

Origins and Consequences of Age at First Drink. II. Familial Risk and Heritability

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Background: The association of age at first drink (AFD) and alcoholism may reflect a common inherited vulnerability to disinhibitory behavior and psychopathology rather than a direct influence of the former on the latter. We tested the common-inherited-vulnerability hypothesis by determining whether AFD is familial and heritable.

Methods: A sample of 1,232 14-year-old twins was classified according to their biological parents' AFD.

Results: Lifetime symptoms of externalizing disorders (i.e., conduct disorder and oppositional defiant disorder) were significantly higher in the sons but not the daughters of parents whose AFD came before age 15 years. Offspring symptoms of internalizing disorders (i.e., major depressive disorder, separation anxiety disorder, and overanxious disorder) were not significantly associated with parental early use of alcohol in either sons or daughters. Early use of alcohol in mothers but not fathers was associated with a significant increase in both sons' and daughters' risk of alcohol use by age 14. The contribution of genetic and environmental factors to risk of early alcohol use was investigated in a sample of 416 monozygotic (MZ) and 225 like-sex dizygotic (DZ) 14-year-old twin pairs. Twin similarity for early alcohol use was substantially greater in MZ than DZ twins in boys but about equally similar in MZ and DZ twins in girls. Estimated heritability of early alcohol use was significantly greater in boys (55%) than girls (11%), in part because the genetic factors underlying symptoms of disinhibitory psychopathology contributed more to risk of early alcohol use in boys than girls.

Conclusions: Early use of alcohol is familial and, at least in males, heritable. The familial transmission of early alcohol use is caused in part by genetic risk for disinhibitory psychopathology in males and to shared environmental factors in girls. These results provide some support for a common-inherited-vulnerability hypothesis, and suggest that the processes underlying early alcohol use may differ in boys and girls.

Key Words: Age at First Drink, Alcoholism, Disinhibitory Psychopathology, Heritability, Sex Differences.

INDIVIDUALS WHO TAKE their first drink of alcohol before the age of 15 years are substantially more likely to become alcoholic than those whose first drink comes after the age of 20 years (Grant and Dawson, 1997). In the first article in this series, we further showed that an early age at first drink (AFD) is also associated with increased rates of nicotine dependence, illicit substance abuse, antisocial personality and conduct disorder, academic underachievement, relatively low scores on a personality measure of constraint, and reduced P3 amplitude (McGue et al., 2001). One explanation for these associations is that an early AFD disrupts normal social and intellectual development and so increases the risk for a wide range of social and psychological pathologies (Dewit et al., 2000; York, 1999). This interpretation is challenged, however, by our observation that

some of the behavioral problems seen in individuals with an early AFD exist before their first trying alcohol (McGue et al., 2001).

An alternative explanation for the association of AFD with substance-use disorders and psychopathology is that both are manifestations of an underlying susceptibility to disinhibitory behavior and psychopathology. This common-vulnerability hypothesis could account for the existence of childhood behavioral problems that predate AFD and the multiple diverse outcomes associated with an early AFD, all of which seem to be linked to disinhibitory processes (Iacono et al., 1999).

Jessor and Jessor (1977) were among the first to show that multiple indicators of behavioral deviance, including the early use of alcohol, substantially covary in adolescence. Prescott and Kendler (1999) were the first to present empirical support for the hypothesis that the association of AFD with alcoholism was caused by a common inherited vulnerability. Specifically, from a biometrical analysis of data from nearly 9000 adult twins, Prescott and Kendler concluded that the association of AFD with alcoholism was genetically rather than environmentally mediated. AFD and alcoholism both seemed to be manifestations of a

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common inherited liability, which they labeled a “general vulnerability to problem behaviors.” Because the outcomes associated with early AFD imply a somewhat more specific diathesis than “problem behavior,” we prefer the phrase “common vulnerability to disinhibited behavior and psychopathology.”

In this study, we used a twin-family design to test some of the implications of the common inherited vulnerability hypothesis. Specifically, we sought to determine whether early AFD in parents is associated with increased behavioral problems and an early AFD in their adolescent offspring and whether AFD is heritable.

METHODS

Subjects

Subjects were drawn from the Minnesota Twin Family Study, a longitudinal study of the development of alcoholism and substance-use disorders. Details of the community-based ascertainment procedures and analysis of nonparticipants is given in Iacono et al. (1999) and in the first article in this series (McGue et al., 2001). Results for two overlapping samples are reported here. The first sample will be referred to as the family sample. It is based on the 1232 individual twins who completed both an intake assessment at age 11 years and a follow-up assessment at age 14 years and for whom AFD could be determined for both biological parents. This sample represents 81% of the 1518 11-year-old twins who completed the Minnesota Twin Family Study intake assessment. The family sample was used to explore the offspring correlates of having a parent with an early AFD. It consisted of 625 (51%) girls and 607 boys.

The second sample, which will be referred to as the twin sample, was used to explore genetic and environmental contributions to AFD. This sample consists of 641 twin pairs in which both members completed an intake and follow-up assessment. The twin and family samples substantially overlap, with the difference in the two samples owing to the requirement of biological parental assessment of AFD in the latter but not the former. The 641 pairs in the twin sample included 215 male monozygotic (MZ), 103 male dizygotic (DZ), 201 female MZ, and 122 female DZ twin pairs.

Measures

AFD. As part of a comprehensive assessment of clinical status and substance use/abuse, parents were asked if they had ever used alcohol. If they reported having used alcohol, they were further asked, “How old were you the first time you used alcohol (on your own; more than your parents allowed you to)?” Although the amount of alcohol sampled was not explicitly specified in the question, interviewers were instructed to record the age at which a respondent first had a drink of alcohol (rather than merely a sip). Parents were classified as having an early AFD if they reported having used alcohol before the age of 15 years and a late AFD otherwise. Although parent AFD is actually continuous, we have elected to dichotomize it in this way both because AFD before age 15 is strongly associated with behavioral problems and alcoholism in adulthood (Grant and Dawson, 1997; McGue et al., 2001) and because we could establish use of alcohol only through age 14 in their participating adolescent offspring in the analysis of familial resemblance. Included in the late-AFD parent group were the fewer than 2% of parents who reported never having drunk alcohol. Thus, parents were actually classified as having early versus nonearly AFD, but we use the term “late AFD” to ease presentation. At the age-14 follow-up, twins were designated as early users if they reported ever having used alcohol without parental permission and non-users otherwise.

Among parents, 279 (23%) of the fathers and 159 (13%) of the mothers reported having had their first drink of alcohol before age 15. There was

also a slight, but statistically significant, tendency for a mother with an early AFD to be paired with a father with an early AFD (odds ratio = 1.7, tetrachoric correlation = 0.17). Among their adolescent offspring, 208 (34%) of the boys and 188 (31%) of the girls reported having tried alcohol by age 14. The substantially higher rate of AFD by age 14 and the narrowing of the sex difference in the offspring as compared with the parental generation could reflect the effect of cultural factors on adolescent drinking behavior. Alternatively, parents may misperceive their AFD as having occurred more recently than it actually occurred (i.e., telescoping; Groves, 1989). Nonetheless, even if telescoping did occur, it is not clear that it could explain the substantial reduction in the sex difference.

Clinical Outcomes in Twin Offspring Assessed at Ages 11 and 14. The Diagnostic Interview for Children and Adolescents (DICA-R; Reich, 2000; Welner et al., 1987), modified to provide coverage of DSM-III-R criteria, was administered at both the intake and follow-up assessments of the twins. DSM-III-R was the diagnostic standard when the longitudinal study began. The mothers of the twins also completed the parent version of the DICA at both assessments. At a given assessment, mothers and their twins were interviewed by different interviewers. Before the assignment of diagnoses, interviewer notes and, when ambiguities remained, the audio tapes of the interviewing sessions were reviewed in a consensus case conference. The consensus conference included at least two advanced clinical psychology students who reviewed the evidence for every symptom with some indication of being present. Symptoms were considered to be present only if judged to be clinically significant in severity and frequency. Symptom reports from twins and their mothers were combined by using best-estimate procedures (Reich and Earls, 1987). Specifically, a symptom was considered to be present if either the mother or the twin reported that it was present.

At both the intake and follow-up assessment of the male twins, the symptom-reporting period was the twin’s lifetime. For female twins, the reporting period was the twin’s lifetime at intake and the period since last assessment at follow-up. Although the reporting periods thus differed slightly for boys and girls, symptom reports were combined across assessments to remove this difference. Specifically, a symptom was considered to be present if it was reported as present at either the intake or follow-up assessment. In this way, all symptoms were lifetime through the first follow-up assessment of the twins.

This report is based on the following DSM-III-R disorders: attention deficit-hyperactivity disorder (ADHD), conduct disorder (CD), oppositional defiant disorder (ODD), major depressive disorder (MDD), separation anxiety (SEP-ANX), and overanxious disorder (OVER-ANX). Statistical analyses focused on the symptom counts for these six disorders as well as total externalizing (Total EXT = ADHD + CD + ODD) and internalizing (Total INT = MDD + SEP-ANX + OVER-ANX) symptom-count scales. Our decision to analyze symptom counts rather than individual diagnoses is based on the arguments presented by Burt et al. (2001). Briefly, although the contribution of genetic and environmental factors seems to be similar for diagnoses and symptom counts (Livesly et al., 1993), the latter provides more statistical power than the former in biometrical analysis of twin data.

For descriptive purposes, we also report lifetime prevalence rates of the DSM-III-R diagnoses as a function of parent AFD. Data from the mother’s and twin’s DICA reports were combined to form best-estimate diagnoses by following the procedures given by Reich and Earls (1987). Best-estimate diagnoses were made at three levels of certainty: definite (all relevant DSM-III-R symptom criteria met), probable (one symptom short of criteria), and possible (two symptoms short). The purpose of the probable and possible diagnoses is to identify adolescents who are likely to develop the disorder as they are followed through the period of risk. Because the diagnoses used here are based on a combination of the longitudinal assessments at ages 11 and 14, only diagnoses at the definite level of certainty were considered positive. An individual was considered to have a lifetime best-estimate diagnosis if he or she met criteria at a definite level of certainty at either the intake or the follow-up assessment.

Zygosity. Zygosity was based on the consensus of three separate estimates: (1) parents’ report of physical similarity (e.g., eye and hair color),

(2) an algorithm that made use of twin similarity for ponderal and cephalic indices and fingerprint ridge, and (3) the judgment of two senior staff. When these three estimates agreed, zygosity was assigned accordingly. When there was disagreement, a serological analysis was performed. To establish the reliability of our method of zygosity determination, we completed serological analyses on 50 twin pairs in whom the three estimates of zygosity had agreed. In every pair, the consensus zygosity was confirmed by the serological analysis.

Statistical Analysis

The relationship between parent AFD and offspring functioning was determined by using logistic regression analysis for the categorical outcome (i.e., early alcohol use) and analysis of variance (ANOVA) for quantitative outcomes (i.e., the symptom-count scales). These analyses involved three main effects: offspring sex (male versus female), mother's AFD (early versus late), and father's AFD (early versus late), and all possible interactions. Because the responses of the two members of a twin pair will be correlated, ANOVA and logistic regression analyses were completed by using hierarchical linear models (HLM; Bryk and Raudenbush, 1992). HLM computes the relevant test statistic, taking into account the correlated nature of the twin data. HLM also allowed us to make use of data from twin pairs in which only one member of the pair completed the relevant assessment. For quantitative outcomes, HLM analyses were completed by using PROC MIXED from the Statistical Analysis System (SAS; Littell et al., 1996). For categorical outcomes, HLM analyses were completed by using PROC GENMOD from SAS (Liang and Zeger, 1986).

Twin intraclass correlations for the symptom count scales and tetrachoric correlations for early alcohol use were estimated by maximum likelihood by using PRELIS2 (Scientific Software International, Lincolnwood, IL). (Jöreskog and Sörbom, 1993). Biometrical analysis of the twin data was based on the correlation matrices estimated in PRELIS2 and the associated asymptotic variance-covariance matrices. These matrices were input into Mx (Neale et al., 1999) for biometrical model fitting by using the weighted least-squares option. Before correlation estimation, the symptom scales were log-transformed and double-entered to improve the distributional properties of the scales. Model degrees of freedom were adjusted to reflect the double entering of the data.

Biometrical analysis of early-alcohol-use status was based on the assumption that early alcohol use is a threshold character. The variability in liability for early alcohol use was assumed to be an additive function of additive genetic effects (a^2), shared environmental effects (c^2), and nonshared environmental effects (e^2). Shared environmental influences contribute to phenotypical similarities, whereas nonshared environmental factors contribute to phenotypical differences among reared-together relatives. The multivariate model used to estimate the contribution of additive genetic, shared environmental, and nonshared environmental factors to early alcohol use is represented schematically in Fig. 1. This model can be conceptualized as involving two parts (although in actuality all analyses were completed in a single step). First, we estimated the total contribution of additive genetic, shared environmental, and nonshared environmental factors to liability variance. Next, the total estimates of a^2 , c^2 , and e^2 were each partitioned into a portion in common with the symptom scales and a residual component. Because our analysis of the family data indicated that only EXT symptoms were associated with parent AFD, only the effects of ADHD, CD, and ODD were considered in the analysis of the twin data. In this way, we sought to determine the extent to which the genetic and environmental influences on early alcohol use were mediated by genetic and environmental effects on indicators of disinhibitory psychopathology.

The model was parameterized by using a Cholesky decomposition. In our application of the Cholesky model, variance in liability to early use of alcohol was partitioned into portions in common with and residual to the effects of disinhibitory psychopathology. Nonetheless, it is important to emphasize that our cross-sectional data do not allow us to unequivocally infer direction of causal influence. In the analysis, model parameters were first estimated separately in males and females and then constrained to be equal in the two samples to determine whether genetic and environmental

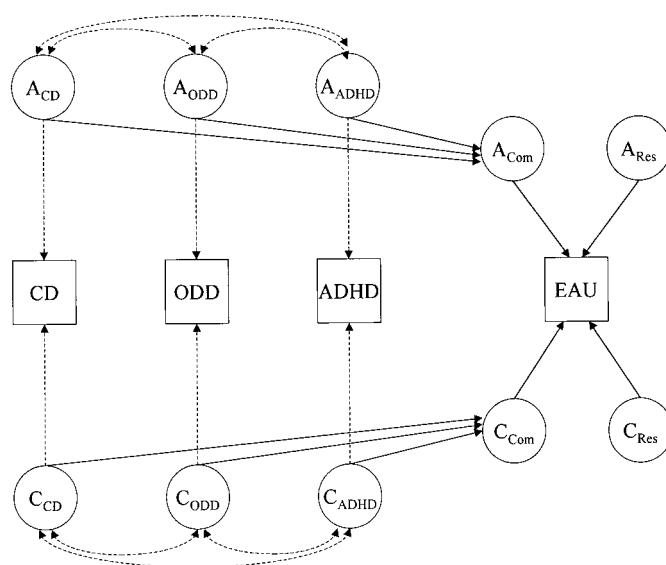


Fig. 1. Biometrical model fit to the twin symptom count and early alcohol use data. Variation in symptoms of conduct disorder (CD), oppositional defiant disorder (ODD), and attention deficit-hyperactivity disorder (ADHD) is decomposed into underlying genetic (A), shared environmental (C), and nonshared environmental (E) components. Variation in liability to early alcohol use (EAU) is also decomposed into A, C, and E factors, which in turn are apportioned into components in common (COM) with (A_{Com} , C_{Com} , E_{Com}) and residual (RES) to (A_{Res} , C_{Res} , E_{Res}) the effects on disinhibitory psychopathology. For ease of presentation, only A and C effects are shown, although E effects were also included in the models fit and reported here. The parameterization of E followed the same pattern as depicted for A and C. Parameters associated with dashed lines did not vary significantly by sex in the best-fitting model, whereas parameters associated with solid lines did.

parameter estimates varied significantly by sex. Model fit was evaluated with both the goodness-of-fit χ^2 test statistic and the Akaike Information Criterion (AIC; Akaike, 1987). Likelihood-based confidence intervals based on the procedures given by Neale and Miller (1997) were derived for parameter estimates.

RESULTS

The Relationship of Parent AFD and Offspring Functioning

Table 1 gives lifetime rates of DSM-III-R diagnoses in the twins as a function of a parent AFD. In boys, rates of EXT diagnoses increase as a function of number of parents with early AFD and are especially high among sons with early AFD in both their mothers and their fathers. In this group, 59% of the boys had CD, 59% had ODD, and 73% had any EXT disorder as compared with rates of 13, 13, and 21%, respectively, among sons whose mothers and fathers both had not drunk before age 15. Parent AFD was not consistently related to EXT diagnoses in daughters or INT diagnoses in both sons and daughters. Also given in Table 1 is offspring rate of alcohol use by age 14 as a function of parental AFD. Early use of alcohol is especially high among both the sons and daughters of parents who both have an early AFD.

Table 2 gives mean symptom counts and rate of early alcohol use among offspring as a function of early use of alcohol in their biological mothers and fathers. The p values for the main and interaction effects from the univariate

Table 1. Lifetime Prevalence (%) of DSM-III-R Diagnoses and Rate (%) of Alcohol Use by Age 14 Among Offspring of Parents Whose AFD Was Either Early or Late

Variable	Father late, mother late	Father early, mother late	Father late, mother early	Father early, mother early	Total
Sons (<i>n</i>)	425	109	51	22	607
ADHD	3.3 ^a	5.5 ^a	9.8 ^a	9.1 ^a	4.4
CD	12.5 ^a	25.7 ^b	21.6 ^{a,b}	59.1 ^c	17.3
ODD	12.9 ^a	20.2 ^a	13.7 ^a	59.1 ^b	16.0
Any EXT	20.8 ^a	32.1 ^a	29.4 ^a	72.7 ^b	25.4
MDD	2.1 ^a	3.7 ^a	0.0 ^a	4.5 ^a	2.3
SEP-ANX	2.1 ^a	3.7 ^a	2.0 ^a	0.0 ^a	2.3
OVER-ANX	2.1 ^a	1.8 ^a	2.0 ^a	0.0 ^a	2.0
Any INT	6.1 ^a	8.3 ^a	3.9 ^a	4.5 ^a	6.3
Early alcohol use	31.5 ^a	33.0 ^a	51.0 ^b	54.5 ^b	34.3
Daughters (<i>n</i>)	429	110	58	28	625
ADHD	2.3 ^a	9.1 ^a	0.0 ^a	0.0 ^a	1.8
CD	2.5 ^a	4.9 ^a	7.0 ^a	7.1 ^a	3.5
ODD	2.5 ^a	5.8 ^a	5.4 ^a	7.1 ^a	3.5
Any EXT	3.4 ^a	9.7 ^a	10.7 ^a	7.1 ^a	5.4
MDD	6.4 ^a	6.8 ^a	8.8 ^a	3.7 ^a	6.6
SEP-ANX	2.5 ^a	0.0 ^a	1.8 ^a	0.0 ^a	1.9
OVER-ANX	1.0 ^a	2.9 ^a	1.8 ^a	0.0 ^a	1.3
Any INT	8.4 ^a	8.8 ^a	10.5 ^a	3.7 ^a	8.4
Early alcohol use	28.2 ^a	30.9 ^{a,b}	34.5 ^{a,b}	46.4 ^b	30.1

Early, age 14 or younger; late, age 15 or later or lifetime nondrinkers.

ADHD, attention deficit-hyperactivity disorder; CD, conduct disorder; ODD, oppositional defiant disorder; Any EXT, any externalizing disorder (ADHD, CD, or ODD); MDD, major depressive disorder; SEP-ANX, separation anxiety disorder; OVER-ANX, overanxious disorder; INT, any internalizing disorder (MDD, SEP-ANX, or OVER-ANX).

Rates with different superscripts are significantly different by post hoc analysis at $p < 0.05$.

ANOVAs and logistic regression analyses by HLM analysis are given in Table 3; post hoc comparisons of means by HLM are summarized in Table 2. Except for symptoms of ADHD, early use of alcohol in both mothers and fathers was significantly associated with higher symptoms of EXT psychopathology in offspring. For CD, ODD, and Total EXT, the main effect of both mother and father AFD was statistically significant. Moreover, the effect of parent AFD interacted with offspring sex, because the sex \times mother AFD interaction was significant for CD, the sex \times father AFD interaction was significant for ODD, and both interaction effects were significant for Total EXT.

Because the pattern of results is very similar for CD, ODD, and Total EXT, we focus on the latter to characterize the nature of the significant effects. The group means for this scale are plotted in Fig. 2 to facilitate interpretation. Mean EXT varies significantly as a function of parents' early alcohol use in sons, but not daughters. For sons, the total number of EXT symptoms was lowest when neither biological parent had tried alcohol before age 15, intermediate when one but not both had used alcohol early, and highest when both biological parents had tried alcohol before age 15. Only the two most extreme EXT means were significantly different in post hoc comparisons. Nonetheless, sons show the monotonic increase in mean EXT score with number of early-alcohol-using parents that is expected if parent early use of alcohol is linked with offspring disinhibitory psychopathology. In girls, the mean number of EXT symptoms varied minimally and nonsignificantly across groups and did not increase monotonically as a function of number of parents with early AFD.

Unlike the EXT symptom scales, there was no significant relationship between parental AFD and offspring INT symptom counts (Table 3). Figure 3 shows that the mean number of INT symptoms varied very little as a function of parent AFD, suggesting that failure to find significant effects did not owe to lack of statistical power.

Twin Correlations

Offspring early use of alcohol was significantly associated with early AFD in mothers, but not fathers (Tables 2 and 3), indicating that AFD is familial. The aim of the analysis of the twin data is to characterize the nature of the familial transmission of AFD. Because the analysis of the family data indicated that parent AFD is associated with offspring EXT but not INT psychopathology, analysis of the twin data focused on ADHD, CD, ODD, and Total EXT. Twin intraclass correlations for these symptom-count scales and tetrachoric correlations for early alcohol use are reported in Table 4. The MZ correlations are consistently greater than the DZ correlations for the four symptom scales, and this implicates the importance of genetic influences. Because the male and female correlations for these scales are quite similar, the magnitude of genetic influence does not seem to vary by sex. In contrast, there is a marked sex difference in the correlations for early alcohol use. For boys, the MZ correlation substantially exceeds the DZ correlation, implicating genetic factors; but for girls, the MZ and DZ correlations are quite similar, implicating the importance of environmental influences only.

Table 2. Mean and SD of DSM-III-R Symptom Counts in Offspring of Parents Whose AFD Was Either Early or Late

Variable	Measure	Father late, mother late	Father early, mother late	Father late, mother early	Father early, mother early
Sons	<i>n</i>	425	109	51	22
ADHD	Mean	2.08 ^a	2.79 ^a	2.67 ^a	2.91 ^a
	SD	2.68	3.17	2.82	2.88
CD	Mean	1.39 ^a	2.06 ^b	2.22 ^b	3.14 ^b
	SD	1.75	2.51	2.04	2.83
ODD	Mean	2.93 ^a	3.41 ^a	3.43 ^a	5.27 ^b
	SD	2.08	2.30	2.17	2.47
Total EXT	Mean	6.40 ^a	8.27 ^b	8.31 ^{a,b}	11.31 ^b
	SD	5.20	6.93	5.47	6.56
MDD	Mean	0.59 ^a	0.74 ^a	0.61 ^a	1.05 ^a
	SD	1.51	1.66	1.47	2.19
SEP-ANX	Mean	0.29 ^a	0.31 ^a	0.33 ^a	0.27 ^a
	SD	0.68	0.70	0.68	0.63
OVER-ANX	Mean	0.37 ^a	0.40 ^a	0.51 ^a	0.41 ^a
	SD	0.86	0.90	0.92	0.67
Total INT	Mean	1.25 ^a	1.46 ^a	1.45 ^a	1.73 ^a
	SD	2.08	2.36	2.30	2.41
Daughters	<i>n</i>	429	110	58	28
ADHD	Mean	1.29 ^a	1.53 ^a	1.26 ^a	0.64 ^b
	SD	1.97	2.47	1.62	1.31
CD	Mean	0.57 ^a	0.86 ^b	0.82 ^{a,b}	0.68 ^{a,b}
	SD	1.17	1.44	1.51	1.12
ODD	Mean	2.17 ^a	2.03 ^a	2.58 ^a	2.89 ^a
	SD	1.91	1.99	2.09	2.02
EXT	Mean	4.02 ^a	4.46 ^a	4.67 ^a	4.21 ^a
	SD	3.93	4.46	3.72	3.80
MDD	Mean	0.74 ^a	0.75 ^a	0.93 ^a	1.14 ^a
	SD	1.53	1.75	1.98	2.08
SEP-ANX	Mean	0.87 ^a	0.89 ^a	0.67 ^a	0.54 ^a
	SD	1.30	1.43	1.30	1.10
OVER-ANX	Mean	0.88 ^a	0.78 ^a	0.88 ^a	0.96 ^a
	SD	1.34	1.29	1.24	1.57
Total INT	Mean	2.49 ^a	2.42 ^a	2.47 ^a	2.64 ^a
	SD	2.79	3.27	3.08	3.28

Early, age 14 or younger; late, age 15 or later or lifetime nondrinkers.

ADHD, attention deficit-hyperactivity disorder; CD, conduct disorder; ODD, oppositional defiant disorder; Total EXT, total externalizing symptoms (ADHD + CD + ODD); MDD, major depressive disorder; SEP-ANX, separation anxiety disorder; OVER-ANX, overanxious disorder; Total INT, total internalizing symptoms (MDD + SEP-ANX + OVER-ANX).

Means with different superscripts are significantly different by post hoc analysis at $p < 0.05$.

Table 3. The p Values From the Hierarchical Linear Analysis of the Effect of Parent AFD (Before Versus After Age 15) and Offspring Sex on Offspring Symptom Counts and Rate of Alcohol Use by Age 14

Outcome	Main effects			Interaction effects			
	Offspring sex	Mother AFD	Father AFD	Sex × mother	Sex × father	Mother × father	Sex × mother × father
Symptom scales (ANOVA)							
ADHD	<0.001	NS	NS	NS	NS	NS	NS
CD	<0.001	0.02	0.01	0.01	NS	NS	NS
ODD	<0.001	<0.001	0.005	NS	0.03	NS	NS
Any EXT	<0.001	0.04	0.02	0.03	0.04	NS	NS
MDD	NS	NS	NS	NS	NS	NS	NS
SEP-ANX	<0.001	NS	NS	NS	NS	NS	NS
OVER-ANX	<0.001	NS	NS	NS	NS	NS	NS
Any INT	<0.001	NS	NS	NS	NS	NS	NS
Categorical (logistic regression)							
Early alcohol use	NS	0.01	NS	NS	NS	NS	NS

ADHD, attention deficit-hyperactivity disorder; CD, conduct disorder; ODD, oppositional defiant disorder; Any EXT, any externalizing disorder (ADHD, CD, or ODD); MDD, major depressive disorder; SEP-ANX, separation anxiety disorder; OVER-ANX, overanxious disorder; INT, any internalizing disorder (MDD, SEP-ANX, or OVER-ANX).

NS, not significant, $p > 0.05$.

Biometrical Analysis

Biometrical methods were used to estimate the contribution of genetic and environmental factors to early alcohol use and to decompose those contributions into portions in common with and residual to genetic and environmental

effects underlying symptoms of disinhibitory psychopathology. The most general multivariate model we fit involved estimating all parameters separately in the male and female samples. This model did not fit the data ($\chi^2_{12} = 29.0, p = 0.004, AIC = 5.0$). Constraining all parameter estimates to

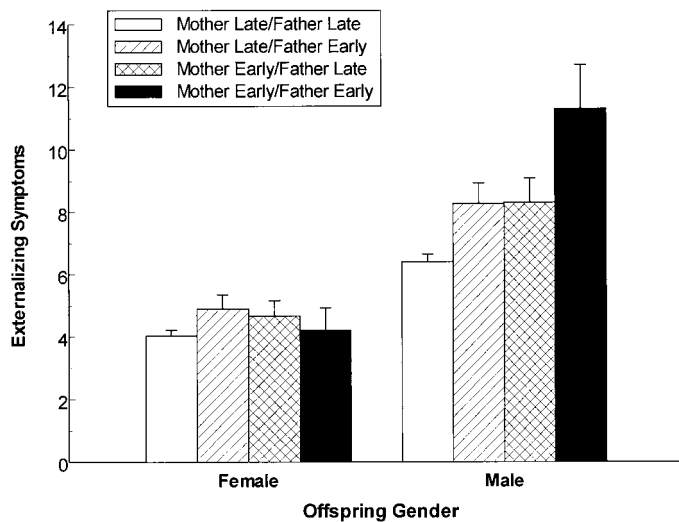


Fig. 2. Interaction of offspring sex and parent early-drinking status (age 14 or younger versus 15 or older) in prediction of mean number of externalizing symptoms. An early age at first drink is associated with a significantly greater number of externalizing symptoms in sons, but not daughters. Error bars demarcate 1 SEM.

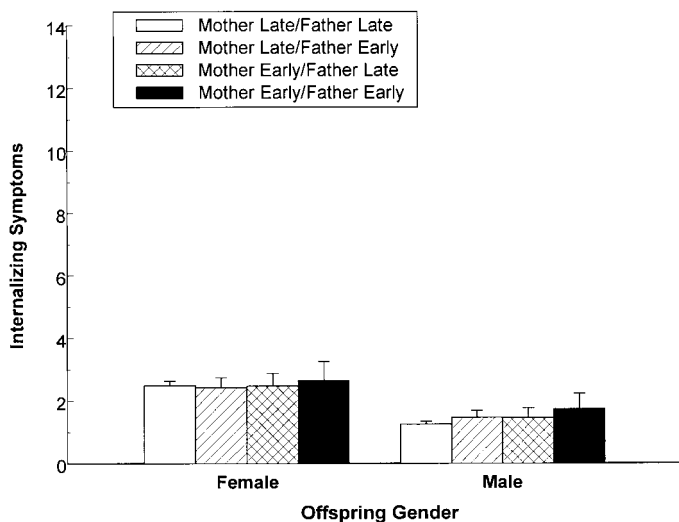


Fig. 3. Relationship of parent early-drinking status (age 14 or younger versus 15 or older) with mean number of internalizing symptoms in their offspring. An early age at first drink was not significantly associated with internalizing symptoms in either sons or daughters. Error bars demarcate 1 SEM.

be equal in boys and girls produced a model with a much poorer fit to the data ($\chi^2_{42} = 100.0, p < 0.001, AIC = 16.0$), implicating sex differences in parameter estimates. In contrast, constraining estimates of only those parameters governing genetic and environmental influences on CD, ODD, and ADHD to be equal in boys and girls (i.e., the parameters indicated by a dashed line in Fig. 1) produced a best-fitting model that fit the data ($\chi^2_{30} = 42.8, p = 0.06, AIC = -17.2$). Thus, sex differences in parameter estimates were specific to those involving early alcohol use, a finding anticipated by the previously reported sex difference in twin correlations. Summary parameter estimates from this best-fitting model are given in Table 5.

The proportion of liability variance for early alcohol use associated with genetic, shared environmental, and non-shared environmental factors was, respectively, 0.55 [95% confidence interval (CI) 0.24, 0.75], 0.20 (0.03, 0.51), and 0.25 (0.18, 0.32) in boys. For girls, the respective estimates were 0.11 (0.01, 0.36), 0.65 (0.42, 0.78), and 0.25 (0.18, 0.31). The major influence on early alcohol use thus seems to be genetic factors in boys and shared environmental factors in girls. At the phenotypical level, CD, ODD, and ADHD were substantially correlated with early alcohol use. The proportion of liability variance associated with symptoms of disinhibitory psychopathology (i.e., the squared multiple correlation between the three symptom scales and early use liability) differed minimally in girls (0.19; 95% CI 0.09, 0.32) and boys (0.18; 95% CI 0.08, 0.33).^{*} The genetic and environmental factors underlying the association of disinhibitory symptoms with early alcohol use, however, did differ in the two sexes. This association was mediated predominantly by shared environmental factors in girls but by both genetic and shared environmental factors in boys.

DISCUSSION

The observation of a strong association of AFD with risk of alcoholism has had a major effect on thinking about prevention efforts and etiological models of alcoholism. In the first article in this series, we showed that rather than being specifically associated with alcoholism, AFD is predictive of a wide range of adult pathologies. A common factor underlying the multiple correlates of early AFD is disinhibitory behavior and psychopathology, with indications of disinhibitory processes both predating and following an early AFD.

On the basis of an analysis of retrospective reports of AFD in a large sample of adult twins, Prescott and Kendler (1999) concluded that the association between alcoholism and AFD is genetically and not environmentally mediated. In this report we have explored several predictions of the common inherited vulnerability hypothesis advanced by Prescott and Kendler: namely, is AFD familial and heritable, and do heritable effects on AFD overlap with those on disinhibitory psychopathology?

We have shown that parents who first drank before age 15 have sons, but not daughters, who evidence increased risk of disinhibitory psychopathology. As compared with boys whose parents both did not drink before age 15, the

^{*} The squared multiple correlations of 0.19 in girls and 0.18 in boys may seem inconsistent with the parameter estimates reported in Table 5. The latter indicate that 0.69 (i.e., 0.03 + 0.65 + 0.01) of the liability variance in early alcohol use in girls and 0.38 of the liability variance in boys (i.e., 0.16 + 0.20 + 0.02) is associated with the additive genetic, shared environmental, and nonshared environmental factors underlying ADHD, CD, and ODD. But the squared multiple correlations give the proportion of liability variance attributable to the observed ADHD, CD, and ODD symptom counts, whereas the model-based estimates give the proportion of liability variance attributable to underlying latent factors. Consequently, there is no inconsistency.

Table 4. Twin Correlations (95% Confidence Intervals) for Externalizing Symptom Count Scales and Early Use of Alcohol

Measure	Males		Females	
	MZ (<i>n</i> = 215)	DZ (<i>n</i> = 103)	MZ (<i>n</i> = 201)	DZ (<i>n</i> = 122)
ADHD	0.63** (0.53, 0.73)	0.26 (0.08, 0.43)	0.65** (0.55, 0.76)	0.23 (0.07, 0.38)
CD	0.73** (0.65, 0.81)	0.53 (0.39, 0.67)	0.68* (0.57, 0.79)	0.50 (0.35, 0.66)
ODD	0.68** (0.60, 0.77)	0.41 (0.24, 0.58)	0.68** (0.59, 0.77)	0.45 (0.33, 0.57)
EXT	0.74** (0.67, 0.82)	0.50 (0.35, 0.66)	0.67 (0.58, 0.76)	0.53 (0.41, 0.65)
Early alcohol use	0.76** (0.69, 0.36)	0.36 (0.12, 0.60)	0.76 (0.70, 0.82)	0.67 (0.55, 0.79)

ADHD, attention deficit-hyperactivity disorder; CD, conduct disorder; ODD, oppositional defiant disorder; EXT, total number of externalizing symptoms (ADHD + CD + ODD).

Estimates are tetrachoric correlations. MZ correlations significantly different from DZ correlation at * $p < 0.05$; ** $p < 0.01$.

Table 5. Proportion of Liability Variance in Early Alcohol Use in Common With and Residual to the Effects Underlying Symptoms of Conduct Disorder, Oppositional Defiant Disorder, and ADHD

Variance component	Males	Females
a^2		
Common	0.16	0.03
Residual	0.39	0.08
Total (95% CI)	0.55 (0.24, 0.75)	0.11 (0.01, 0.36)
c^2		
Common	0.20	0.65
Residual	0.00	0.00
Total (95% CI)	0.20 (0.03, 0.51)	0.65 (0.42, 0.78)
e^2		
Common	0.02	0.01
Residual	0.23	0.23
Total (95% CI)	0.25 (0.18, 0.32)	0.24 (0.18, 0.31)

ADHD, attention deficit-hyperactivity disorder.

a^2 is proportion of variance associated with additive genetic factors, c^2 is the proportion associated with shared environmental factors, and e^2 is the proportion associated with nonshared environmental factors. Parameters derived from the best-fitting biometrical model are described in the text.

average number of symptoms of disinhibitory psychopathology increased by approximately two in sons with one early-drinking parent and by approximately five in sons with two early-drinking parents. Early AFD did not, however, have a consistent effect on daughters' rate of disinhibitory psychopathology, nor did it have an effect on INT symptoms in either sons or daughters.

An early AFD was also associated with increased likelihood of alcohol use before age 15 in offspring, although the familial pattern here was a bit more complicated than with the symptom scales. Specifically, early use of alcohol in biological mothers, but not biological fathers, was significantly associated with an increased rate of early alcohol use in both sons and daughters. In interpreting this result, it is important to recognize that in the parent generation, use of alcohol before age 15 selects for a more extreme phenotype in women than men. Thus if parent early AFD is an indicator of genetic liability for early alcohol use, early-drinking mothers may carry a greater genetic loading than early-drinking fathers [cf Cloninger et al. (1978)].

Biometrical analysis of twin data on early alcohol use and symptoms of disinhibitory psychopathology provided further support for the effects revealed in the analysis of the

family data. For boys, the heritability of early alcohol use was moderate to strong ($a^2 = 0.55$). Consistent with the finding that parent early alcohol use was associated with increased EXT symptoms in sons, early alcohol use in sons was in part attributable to genetic influences on disinhibitory psychopathology. In girls, the heritability of early alcohol use was modest ($a^2 = 0.11$). Consistent with the finding that parent early alcohol use was not associated with increased EXT symptoms in daughters, early alcohol use in daughters is largely independent of genetic influences on disinhibitory psychopathology.

Our findings thus support the existence of a common inherited vulnerability to early alcohol use and disinhibitory psychopathology. They further suggest that the mechanisms underlying this vulnerability may differ in boys and girls. Previous research on the heritability of alcohol use in adolescence has not always observed sex differences in the magnitude of genetic influences. For example, in a sample of 15- to 16-year-old Dutch twins, Koopmans et al. (1997) reported that shared environmental factors accounted for 58% and genetic factors for 34% of the variance in alcohol use liability; these estimates did not vary significantly by sex. Nonetheless, other studies suggest that the contribution of genetic factors to adolescent alcohol use may differ in girls and boys. On the basis of a large sample of adult Australian twins who retrospectively reported the age at which they first used alcohol, Heath and Martin (1988) reported that genetic factors accounted for 47% of the variance in abstinence through age 20 in males and 35% in females. In a report on an independent sample of 17-year-old twins from this study, Han et al. (1999) reported that the heritability of lifetime alcohol use was 60% in males and 10% in females, although in that sample the two estimates did not differ significantly.

Even though the literature is not altogether consistent, the hypothesis that adolescent alcohol use is most strongly influenced by environmental factors in girls and genetic factors in boys warrants additional investigation. How the contribution of disinhibitory psychopathology to early alcohol use differs in boys and girls may be important to

understanding this sex difference. Our findings suggest that the magnitude of genetic and environmental influences on symptoms of disinhibitory psychopathology do not vary significantly by sex. Similarly, the overall contribution of disinhibitory psychopathology to early alcohol use does not seem to vary by sex (i.e., at the phenotypical level, symptoms of disinhibitory psychopathology accounted for approximately 20% of the liability variance in early alcohol use for both girls and boys). However, the basis for the association between early alcohol use and disinhibitory psychopathology does seem to vary by sex. This association seems to be almost exclusively environmentally mediated in girls, but both genetically and environmentally mediated in boys. Clearly such a finding must be interpreted cautiously until independently replicated. If this sex difference is replicable, identifying the specific environmental factors that underlie it would likely illuminate the different processes underlying early alcohol use in boys and girls.

We interpret our findings as supporting a common inherited vulnerability model to explain the association of early alcohol use and alcoholism. Early AFD seems to be a risk factor for alcoholism because it is, in part, an indicator of disinhibitory psychopathology. Nonetheless, it would be inappropriate to conclude on the basis of our results that early AFD does not increase risk of alcohol and substance abuse, because early exposure to alcohol among disinhibited youth may increase the likelihood of progression to dependence. In any case, rather than arguing against the importance of prevention efforts, we believe that our finding that adolescents who use alcohol early in life are at increased risk for a wide range of behavioral problems supports an increased emphasis on early prevention efforts. Where our findings might challenge conventional wisdom is in terms of the appropriate target of prevention efforts. That is, delaying AFD may prove less effective in the long term than addressing the multitude of behavioral problems that exist among a vulnerable subset of adolescents.

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