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Origins and Consequences of Age at First Drink. I. Associations With Substance-Use Disorders, Disinhibitory Behavior and Psychopathology, and P3 Amplitude

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Background: Although an early age at first drink has been repeatedly associated with substantially elevated rates of alcoholism, the mechanisms underlying this association remain unclear. We investigated whether the association of age at first drink (AFD) with alcoholism was more consistent with the hypothesis that the former causes the latter or the hypothesis that both are manifestations of some common vulnerability.

Methods: We investigated whether substance use and mental health disorders, education, IQ, and personality were associated with AFD in a sample of 2670 adults; whether P3 amplitude was associated with AFD in a sample of 1127 17 year olds; and whether indicators of disinhibitory psychopathology assessed at age 11 predicted AFD by age 14 in a sample of 1343 adolescents.

Results: In adults, AFD was associated not only with alcohol dependence, but also with a broad array of indicators of disinhibitory behavior and psychopathology including nicotine dependence, illicit drug abuse and dependence, conduct disorder, antisocial personality disorder, underachievement in school, and the personality trait of constraint. In 17 year olds, AFD was also associated with reduced P3 amplitude, a well-documented psychophysiological marker of alcoholism risk. Finally, in the early-adolescence sample, measures of behavioral disinhibition, including oppositionality, hyperactivity/impulsivity, and inattentiveness assessed at age 11 predicted drinking onset by age 14.

Conclusions: Our findings indicated that AFD is not specifically associated with alcoholism but rather is correlated with a broad range of indicators of disinhibited behavior and psychopathology. Moreover, individuals who first drink at a relatively early age manifest elevated rates of disinhibitory behavior and psychopathology before they first try alcohol. Taken together, these findings suggest that the association of AFD with alcoholism reflects, at least in part, a common underlying vulnerability to disinhibitory behavior. Whether an early AFD directly influences risk of adult alcoholism remains unclear.

Key Words: Age at First Drink, Alcoholism, Disinhibitory Behavior, Disinhibitory Psychopathology.

IN 1997 GRANT and Dawson published an influential analysis of the National Longitudinal Alcohol Epidemiologic Survey in which they reported a striking association between age at first drink (AFD)* and rate of alcoholism (Grant and Dawson, 1997). In a sample of more than 27,000 ever-drinking adults, the rate of lifetime alcohol dependence (AD) was four times higher among those who started to drink by age 14 years compared with those who had not started to drink until age 20 years or older (lifetime rates of 40 vs. 10%). Not only has Grant and Dawson's finding been replicated in subsequent research (Dewit et al., 2000), but AFD has also been associated with a range of other negative life outcomes, including increased likelihood of heavy drinking (Muthén and Muthén, 2000), abuse of tobacco and other illicit substances (Schuckit and Russell, 1983), low scholastic achievement (Hawkins et al., 1997), and psychiatric problems (Schuckit and Russell, 1983).

Although the association between AFD and alcoholism seems to be robust and replicable, the causal mechanisms that underlie this association remain obscure. One explanation favored by several investigators is that an early AFD, perhaps by interfering with normal developmental processes, exerts a relatively direct causal influence on alcoholism risk (Dewit et al., 2000; York, 1999). In this case, prevention efforts aimed at delaying the AFD might be expected to effect subsequent reductions in the rate of

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**Throughout the paper we use the term "age at first drink" rather than "age at drinking onset" because most studies, as well as ours, assess the age at which respondents first tried alcohol rather than the age at which they first established a regular pattern of drinking. Although correlated, the two ages are likely to differ markedly, at least for some adolescents.*

alcoholism. Early use of substances other than alcohol, however, is also associated with various negative life outcomes, including alcoholism. For example, both early onset of smoking (Grant, 1998) and drug use (Grant and Dawson, 1998) are associated with increased rates of alcoholism, suggesting that early exposure to alcohol per se may not be an essential causal factor in the etiology of alcoholism. Moreover, early initiation of smoking and drug use is associated with increased rates of illicit drug abuse and depressive disorders (Grant and Dawson, 1998; Hanna and Grant, 1999). It thus seems that, regardless of the specific substance involved, early substance use portends increased risk of substance abuse and psychiatric disturbance.

But is early substance use a critical causal influence on increased rates of substance abuse and related psychopathology? It may be that the multiple outcomes associated with an early AFD reflect a gateway phenomenon (e.g., early age at first use of tobacco leads to early age at first use of alcohol, etc.) Alternatively, the association of AFD with alcoholism may arise not because the former causes the latter but rather because both are manifestations of some underlying vulnerability to developing behavioral problems. That AFD and alcoholism might share an inherited vulnerability is supported by the observation that familial density of alcoholism is associated with an increased likelihood of an early AFD (Hill and Yuan, 1999). Nonetheless, the AFD effect may not owe entirely to family-history factors. AFD remains associated with alcoholism after controlling for a family history of alcoholism (Grant and Dawson, 1997) or parental drinking (Hawkins et al., 1997), although this residual association may reflect limitations in the assessment of family history.

Because parental phenotype is an imperfect indicator of inherited genotype, a positive family history is not equivalent to an inherited vulnerability. The strongest support for the common-inherited-vulnerability hypothesis comes from an analysis of more than 9000 adult twins by Prescott and Kendler (1999). By using multivariate biometric models, these investigators showed that the association between AFD and alcoholism was mediated by common genetic factors, and this suggests that both are manifestations of some common inherited vulnerability. In contrast to the general consensus about the prevention implications of the Grant and Dawson study, Prescott and Kendler stated, "These results suggest that the association between drinking onset and diagnosis is *noncausal*, and attempts to prevent the development of AD by delaying drinking onset are unlikely to be successful" (p 101, emphasis in original). Although some might challenge the strength of their conclusion given the findings they presented, the quote serves to indicate that the basis for the AFD-alcoholism association remains uncertain.

This is the first of two studies aimed at exploring the mechanisms underlying the association of AFD and alcoholism. In this first study, we explore multiple associations of AFD and also investigate whether some of these correlates predate the first use of alcohol. In the second study, we explore the familial transmission of AFD by using a behavioral genetic design. Here, we sought to address the following specific questions derived from the common-inherited-vulnerability hypothesis of the AFD effect: (1) Is AFD associated with a range of indicators of inherited vulnerability to problem behavior, including substance abuse disorders, psychiatric and behavioral problems, and psychophysiological markers of vulnerability? (2) Is AFD predicted by indicators of behavioral problems that predate drinking onset?

METHODS

Subjects

Subjects were drawn from the Minnesota Twin Family Study (MTFS), a longitudinal investigation of the development of alcoholism, substance abuse, and related disorders (Iacono et al., 1999). The MTFS sample consists of 1383 families, each composed of a pair of like-sex adolescent twins and their parents. The sample was ascertained with a population-based method. Starting from birth records, the current status and location of more than 90% of twins born in Minnesota in the relevant birth years was determined by using various public databases (e.g., telephone directories). Among those eligible to participate (i.e., twins living within a day's drive of our laboratories in Minneapolis, having at least one living biological parent, and not having a physical or mental disability that would preclude their completing the day-long intake assessment), 17.3% declined our invitation to participate in the study. We have completed brief assessments over the phone or by mail survey of more than 80% of the nonparticipating families. From these we have shown that although parents in participating families have slightly higher educational and occupational attainment than parents in nonparticipating families (e.g., mean difference in educational attainment of 0.3 years in fathers and 0.2 years in mothers), there are no significant differences between the two types of families in self-reported mental health. A detailed description of the methodology used in the MTFS, including analysis of nonparticipants, is provided in the report by Iacono et al. (1999).

Results reported here for MTFS parents are based on the 1309 (98.6%) of 1328 participating fathers and 1361 (98.3%) of 1384 participating mothers who reported ever having drunk alcohol. The mean (SD) age of the ever-drinking parent sample is 43.7 (5.9) years for fathers and 41.5 (5.3) years for mothers. Consequently, the parent sample has lived through most of the risk period for substance abuse and related psychiatric disorders. The sample of parents included 470 (35.5%) fathers and 132 (9.7%) mothers who met DSM-III-R lifetime criteria for AD. The mean (SD) number of years of education is 14.1 (2.3) for fathers and 13.7 (1.9) for mothers. Consistent with Minnesota demographics for the birth years sampled, 97.6% of fathers and 97.8% of mothers reported their race as white.

Two twin cohorts completed the intake MTFS assessment. The younger cohort consists of twins who on average were 11 years old at intake (range, 10–12 years), and the older cohort consists of twins with an average age of 17 years (range, 16–18 years) at intake. For convenience, we will call these the 11- and 17-year-old cohorts. This report will focus on data from the intake assessment of all participants, as well as on data from the first follow-up assessment of the 11-year-old cohort 3 years after intake. Of the 754 boys and 764 girls who completed the age-11 intake assessment, 666 (88.3%) boys and 702 (91.9%) girls completed the age-14 follow-up substance-use assessment (see below). Compared with nonparticipants, participants at the first follow-up were more likely to have an age-11 diagnosis at either a definite or probable level of certainty (see "Measures" for discussion of diagnostic procedures) of attention deficit-hyperactivity disorder (ADHD; 6.8 vs. 5.7%), conduct disorder (CD; 12.3 vs. 2.8%), oppositional defiant disorder (ODD; 12.6 vs. 8.5%), and major depressive disorder (MDD; 3.1 vs. 1.9%).

Of the 1368 members of the 11-year-old cohort who completed the first follow-up assessment, 21 (2.8%) boys and 4 (0.5%) girls reported having used alcohol without parental permission at their age-11 assessment. These 25 individuals were not included in the longitudinal analysis. This left a sample of 698 girls and 645 boys for whom we had clinical assessments at age 11 years and alcohol use reports at age 14 years. Finally, scored P3 data were available on a sample of 500 boys and 627 girls from the 17-year-old cohort.[†]

Measures

Parent Measures. The clinical assessment of the parents included administration of an expanded substance abuse module developed by Robins et al. (1987, 1988), the Structured Clinical Interview for DSM-III-R to assess mood disorders (Spitzer et al., 1987), and an interview developed by MTFS staff to assess antisocial personality disorder (ASPD). In this report, all diagnoses for parents are lifetime and based on DSM-III-R, the diagnostic standard in place when the MTFS was begun. In the MTFS, diagnoses are made at multiple levels of certainty. A definite diagnosis is assigned if all relevant DSM criteria are met; probable diagnoses are given when all but one symptom are present. The use of a probable diagnosis with adolescents and young adults thus allows us to identify as cases individuals who are likely to subsequently meet lifetime diagnostic criteria. Because the parents are predominantly middle-aged and have thus lived through most of the risk period for developing substance-use and behavioral disorders, however, we report only rates of definite diagnoses in the parents. The following diagnoses are considered here: AD, nicotine dependence (ND), MDD, ASPD, and CD. In addition, a composite drug diagnosis (designated any drug diagnosis) was formed by aggregating abuse and dependence diagnoses across the following eight substances: amphetamines, cannabis, cocaine, hallucinogens, inhalants, opiates, phencyclidine-related substances, and sedatives. An individual was considered to have a drug diagnosis if he or she met DSM-III-R lifetime criteria for either abuse or dependence on at least one of the eight substances.

Parents completed the Multidimensional Personality Questionnaire (Tellegen and Waller, 2001), which provides scores on 11 primary and 3 higher-order scales. Only findings from the three higher-order scales, Positive Emotionality (i.e., the tendency to be positively and actively engaged with social and work environments), Negative Emotionality (i.e., the tendency to experience negative mood states and psychological distress), and Constraint (i.e., the tendency to endorse conventional moral standards and inhibit behavioral impulses) are reported here. Before analysis, the three higher-order MPQ scales were transformed separately in the male and female samples to a T-score metric (i.e., scores were transformed in the current sample to have a mean of 50 and an SD of 10 for each sex group). Parents also completed an abbreviated version of the Weschler Adult Intelligence Scale-Revised (Weschler, 1981) consisting of two verbal (Vocabulary and Information) and two performance (Block Design and Picture Arrangement) subtests.

In determining AFD, parents were first asked if they had ever used alcohol (i.e., a drink rather than just a sip). If they indicated they had, they were further asked, "How old were you the first time you used alcohol (on your own; more than your parents allowed you to)?" To provide adequate sample sizes in each group, parents' AFD was categorized into the following eight age groups for purposes of analysis: less than 14, 14, 15, 16, 17, 18, 19, and more than 19 years. Sample sizes in these groups ranged from 73 to 239 in the male sample and from 81 to 263 in the female sample (see Table 1).

Measures on the 11-Year-Old Twin Cohort. The intake clinical assessment of the younger twin cohort consisted of the Diagnostic Interview for Children and Adolescents (Reich, 2000; Welner et al., 1987), which was modified to provide complete coverage of DSM-III-R criteria. Twins completed the self-report version of the Diagnostic Interview for Children and Adolescents interview while their mothers completed the parent version. Data from the mothers and the twins were combined to arrive at best-estimate diagnoses, by using as a starting point the provisional rules established by Reich and Earls (1987). Because the 11-year-old twins would not have completed the risk period for the onset of behavioral disorders, their diagnoses were considered to be positive if criteria were met at either a definite or probable level of certainty. The following diagnoses are reported here: ADHD, CD, ODD, and MDD. In addition, we report results for an aggregate of the three externalizing disorders; this aggregate was positive if lifetime DSM-III-R diagnoses at either a definite or probable level of certainty were met for ADHD, CD, or ODD.

As part of the intake assessment, up to three teachers of the 11-year-old twins were asked to complete a Teacher Rating Form consisting of 129 behavioral, personality, and academic items. Results from the following Teacher Rating Form scales are reported here: Oppositional, Hyperactive/Impulsive, Inattentive, and Grades. The Oppositional scale has an internal consistency reliability of 0.96 and consists of 20 items that tap defiance of authority (e.g., "Is uncooperative") and hostility and aggression toward peers (e.g., "Bullies or intimidates other students"). The Hyperactive/Impulsive scale has an internal consistency reliability of 0.92 and consists of eight items that tap overactivity (e.g., "Often fidgets with hands or feet or squirms in seat") and the inability to inhibit behavioral responses (e.g., "Often acts before thinking"). The Inattentive scale has an internal consistency reliability of 0.96 and consists of 10 items that tap the inability to concentrate, maintain attention, and complete work assignments (e.g., "Has difficulty concentrating on schoolwork or other tasks requiring sustained attention"). The Grades scale has an internal consistency reliability of 0.92 and consists of five items that tap scholastic performance overall and in specific subject areas.

At intake, twins in both the 11- and 17-year-old cohorts completed a substance-use assessment administered by computer. As part of this assessment, twins were asked if they had ever used alcohol without parental permission and, if so, at what age they first tried alcohol. AFD for the 17-year-old sample was based on responses to these questions and classified as less than 14 [n = 74 (14.8%) boys and 56 (8.9%) girls], 14 [n = 55 (11.0%) boys and 69 (11.0%) girls], 15 [n = 98 (19.6%) boys and 131 (20.9%) girls], 16 [n = 102 (20.4%) boys and 123 (19.6%) girls], 17 and 18 [n = 39 (7.8%) boys and 52 (8.3%) girls], and never used [n = 132 (26.4%) boys and 196 (31.3%) girls]. At the follow-up of the 11-year-old cohort, twins who completed an in-person assessment were re-administered the computerized substance-use assessment, whereas twins who completed their assessment over the telephone were asked the same substance-use questions in an interview. For these twins, presence or absence of an early AFD was based on whether they reported having used alcohol without parental permission at the age-14 assessment.

Psychophysiological Assessment of 17-Year-Old Twins As part of their intake assessment, twins completed a 3.5-hr battery of psychophysiological tests. Included toward the end of the psychophysiological assessment was an event-related potential (ERP) task that took approximately 15 min to administer. A detailed description of the ERP paradigm is available in Katsanis et al. (1997) and Carlson et al. (1999). Electroencephalographic activity was recorded with a Grass Model 12A Neurodata Acquisition System (Quincy, MA) from the Pz, P3, and P4 scalp sites referenced to linked earlobes. Electro-oculographic activity was recorded from electrodes placed above the pupil and near the outer canthus of one eye. Data were digitized over a 2000-msec epoch at a rate of 256 Hz. The task used to elicit the ERP was a visual, oddball paradigm patterned after that of Begleiter et al. (1984). The target stimulus was an oval representing the superior view of a head, depicting a nose and one ear. Participants pressed a button to indicate on what side of the head the nose appeared. Two hundred forty trials were presented: 160 neutral presentations consisting of a simple oval in the center of the screen, and 80 target trials. Stimuli were presented for 98 msec each with a random interstimulus interval ranging between 1 and 2 sec. A computer program identified the largest peak amplitude occurring between 200 and 800 msec after stimulus onset. The blink correction method of Gratton et al. (1983) was used to reduce contamination of the electroencephalogram by eye blinks and other ocular

[†] *Although the P3 task was a part of the intake psychophysiological assessment of twins in both the 11- and 17-year-old cohorts as well as their fathers, at the time of this report processed data were available only for the twins in the older cohort.*

Table 1. Lifetime Prevalence of DSM-III-R Diagnoses in Ever-Drinking Women and Men as a Function of Age at First Drink

Age at first drink (yr)	Women							Men						
	n	AD	ND	Any drug	CD	ASPD	MDD	*n*	AD	ND	Any drug	CD	ASPD	MDD
<14	81	0.259	0.568	0.395	0.123	0.012	0.363	164	0.561	0.622	0.488	0.442	0.184	0.146
14	85	0.235	0.471	0.271	0.106	0.012	0.238	123	0.463	0.512	0.431	0.350	0.098	0.165
15	123	0.236	0.463	0.244	0.049	0.016	0.244	203	0.463	0.517	0.369	0.192	0.044	0.141
16	248	0.097	0.435	0.133	0.024	0.000	0.248	240	0.417	0.496	0.258	0.113	0.029	0.096
17	207	0.101	0.329	0.111	0.019	0.000	0.237	198	0.268	0.414	0.182	0.131	0.020	0.132
18	263	0.030	0.227	0.049	0.011	0.004	0.201	189	0.238	0.342	0.084	0.079	0.021	0.124
19	117	0.043	0.188	0.043	0.000	0.000	0.214	73	0.164	0.274	0.082	0.096	0.000	0.042
>19	223	0.017	0.156	0.059	0.008	0.000	0.217	119	0.143	0.176	0.017	0.042	0.000	0.143

All diagnoses are lifetime and based on DSM-III-R criteria.

artifacts. Only data from Pz are reported because it has been the site of focus in studies of alcohol disorder risk and P300.

Statistical Analysis

In the parent sample, the effect of AFD was investigated by using logistic regression analysis for diagnostic outcomes and linear regression analysis for quantitative outcomes. For each outcome, two regression models were fit. The first regression model included as independent variables sex, age, AFD, and the interaction of AFD and sex. To determine whether the association of AFD with diverse adult outcomes was mediated by its relationship with alcoholism risk, AD was added as an independent variable in a second set of regression models. The strength of the AFD effect was estimated using odds ratios (ORs) for diagnostic outcomes and regression coefficients for quantitative outcomes. To adjust for the multiple outcomes being investigated, effects were considered statistically significant only if the two-tailed p was ≤ 0.01.

In the 11-year-old twin sample, the effect of being an early drinker (age 14 years or younger) was investigated by using a logit analysis for diagnostic outcomes and analysis of variance (ANOVA) for quantitative outcomes. In both cases, effects were investigated in a model that included sex and early-drinking main effects as well as a sex × early-drinking interaction. Strength of effect was assessed by using ORs for diagnostic outcomes and standardized effect sizes (i.e., mean differences in SD units) for quantitative outcomes. As with the analysis of the parent data, the significance level was set at 0.01 (two-tailed) in the analysis of the 11-year-old outcome data. The analysis of the ERP data in the 17-year-old cohort consisted of a two-way ANOVA with AFD and sex as independent variables and P3 amplitude as the dependent variable. Unlike the parent sample, in which individuals who had never tried alcohol were dropped from the analysis, never-drinkers were included as a separate group in the analysis of the P3 data from the 17-year-old cohort. Given that the vast majority of adolescents who had never tried alcohol by age 17 or 18 years can nevertheless be expected to try alcohol sometime in their lives, including them as a separate group was preferable to dropping them from the analysis.

RESULTS

The Correlates of AFD Among Parents

Table 1 gives rates of lifetime DSM-III-R diagnoses in the parents according to AFD. We replicated Grant and Dawson's finding of a substantial association between AFD and rate of AD. For parents who reported having their first drink before age 15 years, rates of AD exceeded 45% in men and 20% in women. By contrast, for parents who did not drink for the first time until they were older than 19, the rate of AD was 13% among men and 2% among women. AFD was also substantially related to rates of ND, any drug diagnosis, CD, and ASPD. Rates of all these disorders were substantially higher among those who first drank in early adolescence compared with those who first drank in late adolescence or early adulthood. The association of AFD with rate of MDD, however, seems to be weak, especially in males.

Table 2 gives means and SDs for the quantitative mea-

Table 2. Mean (SD) Education, IQ, and Personality Scores in Ever-Drinking Men and Women as a Function of Age at First Drink

Age at first drink (yr)	Women					Men				
	Education (yr)	IQ	Positive Emotionality	Negative Emotionality	Constraint	Education (yr)	IQ	Positive Emotionality	Negative Emotionality	Constraint
<14	13.4	100.8	49.4	48.4	48.3	13.7	105.3	50.4	50.8	47.6
	(2.0)	(14.6)	(10.0)	(9.2)	(9.6)	(2.3)	(13.6)	(10.2)	(9.6)	(9.8)
14	13.0	96.8	50.1	50.8	49.3	14.0	103.9	48.8	50.4	46.5
	(1.5)	(12.3)	(10.9)	(9.9)	(11.6)	(2.2)	(16.0)	(9.8)	(10.2)	(9.7)
15	13.4	99.2	49.4	51.1	48.0	13.6	105.3	49.1	50.3	49.6
	(1.9)	(11.8)	(10.5)	(9.9)	(10.1)	(1.9)	(14.9)	(10.7)	(9.8)	(9.7)
16	13.4	100.5	50.4	50.0	48.7	13.7	103.1	50.0	50.2	50.2
	(1.7)	(13.1)	(9.7)	(10.2)	(9.8)	(2.1)	(13.8)	(9.9)	(10.1)	(9.1)
17	13.7	101.6	50.5	51.2	50.3	14.3	107.2	50.4	50.0	50.4
	(1.8)	(13.3)	(9.8)	(9.8)	(9.7)	(2.2)	(14.8)	(9.5)	(9.7)	(9.8)
18	13.9	103.6	49.3	49.6	50.8	14.4	106.5	49.6	50.1	51.3
	(1.9)	(12.7)	(9.9)	(10.5)	(9.0)	(2.5)	(14.1)	(10.3)	(10.3)	(9.6)
19	14.3	103.9	51.5	48.7	50.3	15.3	109.3	50.3	47.6	51.8
	(2.0)	(13.7)	(10.1)	(9.2)	(10.8)	(2.5)	(14.0)	(9.8)	(10.4)	(11.8)
>19	14.2	104.6	49.5	49.8	51.4	15.0	109.7	51.8	49.0	52.4
	(2.1)	(15.0)	(9.7)	(10.8)	(10.3)	(2.6)	(16.6)	(9.6)	(10.4)	(10.5)

Positive Emotionality, Negative Emotionality, and Constraint have been transformed separately in the male and female samples to have an overall mean of 50 and an SD of 10 (i.e., a T-score metric).

sures by AFD separately for men and women. Men and women who started to drink earlier than age 15 years averaged approximately 1 year less of education and nearly five IQ points less than those who started to drink after age 19 years. Of the three personality scales, only Constraint seems to be associated with AFD. The Constraint scores of those with an early AFD averaged nearly a half SD lower among men and a third of an SD lower among women compared with the scores of those with a late AFD.

Statistical analysis of the relationship of AFD with the diagnostic and quantitative outcomes in the parents is summarized in Table 3. For both diagnostic and quantitative outcomes, a regression model that included AFD, sex, age, and the sex × AFD interaction was first fitted to the observed data. None of the 12 sex × AFD interaction effects was significant at $p < 0.01$ (the interaction term was significant at $p = 0.03$ when AD was the outcome). Consequently, in addition to the sex-specific estimates, for each outcome a common OR or regression coefficient is reported that was based on the regression model that did not contain the interaction term.

For diagnostic outcomes, AFD was significantly associated with AD, ND, any drug diagnosis, CD, and ASPD at $p < 0.0001$. For MDD, the association with AFD was not quite significant ($p = 0.015$). The ORs, which are generally comparable in men and women, give the reduction in odds of a diagnosis associated with each year's delay in AFD. Thus, overall the odds of developing AD is only 72% as large with each successive year's delay in AFD. Of note is that AFD is more strongly associated with CD (common OR = 0.65) and ASPD (OR = 0.54) than with either AD (OR = 0.72) or ND (OR = 0.75).

For quantitative outcomes, AFD was significantly associated with years of education ($p < 0.001$), IQ ($p = 0.002$), and Constraint ($p < 0.001$), but was not associated with Positive Emotionality or Negative Emotionality ($p > 0.25$ in both cases). To determine whether IQ mediated the AFD effect on education, analysis of education was repeated with IQ partialled out. The association of AFD and education remained significant in this analysis ($p < 0.001$), indicating that AFD was associated with whether an individual's educational attainment fell short of his or her level of ability as reflected by IQ. In none of these analyses was the sex × AFD interaction effect statistically significant. The common regression coefficients given in Table 3 indicate that each year's delay in AFD was associated with 0.17 more years of education (0.13 more years if the IQ effect is removed), 0.43 more IQ points, and 0.05 SDs lower on the Constraint scale.

To determine whether the association of AFD with the

Table 3. Odds Ratios and Regression Coefficients for Prediction of Diagnostic and Quantitative Outcomes from Age at First Drink in Parents

	Odds ratio (95% CI)			Adjusted odds ratio (95% CI)		
Diagnostic outcome	Women	Men	Common	Women	Men	Common
Alcohol dependence	0.68 (0.61, 0.75)	0.74 (0.70, 0.79)	0.72** (0.68, 0.76)	NA	NA	NA
Nicotine dependence	0.73 (0.69, 0.78)	0.77 (0.72, 0.81)	0.75** (0.72, 0.78)	0.73 (0.69, 0.78)	0.80 (0.76, 0.85)	0.78** (0.75, 0.82)
Drug abuse or dependence	0.71 (0.65, 0.78)	0.66 (0.61, 0.71)	0.69** (0.65, 0.73)	0.76 (0.69, 0.83)	0.69 (0.64, 0.75)	0.72** (0.68, 0.77)
Conduct disorder	0.63 (0.53, 0.77)	0.66 (0.61, 0.72)	0.65** (0.60, 0.70)	0.69 (0.56, 0.83)	0.67 (0.62, 0.74)	0.67** (0.62, 0.73)
Antisocial personality disorder	0.62 (0.37, 1.03)	0.55 (0.47, 0.65)	0.54** (0.46, 0.64)	0.70 (0.40, 1.21)	0.58 (0.48, 0.69)	0.59** (0.49, 0.70)
Major depressive disorder	0.91 (0.85, 0.98)	0.97 (0.89, 1.05)	0.94ns (0.89, 0.99)	0.94 (0.88, 1.01)	1.00 (0.91, 1.09)	0.97ns (0.91, 1.02)
	Regression coefficient (95% CI)			Adjusted regression coefficient (95% CI)		
Quantitative outcome	Women	Men	Common	Women	Men	Common
Education	0.12 (0.07, 0.18)	0.20 (0.14, 0.26)	0.17** (0.13, 0.21)	0.11 (0.06, 0.17)	0.15 (0.09, 0.21)	0.14** (0.10, 0.18)
Education net IQ	0.10 (0.05, 0.15)	0.15 (0.10, 0.20)	0.13** (0.09, 0.17)	0.09 (0.05, 0.14)	0.12 (0.07, 0.17)	0.11** (0.07, 0.15)
IQ	0.23 (−0.15, 0.61)	0.51 (0.10, 0.91)	0.43* (0.15, 0.71)	0.07 (−0.31, 0.46)	0.33 (−0.08, 0.75)	0.27ns (−0.01, 0.55)
Positive Emotionality	0.06 (−0.24, 0.37)	0.20 (−0.10, 0.49)	0.12ns (−0.10, 0.34)	0.05 (−0.26, 0.36)	0.11 (−0.20, 0.41)	0.07ns (−0.15, 0.29)
Negative Emotionality	0.08 (−0.23, 0.38)	−0.23 (−0.52, 0.07)	−0.09ns (−0.31, 0.13)	0.20 (−0.11, 0.51)	−0.02 (−0.32, 0.28)	−0.08ns (−0.30, 0.14)
Constraint	0.50 (0.20, 0.81)	0.59 (0.30, 0.87)	0.51** (0.29, 0.73)	0.47 (0.16, 0.78)	0.45 (0.16, 0.75)	0.42** (0.20, 0.64)

Diagnoses are lifetime at the definite level of certainty according to DSM-III-R criteria. Unadjusted odds ratios and regression coefficients were estimated in model that included age and sex effects; adjusted odds ratios and regression coefficients were computed in a model that also included the effect of alcohol dependence. Positive Emotionality, Negative Emotionality, and Constraint have been transformed separately in the male and female samples to have an overall mean of 50 and an SD of 10 (i.e., a T-score metric).

CI, confidence interval; NA = not applicable.

Because none of the odds ratios or regression coefficients differed significantly by sex at $p \leq 0.01$, significance is reported only for the common estimates as * $p \leq 0.01$; ** $p < 0.001$; and ns, not significant at $p \leq 0.01$.

multiple diagnostic and quantitative outcomes could be attributed to a primary effect of AD with secondary effects on all other outcomes, all relevant regressions were repeated with AD included as an independent variable. Adjusted ORs and regression coefficients are given in Table 3. AFD was still significantly associated with ND, any drug diagnosis, CD, ASPD (all at $p < 0.0001$), education, and Constraint (at $p < 0.001$). The associations of AFD with MDD and IQ, however, were nonsignificant once AD was included in the model.

P3 Amplitude in 17-Year-Olds

In our sample of 500 17-year-old boys and 627 17-year-old girls, P3 amplitude was significantly associated with AFD ($p < 0.001$) and sex ($p < 0.001$, with girls having higher mean P3 amplitude than boys). The sex × AFD interaction was not statistically significant ($p = 0.41$), indicating that the association between P3 amplitude and AFD is similar for boys and girls. The significant AFD effect reflects that P3 amplitude is lower among boys and girls who had their first drink before age 14 years than among those who first drank at a later age. To illustrate the AFD effect on P3 amplitude, Fig. 1 reports the grand mean ERP waveforms for those 17-year-olds who reported having had their first drink at or before age 14 years versus those who either had never drunk or whose first drink came after age 14 years. The figure clearly indicates that in both the male and female samples, a difference in P3 amplitude is the major difference in the ERP waveforms between those with an early versus a late AFD.

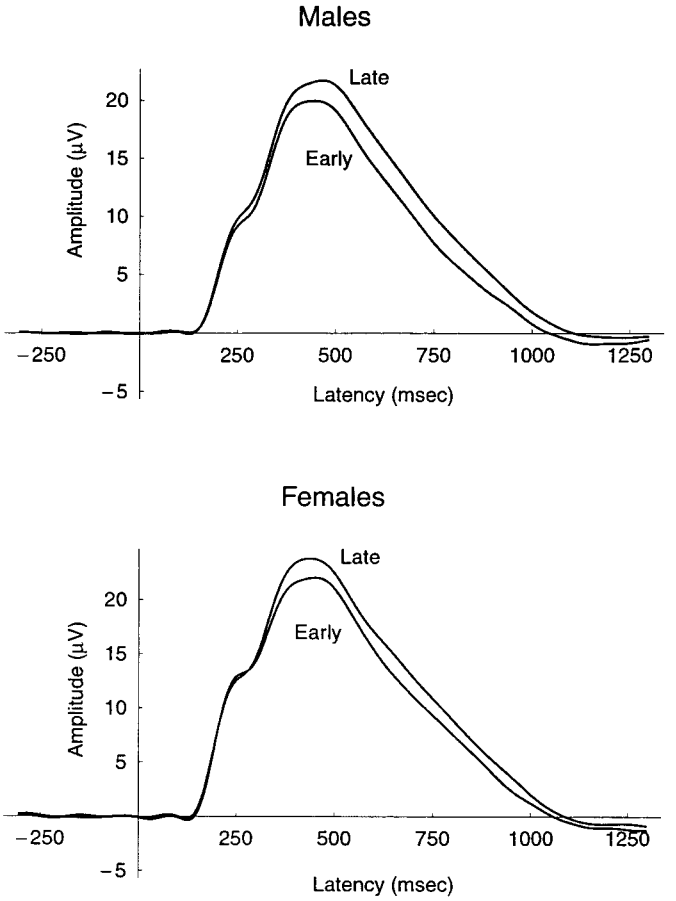

Fig. 1. Grand mean ERP waveforms for 17-year-olds as a function of age at first drink. Average waveforms were derived separately for males and females and separately for early and late drinkers. The early age at first drink group includes those boys ($n = 129$) or girls ($n = 125$) who reported having had their first drink of alcohol at or before age 14 years; the late age at first drink group includes those boys ($n = 371$) or girls ($n = 502$) who reported an age at first drink after age 14 years or reported never having used alcohol. Amplitude is measured in microvolts (μV).

Prospective Prediction of Early Use of Alcohol in the 11-Year-Old Cohort

Among the 1343 twins who completed the first follow-up substance use assessment at age 14 years and had not reported having drunk alcohol at their intake assessment, 221 (34.3%) boys and 207 (29.7%) girls reported ever having used alcohol without parental permission by age 14 years. The sex difference in rate of early drinking is not quite statistically significant ($\chi^2_1 = 3.26, p = 0.07$). Table 4 gives the rates of diagnosis at age 11 years as a function of ever having used alcohol by age 14 years. The significance of the early-drinking effect was assessed by using a logit analysis, with diagnosis as the dependent variable and sex, early drinking, and the sex × early-drinking interaction as the independent variables. Although the ORs tend to be higher in the boys than the girls, none of the sex × early-drinking interaction terms was statistically significant. Therefore, in addition to the ORs estimated separately in the male and female samples, we report a common OR estimate derived from the no-interaction model. The rate of CD, ODD, and any externalizing disorder was significantly and substantially increased among early drinkers (common OR of approximately 2.00 and $p < 0.001$ in each case). Although the rate of ADHD was modestly increased among early drinkers, the observed OR was not significantly greater than 1.0 by using our stringent significance level (OR = 1.57, $0.01 < p < 0.05$). There was no significant association between MDD and early drinking (OR = 1.32, $p > 0.25$).

Teacher-rating data at age 11 years were available for 588 (91%) boys and 612 (88%) girls who completed the age-14 substance-use assessment. Means and SDs for the four teacher-rating scales are given in Table 5. The association of the teacher-rating scales and early drinking was assessed with a two-way ANOVA that included sex, early-drinking status, and the sex × drinking-status interaction. For all four scales, the early-drinking main effect was statistically significant at $p = 0.008$ or less. For both the Oppositional and Hyperactive/Impulsive scales, the sex × drinking-status interaction was also statistically significant ($p \leq 0.01$ in both cases). Because the teacher-rating scales were transformed to a T-score metric, the effect sizes associated with the early-drinking effect can be readily determined from the data presented in Table 5. On average,

Table 4. Lifetime Prevalence of DSM-IIR Diagnoses at Age 11 Years as a Function of Ever Use of Alcohol by Age 14 Years

	Rate in girls		Rate in boys		Odds ratio (95% CI)		
Age-11 diagnosis	Never used (n = 491)	Ever used (n = 207)	Never used (n = 424)	Ever used (n = 221)	Girls	Boys	Common
Attention deficit-hyperactivity disorder	0.041	0.053	0.068	0.113	1.32 (0.62, 2.81)	1.74 (0.99, 3.05)	1.57^{ns} (1.01, 2.46)
Conduct disorder	0.045	0.053	0.137	0.294	1.20 (0.57, 2.51)	2.63 (1.76, 3.93)	2.18** (1.54, 3.09)
Oppositional defiant disorder	0.079	0.145	0.116	0.190	1.96 (1.18, 3.26)	1.80 (1.15, 2.81)	1.87** (1.33, 2.61)
Any externalizing disorder	0.126	0.184	0.222	0.394	1.56 (1.01, 2.42)	2.28 (1.60, 3.25)	1.96** (1.49, 2.58)
Major depressive disorder	0.024	0.039	0.033	0.036	1.60 (0.65, 3.98)	1.10 (0.45, 2.66)	1.32^{ns} (0.70, 2.48)

All diagnoses are lifetime by age 11 years at the probable or definite level of certainty by using DSM-III-R criteria. Odds ratio gives the increase in odds of the diagnosis associated with ever-use of alcohol by age 14 years.

Because none of the odds differed significantly by sex at $p \leq 0.01$, significance is reported only for the common estimates as * $p \leq 0.01$; ** $p < 0.001$; and ns, not significant at $p \leq 0.01$.

Table 5. Mean (SD) Teacher Rating Scale Scores at Age 11 Years as a Function of Having Used Alcohol by Age 14 Years

	Girls		Boys		ANOVA p value	
Teacher Rating Scale	Never used (n = 436)	Ever used (n = 176)	Never used (n = 385)	Ever used (n = 217)	Ever used main effect	Ever used × sex interaction
Oppositional	49.2 (9.0)	51.4 (11.0)	48.1 (7.9)	53.3 (12.1)	<0.001	0.010
Hyperactive/Impulsive	49.4 (9.7)	51.1 (10.4)	48.1 (8.5)	53.1 (11.4)	<0.001	0.008
Inattentive	49.3 (9.1)	50.7 (10.8)	48.8 (9.2)	52.1 (10.8)	<0.001	0.13
Grades	50.9 (10.0)	48.8 (9.1)	50.6 (9.9)	49.1 (10.0)	0.008	0.65

Teacher Rating Scales have all been transformed separately in the male and female samples to have an overall mean of 50 and an SD of 10 (i.e., a T-score metric); consequently, the sex main effect is not meaningful.

early drinkers scored 0.20 to 0.50 SDs higher on the Oppositional, Hyperactive/Impulsive, and Inattentive scales and 0.20 SDs lower on Grades than nondrinkers. The significant sex × drinking-status interaction for the Oppositional and Hyperactive/Impulsive scales reflects that the difference between early drinkers and nondrinkers was greater among boys (approximately 0.50 SDs) than girls (approximately 0.20 SDs).

DISCUSSION

The Generality of the Age-at-First-Drink Effect

In a sample of more than 2700 parents, we have extended the Grant and Dawson finding by showing that AFD is not specifically associated with AD but rather is associated with other substance abuse and dependence disorders, mental health, educational attainment, IQ, and the personality dimension of constraint. Indeed, AFD was more strongly associated with ASPD and CD than with AD. Moreover, the association of AFD with this diverse set of outcomes could not be attributed to a secondary effect of early use on AD because, except for IQ and MDD, adjusting for AD in the regression models minimally affected the relevant indexes of strength of effect and did not render significant effects nonsignificant.

These multiple correlates of AFD are all indicators of disinhibitory behavior or psychopathology. That is, compared with individuals who are inhibited, disinhibited individuals are more likely to engage in undersocialized behavior (e.g., CD, ASPD), abuse substances (e.g., AD, ND, any drug diagnosis), underachieve in school (e.g., low educational attainment), and score low on personality measures of behavioral restraint (e.g., Constraint; Sher and Trull, 1994). We also know that an early onset of alcoholism is associated with increased likelihood of antisocial behavior (Babor et al., 1992; Cloninger, 1987) and personality characteristics associated with novelty seeking, impulsivity, and disinhibitory processes (McGue et al., 1997, 1999; Tarter, 1988). Our findings suggest that an early AFD, like an early onset of alcoholism, may also reflect a vulnerability to disinhibitory behavior.

The strength of association of AFD with AD reported here (OR of 0.68 in women and 0.74 in men) is stronger than that reported either in the original Grant and Dawson (1997; ORs of 0.85 to 0.87) study or the Prescott and Kendler (1999; OR of 0.78 in women and 0.84 in men) replication. This difference may owe to how AFD was assessed in the separate studies. We assessed age at which respondents first used alcohol without parental permission, whereas Grant and Dawson (1997) assessed "how old [respondents] were when they first started drinking, not counting small tastes or sips of alcohol" (p105), and Prescott and Kendler (1999) asked "How old were you when you first had a drink, other than as part of a religious ceremony?" (p

102). By requiring absence of parental permission, we may have increased the likelihood of identifying individuals likely to engage in other antisocial behavior.

Our findings with P3 amplitude provide additional support for the proposition that early AFD is a symptom of disinhibitory vulnerability. Reduced P3 amplitude has been associated with ASPD (Bauer et al., 1994), impulsivity and aggression (Barratt et al., 1997), substance abuse and dependence (Biggins et al., 1997; Branchey et al., 1988; Iacono, 1998; Taylor et al., 1999), externalizing psychopathology of childhood (Carlson et al., 1999), and a family history of alcoholism (Begleiter et al., 1984; Polich et al., 1994), but it does not seem to be a consequence of drinking history (Pfefferbaum et al., 1991). P3 amplitude is also strongly heritable. In a sample of adolescent male twins, we estimated the heritability of P3 amplitude to be 79% (Katsanis et al., 1997). In short, P3 amplitude seems to be a generalized marker of inherited vulnerability to disinhibitory behavior and psychopathology (Iacono et al., 1999). Here, we have shown that reduced P3 amplitude is also associated with an early AFD.

Disinhibitory Behavior and Psychopathology Predate Drinking Onset

If AFD is a manifestation of vulnerability to engage in disinhibited behavior, then we should be able to find indications of disinhibitory processes that both predate and predict AFD. Our 11-year-old cohort provides an excellent opportunity to address this issue. We assessed multiple indicators of disinhibitory behavior and psychopathology at age 11 years, before the onset of drinking for our sample. At their age-14 follow-up assessment we were able to establish whether they were early drinkers. Rates of CD, ODD and any externalizing disorder at age 11 years were all significantly higher among individuals who drank alcohol for the first time between their age-11 and age-14 assessments compared with those who had never tried alcohol. Similarly, boys and girls who had tried alcohol by age 14 years were seen by their teachers to be more oppositional, hyperactive/impulsive, inattentive, and academically weak at age 11 years than boys and girls who had never drunk without parental permission.

Others have, of course, found that early initiation of substance use is associated with a range of pre-existing individual-level risk factors (Boyle et al., 1993; Brook et al., 1995; Hawkins et al., 1992; Mâsse and Tremblay, 1997). The significance of the associations we report here, however, is that they help to establish a temporal sequencing of early drinking and its behavioral correlates. That is, disinhibitory behavior and psychopathology may seem to be a consequence of early drinking when assessed in adulthood but a precipitating factor when assessed in adolescence. It is difficult to conclude that early drinking exerts a major causal influence on the broad range of adult outcomes we explored when indications of the types of behaviors AFD predicts in adulthood already exist before drinking onset. Our interpretation gains additional support from the longitudinal research by Jessor and Jessor (1977) showing that indicators of behavioral disinhibition differentiate nondrinking from early-drinking adolescents before drinking onset.

Sex Differences

In the analysis of the parent data, there was no evidence that sex moderated the strength of the association of AFD with clinical and quantitative outcomes. In the prospective analysis of the adolescent data, however, we did find statistically significant interaction effects for two of the four teacher rating scales. In both cases, the form of the interaction was ordinal rather than disordinal, with age-11 quantitative indicators of behavioral disinhibition being more strongly associated with an early AFD in boys than girls. Moreover, although there were no significant sex $\times$ diagnosis interactions in the prediction of early alcohol use, the direction of sex differences with the diagnostic predictors was the same as with the quantitative data (i.e., greater association in boys than girls), and the lack of significance might reflect low power in the analysis of categorical outcomes. These data thus suggest that although the association of AFD and alcoholism may be similar in men and women, the etiological processes that underlie this association may not.

Delaying AFD

Although our data, like those of Prescott and Kendler (1999), serve to question the conclusion that the association of AFD with alcoholism simply reflects the causal effect of the former on the latter, we do not want to suggest that delaying the age when adolescents first use alcohol is an inappropriate target for prevention efforts. Adolescents who drink are at an increased risk of driving while intoxicated, engaging in risky sex, and becoming victims of violence (Fromme et al., 1997; Kim et al., 1997; Testa et al., 2000; Thomas et al., 2000). Even if delaying drinking onset had no benefit in reducing the chronic problems associated with drinking, it would be expected to reduce the acute problems associated with adolescent intoxication. Nonetheless, we agree with Prescott and Kendler (1999) that "measures designed to interrupt the path from early use to heavy drinking may be a more fruitful approach for decreasing risk for alcoholism than attempts to delay initiation of alcohol use" (p 106). In any case, although we interpret our findings as indicating that early AFD is a symptom of an underlying vulnerability that increases risk of alcoholism, we cannot reject the possibility that early use of alcohol exacerbates this vulnerability. Determining whether AFD exerts a causal influence on alcoholism risk independent of its association with pre-existing indicators of behavioral disinhibition will require long-term follow-up data.

Limitations

Although the findings reported here are strengthened by our large epidemiological sample, comprehensive assessment, and use of prospective as well as retrospective approaches, this study is not without its limitations. Foremost among these is that our study is based almost entirely on whites. Although our sample is broadly representative of Minnesota families (Iacono et al., 1999), our findings may not generalize to other ethnic groups. Grant and Dawson reported that the association of AFD and alcoholism was weaker among black compared with nonblack Americans (Grant and Dawson, 1997). The generalizability of our findings to nonwhite ethnic groups is uncertain. Also, as in most studies in this area, the association of AFD with alcoholism that we observed is based on retrospective reports of AFD. Although observations in our adolescent sample help to resolve the sequencing of AFD and some its correlates, careful prospective studies are clearly needed. Finally, statistical significance does not always imply clinical significance, especially in samples as large as that reported here. Some of the associations with AFD, although statistically significant, may have limited clinical utility (e.g., the association with IQ).

We found that an early AFD, rather than being specifically associated with AD, is associated with a range of behavioral problems, including increased rates of ND, illicit substance abuse and dependence, ASPD, CD, and academic underachievement. Low scores on the personality dimension of constraint, reduced IQ, and reduced P3 amplitude were also associated with an early AFD. Analysis of longitudinal data from a cohort of early adolescents showed that indications of behavioral disinhibition predate and predict drinking onset. Taken together, these findings suggest that AFD may be a symptom of an underlying vulnerability to behavioral disinhibition; its causal influence on adult alcoholism remains unclear.

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