

# Genetic and Environmental Contributions to the Development of Alcohol Dependence in Male Twins

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**Background:** Information on the heritability of the development of alcohol dependence could provide a better understanding of the importance of genetic components in disease transition.

**Objective:** To examine the genetic and nongenetic contributions to the age at onset of regular alcohol use, the age at diagnosis of alcohol dependence, and the transition from regular alcohol use to alcohol dependence.

**Design:** Classic twin study.

**Setting:** General community.

**Participants:** This study included 3372 twin pairs of known zygosity from the Vietnam Era Twin Registry. The diagnosis of DSM-III-R–defined alcohol dependence and related information were obtained through telephone-administered interviews conducted in 1992.

**Main Outcome Measures:** Standardized proportions due to genetic vs nongenetic factors of the total variation in twin resemblance on the age at onset of regular

alcohol use, the age at meeting criteria for a diagnosis of alcohol dependence, and the transition period from regular alcohol use to a diagnosis of alcohol dependence.

**Results:** Genetic influence accounted for 49% of the variation in the age at diagnosis of alcohol dependence. After adjusting for co-occurring psychiatric diseases, additive genetic factors still explained more than 37% of the variance in age at onset of alcohol dependence and at least 25% of the variance in the transition period between regular drinking and the diagnosis of alcohol dependence. Additionally, after grouping participants as early and late regular users of alcohol, the genetic effects on the transition period for early regular users were statistically significantly greater than those for late regular users.

**Conclusion:** Our results demonstrate a substantial heritable basis for alcohol dependence according to its developmental sequence, including age at onset of regular use, age at diagnosis, and the transition period between regular use and diagnosis.

*Arch Gen Psychiatry.* 2004;61:897-903

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**A**LCOHOL USE DISORDER HAS long been considered an important issue in public health and medicine because of its high prevalence and devastating effect on individuals, families, and society.<sup>1,2</sup> Twin studies<sup>3-5</sup> have revealed a substantial genetic influence on liability for alcohol dependence in registry data and clinically ascertained samples. However, still unclear is the extent to which genetic factors affect the developmental course of alcohol dependence. The developmental sequence for alcohol dependence might be conceptualized as a series of steps or phases. One step represents the age when an individual becomes a regular alcohol user; a second step would be the age when a regular user becomes an abuser. Genetic factors might contribute to each phase to a different extent.<sup>6,7</sup>

Although knowledge on the role of genetic factors in the early or late developmental stage is of great importance for prevention and early intervention, few studies have focused on this issue. Jennison and Johnson<sup>8</sup> conducted a study to relate the development of alcohol dependence in adult children to a positive family history of alcohol dependence. Obot et al<sup>9</sup> found that children with parental alcohol problems tended to initiate use of alcohol at an earlier age than others. Even fewer twin studies have examined the genetic contribution to the development of alcohol problems because of limited statistical strategies. One study by Stallings et al<sup>10</sup> explored the genetic impact on the ages at onset of regular drinking and smoking, and linear regression analysis was applied to elderly affected twin pairs with the assumption that all of the subjects in the sample had passed

the at-risk period for developing these 2 behaviors. However, this approach is difficult to extend to middle-aged twins or studies that concentrate on diseases rather than behaviors, because outcomes of interest could occur after data collection. In this situation, we need an analysis in which time factors are taken into consideration to appropriately handle censored twin data. Given recent remarkable progress on analytical techniques, we are able to use survival analysis techniques that incorporate random effects to handle these types of data and then to obtain valid estimates of parameters of interest.<sup>11-13</sup>

The primary objective of this study is to apply a proportional hazards regression model with random effects to estimate genetic and nongenetic effects. The study uses middle-aged male twin pairs from the Vietnam Era Twin (VET) Registry. Even though genetic contribution to determine the similarity of alcohol dependence in twins has been confirmed, the heritability of the development of alcohol dependence has yet to be determined. With eyes toward prevention and early intervention, we seek to better understand the role of genetic and nongenetic factors in determining the information on age at onset of regular use of alcohol, age at diagnosis of alcohol dependence, and the transition period from regular alcohol use to a diagnosis of alcohol dependence.

## METHODS

### STUDY POPULATION

The members of the VET Registry are 7375 male-male twin pairs born between 1939 and 1957. Both twins served in the military during the Vietnam War era (1965-1975). In 1992, trained interviewers from the Institute for Survey Research at Temple University invited 5150 twin pairs from the registry to participate in telephone-administrated interviews based on the *Diagnostic Interview Schedule Version III Revised (DIS-III-R)*.<sup>14</sup> Among them, 8169 individuals gave verbal informed consent and were successfully interviewed. The interviews included questions about several aspects of alcohol use, such as the frequency, amount, age at onset of each symptom, how long each symptom lasted, and what mood or perception changes associated with alcohol drinking the twins experienced.

The eligible twins in this study were the 3372 pairs with known zygosity. Zygosity had been previously established based on responses to a questionnaire and limited blood group typing.<sup>15-17</sup> In total there were 1874 monozygotic (MZ) twin pairs and 1498 dizygotic (DZ) twin pairs. The mean age of this sample at interview in 1992 was 41.95 years (SE, 2.75 years; range, 33-52 years). The racial distribution was 93.7% non-Hispanic white, 5.9% African American, 0.3% Hispanic, and more than 0.01% other. Of the sample, 88.4% reported that they were "ever regular drinkers."

### MEASURES OF OUTCOMES AND COVARIATES

The age at onset of regular alcohol use, age at diagnosis of alcohol dependence, and the period from the age at onset of regular alcohol use to the onset of diagnosis of alcohol dependence are the 3 primary outcomes in this study. One question in the interview was, "How old were you when you first had any wine, beer, or other alcohol at least once a month for 6 months or more?" We took the response to this question as the definition for *age at onset of regular alcohol use*. People

who were not regular drinkers were considered as having *censored* observations. Individuals who were not regular drinkers were by definition precluded from developing alcohol dependence.

Using standard *DIS-III-R* computer algorithms, we derived individual symptoms and the diagnosis of alcohol dependence based on *DSM-III-R*.<sup>18</sup> We ordered the ages at onset for the 9 *DSM-III-R*-defined diagnostic symptoms for individuals who were regular drinkers. Because the occurrence of at least 3 of the symptoms is the first criterion for making a diagnosis of alcohol dependence and each of the 3 symptoms must last 1 month to make a diagnosis, the age at onset was defined as the age at onset of the third criterion symptom. Subjects free of the diagnosis at interview were coded as *censored* at the age at interview.

The reliability and validity of the diagnosis of alcohol dependence in the VET Registry cohort were examined in a 1998 study.<sup>19</sup> Researchers invited 146 individuals of 5000 twin pairs to have an additional interview and obtained detailed information regarding the diagnosis of alcohol dependence. The test-retest reliability of the 2 interviews, which were approximately 466 days apart, was assessed with the  $\kappa$  coefficient of 0.61 for alcohol dependence. The long interval between the 2 interviews may be partly responsible for the low reliability in this study. Criterion validity was assessed through comparison with the clinical diagnosis for 89 discharged patients with alcoholism in a Veterans Affairs medical center; the sensitivity of telephone-administrated interviews in this study was 96%.

For individuals who were regular drinkers and ultimately became alcohol dependent, we derived a transition period in years by subtracting the age at regular use from the age at diagnosis. Individuals who were regular users but who did not become alcohol dependent were *censored for transition period*. For this outcome measure, we also stratified the sample based on the mean age at onset of regular use to compare genetic effects in those younger than 17 years with those 17 years and older.

The 1992 *DIS-III-R* interview also included questions that allowed us to define several other psychiatric disorders based on the *DSM-III-R*. The diagnoses include nicotine dependence, antisocial personality disorder, depression, and anxiety disorder. The relationship among these variables, genetic factors, and alcohol dependence has been established in the literature.<sup>20-22</sup> We regarded the variables as potential confounders and handled them as binary data. For example, we coded subjects as having presence of antisocial personality disorder if they had experienced the diagnosis before the interview regardless of age at onset.

### STATISTICAL ANALYSIS

Initial analysis of the data involved the prevalence of 4 co-occurring psychiatric disorders and the mean ages at onset of regular alcohol use and meeting a diagnosis of alcohol dependence (**Table 1** and **Table 2**). We then conducted a biometrical genetic survival analysis of the 3 alcohol dependence development measures. Based on the difference in the genetic relationship in MZ and DZ pairs (MZ pairs share 100% of their genes and DZ pairs share on average 50% of their genes), the method attempts to decompose the phenotypic variance in a trait (such as the alcohol developmental measures) into 3 components, known as ACE: additive genetics (A), common environment (C), and unique environment (E). For regular drinking, we assessed all 3772 twin pairs, whereas the 2740 twin pairs with the experience of regular drinking were further analyzed to investigate the age at onset of alcohol dependence and the transition period between

regular alcohol use and alcohol dependence. Before including co-occurring psychiatric diseases in statistical models, 2 different analytic strategies were used: structural equation models (SEMs) and random-effects models (REMs). We then took comorbid conditions into consideration and treated the age at onset of regular drinking as an effect modifier in subsequent analyses using the REMs we proposed. Each of these approaches is discussed herein.

### STRUCTURAL EQUATION MODELS

The SEMs have been widely used in twin studies to partition the covariance between phenotypes into genetic and environmental parts.<sup>23</sup> However, the application of SEMs to censored data can be complex, because survival data are neither binary nor continuous and individuals can develop an event *after* the time of data collection. The most convenient method is to apply the multiple cut points to censored twin outcomes and construct several contingency tables for the pairwise twin data.<sup>24,25</sup> Then the polychoric correlations for MZ and DZ twins from 2 sets of contingency tables can be compared.

We implemented the SEM approach by classifying twins into 6 age categories: younger than 25 years, 25 to 29 years, 30 to 34 years, 35 to 39 years, 40 to 44 years, and 45 years or older. Using these categories, we cross-classified each of the age at onset phenotypes and calculated polychoric correlations. For twins 45 years or older, ages at onset for both twins were cross-tabulated into a 6 × 6 table in which censored data were placed exclusively in the last column or the last row—the last age category. Then, we created a 5 × 5 table for MZ twins aged 40 to 44 years. The procedure was repeated as subjects aged 30 to 34 years (the youngest age group in our sample) were placed. The same technique for forming contingency tables was then applied to DZ twins.

Next, one summary polychoric correlation coefficient for each zygosity was attained, and the magnitude of genetic contribution was assessed in the best-fitting model based on the principle of parsimony. The model with ACE components was considered the full model, and it was then compared with other reduced models. The analyses were implemented using the computer analysis software package Mx.<sup>26</sup>

**Table 1. The Distribution of 4 Co-occurring Psychiatric Disorders by Zygosity in the Vietnam Era Twin Registry**

Psychiatric Disorders	Subjects, No. (%)	
	Monozygotic Twins (n = 3748)	Dizygotic Twins (n = 2996)
Antisocial personality disorder	108 (2.9)	86 (2.9)
Depressive disorder	352 (9.4)	329 (11.0)
Anxiety disorder	80 (2.1)	76 (2.5)
Nicotine dependence	1734 (46.3)	1487 (49.6)

**Table 2. Age at Interview, Age at Regular Alcohol Use, and Age at Onset of Dependence**

Variable	Monozygotic Twins (n = 3748)			Dizygotic Twins (n = 2996)		
	No. of Subjects	Mean (Range)	SE	No. of Subjects	Mean (Range)	SE
Age, y	3748	41.8 (33-52)	2.9	2996	42.1 (34-51)	2.5
Age at onset of regular alcohol use, y*	3283	18.5 (5-40)	2.9	2684	18.4 (5-39)	2.7
Age at onset of alcohol dependence, y*	1210	25.4 (15-47)	6.3	1036	25.2 (12-45)	6.5

\*Only subjects with onset of regular drinking.

### RANDOM-EFFECTS MODELS

The REMs, in which the random effects are used to explain the heterogeneity in survival time, have become popular for modeling the dependence among the observations of correlated survival data.<sup>27</sup> Their application has been proposed for solving variable ages at onset among family members in human genetics<sup>28,29</sup> and recurrent depressive episodes in a population-based registry.<sup>30</sup>

We used a Cox proportional hazards model with random effects to analyze censored time to event data in twins. Here, random-effects terms were added to describe the relationship within a twin pair. In addition to 2 shared random effects for MZ and DZ twin pairs, individual random effects were used to represent complicated dependence in twin data. Thus, there is 1 shared random effect and 2 individual random effects for MZ and DZ twin pairs, respectively. The formulation of this model is as follows:

$$\lambda_{ij}(t) = \lambda_0(t) \exp(\beta X_{ij} + b_j Z_{ij}), \quad i = 1, 2; j = 1, 2, \dots, n$$

where  $\lambda_{ij}(t)$  denotes the hazard function at time  $t$  for the  $i$ th member of the  $j$ th twin pair, and  $\lambda_0(t)$  is called the baseline hazard function.  $X_{ij}$  denotes a covariate vector for the fixed effects,  $\beta$ , for an individual, and  $Z_{ij}$ , usually a subset of  $X_{ij}$ , denotes a covariate vector for the random effects,  $b_j$ , for observations in the  $j$ th cluster. If there are no covariates,  $Z_i$  is simply a vector of 1 and 0s.

Here,  $b_j$  is a vector of 6 random effects ( $b_0, b_1, b_2, b_3, b_4, b_5$ ) for the  $j$ th twin pair as described.  $b_0, b_1$ , and  $b_2$  are 3 random effects for the MZ pairs. The random effects terms are  $b_0 + b_1$  and  $b_0 + b_2$  for the 2 twins, respectively. Here,  $b_0$  represents the overall mean for the MZ twins, and  $b_1$  and  $b_2$  represent the effect specific to the twins in an MZ pair. Similarly, for the DZ pairs, the random-effects terms are  $b_3 + b_4$  and  $b_3 + b_5$ .

The components of  $b_j$  ( $b_0, b_1, b_2, b_3, b_4, b_5$ ) are assumed to follow independent normal distributions with means equal to zero and with 6 variance parameters ( $\sigma_b^2$ ) to summarize their distributions. Then these 6 parameters are reparameterized to be 3 major parameters of interest in twin studies: the part of the total variance due to A, C, or E effects ( $\sigma_A^2, \sigma_C^2, \sigma_E^2$ ). For example, within MZ twin pairs, the variance of  $b_0$ , the shared part for 2 twins, equals the sum of A effects and C effects ( $\sigma_{b_0}^2 = \sigma_A^2 + \sigma_C^2$ ). Within DZ twin pairs, the variance of  $b_3$  equals the sum of the C effects and half of the A effects ( $\sigma_{b_3}^2 = \sigma_C^2 + [\sigma_A^2/2]$ ). In contrast, the dissimilarity of 2 twins within a DZ twin pair can come from either E factors or the difference of A factors between 2 twins ( $\sigma_{b_4}^2 = \sigma_{b_5}^2 = \sigma_E^2 + [\sigma_A^2/2]$ ). The following equation shows the relationship between the 6 independent random effects and 3 major parameters in twin studies:

$$b_j^T = \begin{pmatrix} b_0 \\ b_1 \\ b_2 \\ b_3 \\ b_4 \\ b_5 \end{pmatrix} \sim N \left( \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_A^2 + \sigma_C^2 & 0 & 0 & 0 & 0 & 0 \\ 0 & \sigma_C^2 & 0 & 0 & 0 & 0 \\ 0 & 0 & \sigma_E^2 & 0 & 0 & 0 \\ 0 & 0 & 0 & \sigma_A^2/2 + \sigma_C^2 & 0 & 0 \\ 0 & 0 & 0 & 0 & \sigma_A^2/2 + \sigma_E^2 & 0 \\ 0 & 0 & 0 & 0 & 0 & \sigma_A^2/2 + \sigma_E^2 \end{bmatrix} \right)$$

**Table 3. Results of Fitting SEMs and REMs to Data From the Vietnam Era Twin Registry**

Variable	SEM Estimates (95% CI), %*	REM Estimate (SE), %*
Age at onset of regular alcohol use (n = 6744)		
Genetic variance ( $\sigma_A^2/\sigma^2$ )	35.2 (9.1-62.3)	34.8 (2.4)
Common environmental variance ( $\sigma_C^2/\sigma^2$ )	31.8 (7.6-54.0)	13.2 (3.5)
Unique environmental variance ( $\sigma_E^2/\sigma^2$ )	33.0 (26.0-41.0)	52.0 (2.6)
Age at onset of alcohol dependence (n = 5480)		
Genetic variance ( $\sigma_A^2/\sigma^2$ )	47.7 (28.7-53.3)	49.4 (6.5)
Common environmental variance ( $\sigma_C^2/\sigma^2$ )	0	0
Unique environmental variance ( $\sigma_E^2/\sigma^2$ )	52.3 (46.7-58.5)	50.6 (6.5)
Transition period (n = 5468)†		
Genetic variance ( $\sigma_A^2/\sigma^2$ )		42.3 (3.0)
Common environmental variance ( $\sigma_C^2/\sigma^2$ )		0.9 (2.5)
Unique environmental variance ( $\sigma_E^2/\sigma^2$ )		56.7 (1.3)

Abbreviations: CI, confidence interval; REM, random-effects model; SEM, structural equation model.

\*The core model with additive genetics (A), common environment (C), unique environment (E) effects. The proportion of total variance for the transition period and age at onset from A, C, or E effects in a linear transformation model.

†The period between age at onset of regular alcohol use and age at onset of meeting a diagnosis of alcohol dependence.

To assess the interaction between age at onset of regular use and A or C effects, we added 6 more random-effect terms ( $b_6, b_7, b_8, b_9, b_{10}, b_{11}$ ) to the model. One set of parameters,  $\sigma_{A1}^2, \sigma_{C1}^2$ , and  $\sigma_{E1}^2$ , was estimated from the first 6 random effects to generate the within-twin dependence among early regular users, whereas a second set of parameters ( $\sigma_{A2}^2, \sigma_{C2}^2$ , and  $\sigma_{E2}^2$ ) was generated based on the second set of 6 random effects for late regular users. In addition to fitting core REMs, we added significant comorbid psychiatric disorders as covariates for fixed effects in the REMs to obtain adjusted estimates of parameters.

We used an expectation-maximization algorithm, which treats random effects as missing data, to obtain maximum likelihood estimates.<sup>13,31</sup> To make the results more interpretable, we used an equivalent linear transformation model to convert the parameter estimate for  $\sigma_E^2$ <sup>32</sup> and calculated standardized proportions of the total variance in similarity of time-scaled outcomes from A, C, and E. All of the analyses used an algorithm developed in C programming language.

## RESULTS

### ADJUSTED GENETIC VS NONGENETIC CONTRIBUTIONS TO ALCOHOL DEPENDENCE

The mean age at meeting a diagnosis of *DSM-III-R*-defined alcohol dependence in the VET Registry cohort is 25.3 years (SE, 6.4 years). **Table 3** presents the parameter estimates for the standardized proportion of variation attributable to ACE components for age at onset of regular alcohol use and age at onset of alcohol dependence. For age at onset of regular alcohol use, genetic

**Table 4. Random-Effects Model Fits to Twin Data on Age at Onset of Alcohol Dependence and Transition Period\***

Variable	Age at Onset (n = 5480)	Transition Period (n = 5468)†
Parameter estimate for fixed effects, $\beta$ (SE)		
Antisocial personality disorder	1.34 (0.13)	0.98 (0.12)
Anxiety disorder	0.39 (0.15)	0.36 (0.14)
Depressive disorder	0.58 (0.08)	0.53 (0.08)
Nicotine dependence	1.03 (0.06)	0.98 (0.06)
Standardized proportion of the total variance, % (SE)‡		
Genetic variance ( $\sigma_A^2/\sigma^2$ )	37.1 (4.0)	25.5 (1.7)
Common environmental variance ( $\sigma_C^2/\sigma^2$ )	0	4.2 (1.5)
Unique environmental variance ( $\sigma_E^2/\sigma^2$ )	62.9 (4.0)	70.2 (2.1)

\*The model with variables, including antisocial personality disorder, anxiety disorder, depressive disorder, and nicotine dependence, in addition to additive genetics (A), common environment (C), and unique environment (E) effects.

†Years between age at onset of regular use and age at onset of alcohol dependence.

‡The proportion of total variance for age at onset of alcohol dependence or transition period from A, C, or E effects in a linear transformation model.

effects are similarly estimated in both types of models with the amount of nearly one third of variation for age at onset of regular use. In contrast, the results from the SEM are different from those from the REM on the C and E parts. More than 30% of the total variance for onset of regular drinking could be attributed to C factors in the SEM, whereas C effects were estimated to affect only 13% of the total variation based on the REM. In the REM for age at onset of diagnosis, the expectation-maximization algorithms converge, with  $\sigma_C^2$  approaching 0, and the results of all estimates approximated those from the SEM. Almost half of the variation in latent liability for age at onset could be explained by A factors, whereas the remaining part of the total variation arose from an E origin unshared by 2 members of a twin pair. As for the transition period from regular alcohol use and onset of diagnosis, SEMs are difficult to handle with bivariate censored data with age-incongruent outcomes like this. According to the REM, A factors could account for a substantial (42%) portion of the total variance in liability.

### GENETIC VS NONGENETIC CONTRIBUTIONS TO ALCOHOL DEPENDENCE

Based on Cox proportional hazards models, univariate analysis showed that all covariates were significant in predicting the outcomes of interest as the dependency within twin pairs was taken into consideration. We retained 4 co-occurring psychiatric disorders for fixed effects in further analyses and presented estimates for the age at onset of diagnosis and the transition period in **Table 4**. According to the 95% confidence intervals, all adjusted estimates of fixed effects remained statistically significant in predicting the hazard rate. For age at onset, people with antisocial personality disorder tended to have a 3.8 ( $\exp[1.34]$ )-fold increase in the hazard rate for developing alcohol dependence at any specific age compared

**Table 5. Random-Effects Model Fits to Twin Data Dichotomized by Age at Onset of Regular Alcohol Use**

Variable	Core Model		Full Model	
	Early Regular Users (n = 1681)	Late Regular Users (n = 3787)	Early Regular Users (n = 1681)	Late Regular Users (n = 3787)
Parameter estimate for fixed effects, $\beta$ (SE)				
Antisocial personality disorder	...	...	1.01 (0.11)	
Anxiety disorder	...	...	0.37 (0.14)	
Depressive disorder	...	...	0.51 (0.07)	
Nicotine dependence	...	...	0.99 (0.05)	
Standardized proportion of the total variance, % (SE)*				
Genetic variance ( $\sigma_A^2/\sigma^2$ )	45.3 (2.1)	16.3 (0.6)	30.9 (2.1)	9.9 (1.3)
Common environmental variance ( $\sigma_C^2/\sigma^2$ )	0	16.7 (1.9)	0	14.5 (2.5)
Unique environmental variance ( $\sigma_E^2/\sigma^2$ )	54.7 (1.0)	67.1 (1.1)	69.1 (2.1)	75.6 (2.6)

\*The proportion of total variance for age at onset of alcohol dependence or transition period from additive genetics, common environment, and unique environment effects in a linear transformation model.

with people without antisocial personality disorder, with the adjustment of other co-occurring diseases and the dependence within a twin pair. Controlling for other co-occurring conditions, subjects with a lifetime history of depressive disorder at interview were more likely to develop alcohol dependence at any specific age than people without depression based on a positive estimate of the fixed effect (0.58).

We calculated the standardized proportion of the total variance in failure time similarity owing to each component here. In these full models, 37% of the total variation in age at meeting a diagnosis can be attributed to genetic factors, which exert less influence than those in the core model given in Table 3. For transition period, the discrepancy in estimates of interest between core and full models becomes more evident with the increment of C from 0% to 4.24% and the decrement of A from 42% to just 25%.

#### EARLY VS LATE REGULAR ALCOHOL USERS

To further examine the genetic contribution to the transition period based on age at onset of regular alcohol use, we fitted the models with interaction between random effects and age at onset of regular use, and the results are presented in **Table 5**. Four co-occurring conditions significantly predicted the transition period. Irrespective of the adjustment of covariates for fixed effects, the C estimate converged to 0 during parameter estimation for early regular users, whereas it accounted for more than 10% of the variability in late regular users. The A variation is consistent in both core and full models to have significantly greater effects on early users than on late users. In the comparison of results in core and full models, A factors made a decreased contribution by controlling for 4 psychiatric disorders, and only 9.9% of variation in the transition time could be explained by A factors among late regular users.

#### COMMENT

Our results demonstrate the heritability of the development course of alcohol dependence. The A factors influence when an individual becomes a regular drinker, how

fast an individual progresses from regular drinking to meeting a diagnosis of alcohol dependence, and when an individual develops alcohol dependence. To our knowledge, this study is the first twin study to address the genetic influence on different phases in the development of alcohol dependence. We could benefit from the present study by having a better understanding regarding the genetic contribution over time. However, our findings seem to be comparable to results from previous studies that focused on the heritable basis for the occurrence of alcohol dependence.

Approximately 40% to 60% of the variation in risk of alcohol abuse and dependence has been identified in the literature as being due to genetic influence.<sup>5</sup> For age at onset of regular alcohol use, C factors have effects in determining twin resemblance, yet A effects were found to contribute approximately one third of the total variation. On the other hand, almost half of the variation in determining age at onset could be explained by A factors. Such a finding must be interpreted cautiously, because, as has been pointed out by Lyons et al,<sup>21</sup> the estimate of genetic contribution could vary with the reliability of the report. Thus, unreliable reports on an earlier event, such as age at onset of regular use, may lead to underestimation of the genetic contribution. Nevertheless, it is reasonable that a shared familial environmental influence may contribute more to a temporally early event than to a late one. Despite the possibility of unreliability of reports, our findings still provide evidence of a strong heritable basis for age at onset of regular alcohol use. As for the transition period, the study shows that once an individual became a regular alcohol user, the length of the progression to alcohol dependence is still substantially affected by underlying genetic factors.

The issue of confounding is not straightforward in twin studies. In 1999, MacGregor<sup>33</sup> cited one example about smoking as a confounding factor for genetic influence on the occurrence of smoking-related disease. The genetic component was incorrectly regarded as an important factor in determining the disease because smoking was ignored. It has long been debated whether there is a common vulnerability for alcohol dependence among people with co-occurring diseases or causally related pathways from these diseases.<sup>34,35</sup> If a common etiologic ba-

sis is adopted, all these diseases would be regarded as manifestations of a general vulnerability. Otherwise, parallel pathways from genetic liabilities to co-occurring diseases, which predispose to the development of alcohol dependence, have to be established. However, the distinction between these 2 hypotheses is barely verified in a retrospective study with an adult sample.<sup>36</sup>

To address this concern, we fitted both core and full models with the adjustment of 4 co-occurring conditions to data from the VET Registry. Not surprisingly, the adjusted estimates of genetic effects from the full models are smaller, especially for the transition period (from 42% to 25%). As mentioned, it is not yet clear which model would give us the best information. However, our findings support the hypothesis that the development of alcohol dependence is substantially heritable, and the adjusted genetic estimates could be deemed the lower boundary of the true effect. In this case, we could claim that A factors account for more than 37% of the variance for age at meeting a diagnosis of alcohol dependence and at least 25% of the variance for the transition period.

Age at first drink has been found to be highly associated with the occurrence of alcohol dependence.<sup>36,37</sup> In our study, age at onset of regular alcohol use acted as an effect modifier in the development of alcohol dependence. Through fitting the models with interaction, we obtained significantly different genetic effects on the length of the transition period. Of the people who had become regular users, early regular users seem to be influenced by genetic factors in the development of alcohol dependence more than late users do. In addition, common environments shared by 2 members of a twin pair play a moderate role in determining the length of the progression to alcohol dependence in late regular users. However, we should cautiously interpret the results because, as is the case with the association between alcohol dependence and associated psychiatric diseases, different hypotheses for the relationship between age at first use and the risk of alcohol dependence have been proposed.<sup>36-38</sup>

As for the comparison of SEMs and REMs, our findings show that the estimates of the variance of random effects are not always similar. Using SEMs we would lose important information by transforming censored data into an ordinal arrangement. In addition, SEMs have limitations when they are extended to handle censored data with age-incongruent outcomes such as the transition period in our study. In performing SEMs, we cannot place all twins with the censored transition period in the last row or column of a contingency table as usual because both twins in a twin pair might have censored outcomes with different magnitudes. In addition, individual covariates or time-varying covariates would be hard to handle in SEMs, whereas even interactive terms can be flexibly examined in REMs. To deal with correlated censored data, we suggest the use of appropriate models based on survival analysis such as REMs. It is important to have future research on the application of REMs, especially model diagnostics concerning the effect of violating the assumption of proportional hazards or the influence, because a great deal of nonaffected individuals exist in data.

There are limitations in our study that should be considered. First, the study results cannot be generalized to women. The role of genetic inheritance in the occurrence of alcohol use disorder has been found to differ by sex in previous twin studies.<sup>39</sup> More studies of women will be needed to confirm the importance of genetic components in disease transition. Second, the equal environment assumption and the lack of assortative mating are 2 critical assumptions to the validity of twin studies.<sup>23</sup> If either of these assumptions is incorrect, the genetic influence will be biased. However, one study<sup>40</sup> conducted to test equal environment assumption for the VET Registry cohort showed no significant violations. Third, the data collection of the VET Registry relied on retrospective reports of age at onset of each symptom, which resulted in an inability to avoid recall bias. In addition, subjects with alcohol dependence would tend to have recall problems regarding age at onset of any alcoholic symptom. However, recall errors for both zygotic types would operate in the same direction and are likely to be of similar magnitude. The recall error would be nondifferential, and the bias of our study results would be toward the null.

Notwithstanding these limitations, our registry-based study has enough power to detect the significance of genetic effects of interest because of the large sample size, and, moreover, sampling bias, which is a major concern in studies using either volunteers or hospital-based samples, can be avoided. Although it is true that this exclusively male-male twin sample limits the generalizability of our study, by restricting sex, we can prevent confounding effects by sex and then explore the pure relation of genetic factors on disease progression.

Our findings confirm a strong heritable basis for the progression from regular drinking to alcohol dependence in men in addition to the risk of alcohol dependence. However, some research questions surrounding the nature of the relationship between this disease and associated psychiatric diseases remain unanswered.

*Submitted for publication June 19, 2003; final revision received March 15, 2004; accepted March 15, 2004.*

*The US Department of Veterans Affairs has provided financial support for the development and maintenance of the VET Registry.*

*Numerous organizations have provided invaluable assistance in the conduct of this study, including Department of Defense (Washington, DC); National Personnel Records Center, National Archives and Records Administration (St Louis, Mo); the Internal Revenue Service (Washington); National Opinion Research Center (Chicago, Ill); National Research Council, National Academy of Sciences (Washington); and the Institute for Survey Research, Temple University (Philadelphia, Pa). Most important, we gratefully acknowledge the continued cooperation and participation of the members of the VET Registry and their families. Without their contribution this research would not have been possible.*

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