,9]

In conclusion, we showed that alcohol use and smoking are associated due to a common set of environmental factors in adolescents and a common set of genes in young adults. Prevention and intervention programs should be aware of the relation between drinking and smoking and should be targeted at both.

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