

# Drinks of the Father: Father's Maximum Number of Drinks Consumed Predicts Externalizing Disorders, Substance Use, and Substance Use Disorders in Preadolescent and Adolescent Offspring

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**Background:** The maximum number of drinks consumed in 24 hr seems to be an interesting phenotype related to alcoholism. The goal of the present study was to determine in an epidemiologic sample whether this measure of drinking history in fathers predicted externalizing behavioral disorders, substance use, and substance abuse in preadolescent and adolescent offspring and whether any such associations would be independent of paternal alcohol dependence diagnoses.

**Methods:** Subjects were male and female twins from both age cohorts of the Minnesota Twin Family Study, a population-based longitudinal study, and were approximately 11 or 17 years of age, respectively, upon study enrollment. In both age cohorts, diagnoses of conduct disorder, oppositional defiant disorder, and attention-deficit/hyperactivity disorder served as outcome measures. In addition, measures of lifetime substance use and of the presence of symptoms of substance abuse were derived for the 11-year-old cohort when subjects were approximately 14 years old and diagnoses of substance abuse were derived for the older cohort at age 17. An extension of logistic regression using generalized estimating equations served to assess whether paternal maximum alcohol consumption predicted filial outcome measures.

**Results:** Paternal maximum alcohol consumption was consistently associated with conduct disorder, substance use, and substance abuse or dependence in male and female offspring. These associations were not mediated by a primary effect of paternal alcoholism.

**Conclusions:** Paternal maximum alcohol consumption was uniquely associated with those offspring characteristics most reliably found in adolescent children of alcoholic parents. This phenotype might supplement DSM diagnoses of alcohol dependence to reduce the number of false positives in genetic research.

**Key Words:** Maximum Alcohol Consumption, Alcoholism, Genetic Risk, Externalizing Disorders.

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**T**HE MAXIMUM NUMBER of drinks consumed in any 24-hr period seems to be an interesting phenotype related to alcoholism. It has face validity, in that consumption of extremely large quantities suggests a significant degree of tolerance, either acute or chronic. Consistent with this notion, Schuckit and colleagues have found that the maximum number of drinks is one of several variables that differentiate individuals whose alcohol dependence includes physiologic features (Schuckit et al., 1998) or severe withdrawal symptoms (Schuckit et al., 1995) from those whose dependence lacks these characteristics. Furthermore, some alcoholics report that avoiding drinking alto-

gether is relatively easy, but once having had one drink they are unable to resist subsequent drinks. Even nonalcoholic individuals may be vulnerable to this tendency if their risk for alcoholism is elevated: Kaplan et al. (1988) found that after drinking a placebo, nonalcoholic males with a positive family history of alcoholism rated themselves as less confident in their ability to resist another drink than subjects without such a family history. The maximum number of drinks consumed may be related to this type of loss-of-control drinking, first described by Jellinek (1960) as the single most important symptom of alcoholism. Loss of control is a distinguishing feature of type 1 alcoholics in Cloninger's (1987) classification, whereas in others (e.g., Babor et al., 1992), loss of control and inability to abstain together constitute the core of a single dimension of dependence.

Individuals who are especially sensitive to alcohol's unpleasant effects, conversely, seem to be somewhat protected from developing dependence, and two recent studies suggest that the maximum number of drinks measure is related to this phenomenon. For instance, individuals with a polymorphism of the gene for aldehyde dehydrogenase

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(ALDH2), typically found only in those of northeast Asian descent, experience intense facial flushing and other uncomfortable reactions to alcohol, and their risk of alcoholism is reduced. Cultural influences moderate this genetic predisposition, such that individuals of Asian descent who have this polymorphism and live in the United States, especially those who are third or fourth generation or are college students, drink more than those who live in their native land (Nakawatase et al., 1993, Tu and Israel, 1995). Wall et al. (2001) recently reported that whereas Asian-American college students with the relevant allele are as likely to have had at least one drink in their lifetimes and in fact become inebriated as often as those without the allele, they are unlikely to become regular drinkers, to engage in binge drinking, or to consume large quantities of alcohol in a 24-hr period. This suggests that the maximum number of drinks consumed may reflect their genotype more closely than whether they have ever had a drink or get inebriated. In addition, investigators with the Consortium for the Genetics of Alcoholism have linked the maximum number of drinks phenotype to a region of chromosome 4 containing the gene cluster for alcohol dehydrogenase (ADH), an enzyme involved in alcohol metabolism (Saccone et al., 2000). By virtue of their effect on enzyme kinetic properties, alleles of two ADH genes seem to be associated with reduced risk for alcoholism in Chinese and Japanese populations.

The maximum number of drinks consumed may also be related to neurophysiologic vulnerability for alcoholism. Iacono et al. (2002) used the maximum number of drinks consumed in 24 hr and age at first drink to define extreme paternal drinking history. They found that the P300 wave of the event-related brain potential elicited in a visual discrimination task was significantly reduced in amplitude among 17-year-old male youths from the Minnesota Twin Family Study (MTFS) whose fathers did not meet diagnostic criteria for alcohol dependence but whose drinking history might nevertheless be considered deviant by virtue of being in the most extreme decile on either drinking history measure. Moreover, mean P300 amplitude in this group was comparable to that of subjects whose fathers did have a dependence diagnosis, suggesting that these two measures of drinking history were tapping into a common underlying liability for alcoholism and related disorders. These results also point to the potential utility of using alcoholism-related phenotypes to supplement DSM alcoholism diagnoses in epidemiologic research.

Reduced P300 amplitude, which in the study of Iacono et al. (2002) characterized sons of fathers with a significant drinking history even in the absence of a dependence diagnosis, is a putative marker of genetic risk for externalizing disorders, such as disruptive behavior and substance use disorders (Begleiter and Porjesz, 1999; Iacono, 1998; Iacono et al., 2002). These are the very disorders that prospective studies have found are increased in prevalence among adolescent and preadolescent children at high risk

for alcoholism. That is, adolescent children of alcoholics face increased risk for substance-related problems, including alcohol or illicit drug use (Chassin et al., 1991) and abuse (Blackson et al., 1999; Chassin et al., 1999; Lynskey et al., 1994; Reich et al., 1993; Sher, 1991; Sher et al., 1991; West and Prinz, 1987). Young children of alcoholics tend to be physically aggressive (Carbonneau et al., 1998) and to have high externalizing scores on Achenbach's (1991) Child Behavior Checklist (Blackson et al., 1999). Children of alcoholics also have higher rates of disruptive behavior disorders, such as attention-deficit/hyperactivity disorder (ADHD) (Lynskey et al., 1994) and oppositional defiant disorder (Lynskey et al., 1994; Reich et al., 1993). However, at this age the behavioral disorder most robustly associated with parental alcoholism is conduct disorder (Blackson et al., 1999; Lynskey et al., 1994; Reich et al., 1993; West and Prinz, 1987).

In light of these data, we asked whether the maximum number of drinks might be related to externalizing and substance-related problems in preadolescent and adolescent children. Several studies of alcoholism risk have focused on paternal alcoholism in particular. Despite some failures to replicate (e.g., Tarter et al., 1997), paternal alcoholism has consistently been associated with increased rates of alcohol problems in both male and female children of alcoholics (Sher, 1991). Moreover, Chassin et al. (1991) found that paternal alcoholism was uniquely predictive of adolescent use of alcohol and other substances. Hence, the goal of the present study was to examine paternal maximum consumption as a phenotype related to risk for externalizing disorders, substance use, and substance use disorders among male and female offspring in late childhood and adolescence. Given that maximum alcohol consumption is necessarily correlated with dependence, we asked whether there is a unique effect of maximum consumption independent of paternal alcoholism.

This study was conducted as part of the Minnesota Twin Family Study (MTFS), a large, ongoing, population-based study of reared-together twins, the primary aim of which is understanding genetic and environmental influences on the development of substance use disorders and related psychopathology. The MTFS sample consists of two age cohorts, with subjects in one being approximately 11 years of age upon study enrollment and subjects in the other being approximately 17 years of age. Using data from participants' initial assessment, we asked whether paternal maximum consumption was associated with filial externalizing diagnoses in both age cohorts as well as with substance use disorders in the older cohort.

The design of the MTFS is longitudinal, with participants returning at 3-year intervals for follow-up assessments. At the time of this study, the first follow-up assessment was complete. Participants in the younger cohort were 14 to 15 years of age at the time, which allowed us to determine whether maximum consumption was associated with early initiation into substance use and early substance-related

**Table 1.** Demographic Characteristics of the Sample

Cohort	N	Mean age (SD)	Paternal years of education	Paternal occupational status
11-year-old male	686	11.7 (0.4)	14.0 (2.0)	3.8 (1.7)
11-year-old female	664	11.7 (0.5)	14.4 (2.4)	3.7 (1.8)
17-year-old male	514	17.5 (0.4)	14.1 (2.4)	3.6 (1.7)
17-year-old female	562	17.5 (0.5)	14.2 (2.4)	3.8 (1.9)

SD, standard deviation.

Occupational status is coded according to Hollingshead's (1957) scale, with 1 representing highest-prestige occupations, such as executives of large companies, lawyers, physicians, and other "major" professionals, and 7 representing unskilled laborers. As the SDs suggest, there was considerable variability in occupational category. In all four age-sex cohorts, category 5, representing skilled manual laborers, was the most common category, with category 3, representing administrative personnel, small business owners, and "minor" professionals, such as laboratory assistants, newspaper reporters, airline pilots, and commercial artists, ranking a close second.

problems. Early initiation into drinking in particular is associated with later abuse and dependence (DeWit et al., 2000; Grant and Dawson, 1997; Hawkins et al., 1992) and with externalizing disorders (McGue et al., 2001). In light of these data, we assessed relations between paternal maximum consumption and early use of alcohol, tobacco, or illicit drugs. In addition, although few 14 year olds have diagnosable substance problems, a number of them have at least one symptom of such disorders. We therefore examined presence of any symptoms of nicotine dependence, alcohol abuse or dependence, and illicit drug abuse or dependence in relation to paternal maximum consumption. Including data from this follow-up assessment in the younger cohort allowed us to determine whether maximum consumption was associated with early substance use and clinically relevant substance-related problems, even before the emergence of diagnosable substance use disorders, and thus to link our analyses in the younger cohort with analyses of substance diagnoses in the older cohort. For both behavioral disorders and substance-related outcomes, then, we were able to assess consistency across age cohorts with respect to the patterns of results.

To address the discriminant validity of maximum consumption as a risk-related phenotype, we also assessed whether paternal maximum consumption was related to an internalizing disorder, major depression. Because adolescent children of alcoholics may not be especially susceptible to depression (Reich et al., 1993), our hypothesis was that maximum consumption would be related to externalizing disorders but not to depression.

## MATERIALS AND METHODS

### Participants

The sample for the present study consisted of all male and female twins in both age cohorts of the MTFs whose biological fathers had completed a diagnostic interview (see Table 1). Twin subjects under the age of 18 gave informed written assent to participate, whereas those who were 18 at the time of enrollment into the study gave informed consent. Parents consented in writing to their children's participation as well as their own. The MTFs used a population-based ascertainment method, identifying study participants on the basis of public birth records and drawing from the entire population of twin births in Minnesota between 1972 and 1982 (male cohort) or between 1975 and 1984 (female cohort). [The interested reader can find a thorough description of the MTFs, including details of sample ascertainment, evaluation of sample bias, and assessment proce-

dures, in Iacono et al. (1999).] In brief, all twins born during these years were identified through public birth records. Ninety-one percent of the twins who survived infancy were successfully located, and approximately 83% of those who met inclusion criteria (the twins lived within a day's drive from the university, they lacked a mental and or physical disability that would preclude completing the entire assessment, and they had not been adopted by someone unrelated) agreed to participate. The sample consists of 1383 twin pairs and their parents. There were few differences between participating and nonparticipating families, and any differences observed were small in magnitude. The sample is representative of the population of individuals born in the state during the relevant years. Consistent with the demographic profile of Minnesota at that time, the majority of participants were white (96.6% in the younger cohort and 98.5% in the older one). Approximately 60% of the fathers in each age-gender cohort had a high school degree, and an additional one fifth to one fourth had a college degree. Other demographic characteristics of the sample for the present study, including average ages of the twins, are given in Table 1.

Subjects in the MTFs are assessed at 3-year intervals. A total of 551 male subjects (mean age, 14.8; range, 13.7–16.2) and 570 female subjects (mean age, 14.7; range, 13.6–16.5) in the younger cohort visited in person and completed a computerized substance use instrument, described below.\* The 92 boys and 57 girls in this sample who participated in the follow-up assessment but did not visit were given diagnostic interviews by telephone. We compared those who visited in person and those who were interviewed by telephone with respect to the outcome and predictor measures considered here and found no significant differences. Eighty subjects (43 male and 37 female, representing <6% of the intake total) did not participate in the follow-up assessment. Nonparticipating subjects were significantly less likely than participating subjects to have a conduct disorder diagnosis at the initial assessment ( $\chi^2 = 6.53, df = 1, p = 0.011$ ). None of the other disorders differentiated between those who participated in the follow-up assessment and those who did not, and their fathers did not differ with respect to the paternal characteristics studied.

### Clinical and Substance Use Assessments

**Diagnostic Interviews.** Trained interviewers with undergraduate or master's degrees collected diagnostic information using structured clinical interviews. Each father's substance use was assessed by means of the Substance Abuse Module (SAM; Robins et al., 1987). The younger twins were assessed by means of the revised Diagnostic Interview for Children and Adolescents (DICA-R; Reich, 2000; Welner et al., 1987), modified to provide complete coverage of DSM-III-R criteria (American Psychiatric Association, 1987), the diagnostic standard in place when the first families were enrolled. The child's primary caregiver, most often the mother, was also interviewed about each twin using the parent version of the DICA-R.

Using the DICA-R interview at both assessments, we determined whether younger-cohort subjects met diagnostic criteria for any symptoms of a substance use disorder by the time of their age-14 assessment. The

\* Because of computer failure, data for 15 male and 6 female subjects were missing.

assessment of male twins was of lifetime use at both visits. Female twins and the interviewed parent, however, reported on lifetime use at the intake assessment but only on the previous 3 years at their follow-up assessment. Owing to this difference between gender cohorts in reporting periods at the follow-up assessment, we combined symptom counts across assessments to derive lifetime estimates in each gender cohort. That is, we considered subjects to have a symptom of substance abuse or dependence if any were reported at either the intake or follow-up assessment. The substance disorders that we examined were nicotine dependence, alcohol abuse or dependence, and illicit drug abuse or dependence.

Assessment of the older twins also included the DICA-R, used to assess ADHD and oppositional defiant disorder. In addition, an interview developed by MTFs staff served to assess antisocial behavior, including symptoms of conduct disorder (see Elkins et al., 1997; Holdcraft et al., 1998; Iacono et al., 1999). This consisted of questions about all DSM symptoms of child and adult antisocial behavior. The SCID (Spitzer et al., 1992) was used to assess major depression. Substance use was assessed through interviews with the SAM. As in the younger cohort, a parent was also interviewed about each twin using the parent version of the DICA-R.

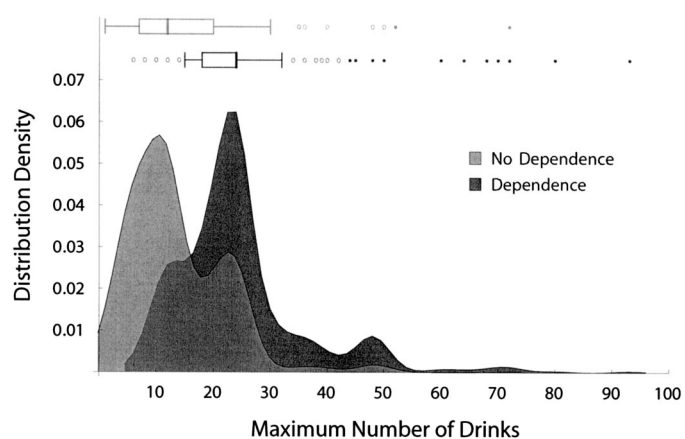
**Assignment of Diagnoses.** For a given subject, a pair of students at advanced stages of graduate training in clinical psychology reviewed coding sheets that the interviewer had completed as well as audiotape recordings of the interview itself. The team arrived at a consensus about whether a given symptom was present, and computer algorithms based on DSM-III-R requirements were subsequently used to assign diagnoses. Members of each team were unaware of any diagnoses assigned for other members of the family. A second consensus team also reviewed a subset of interview protocols and separately determined which symptoms were present, if any. Kappa coefficients assessing the agreement between teams ranged from 0.71 for oppositional defiant disorder to >0.91 for substance use disorders.

For all individuals, diagnoses derived in this manner covered the individual's lifetime. For the twins, these were best-estimate diagnoses combining information from the twin and parent (Kosten and Rounsaville, 1992; Leckman et al., 1982). Because they had not fully passed through the risk period for most disorders assessed, we used a probable certainty level to assign diagnoses, meaning that all diagnostic criteria but one had to be met. The sole exception to this rule was for substance abuse diagnoses: because a single symptom would be sufficient to qualify for a probable diagnosis, we used definite diagnoses of abuse only. We derived diagnoses of conduct disorder, oppositional defiant disorder, ADHD, and depression for both age cohorts, as well as diagnoses of nicotine dependence, alcohol abuse or dependence, and illicit drug abuse or dependence for the older cohort. We considered fathers to have a diagnosis of lifetime alcohol dependence only when all DSM-III-R criteria were fully met.

**Computerized Substance Use Measure.** All twins completed a computer-administered assessment of substance use. This included questions that asked whether subjects had ever used tobacco, alcohol without parental permission, marijuana, or hashish and whether subjects had ever used any of the following, given in order of endorsement frequency, to "get high": inhalants, amphetamines, psychedelics, cocaine, heroin or other opiates, tranquilizers, sedatives or Quaaludes, and steroids. An additional question, administered only to those who report using alcohol without parental permission, asks whether one has ever been intoxicated. For twins at the age-14 assessment, we derived dichotomous measures of early substance use from their responses to these questions. Reports about the different categories of illicit drugs, including marijuana, were combined into a single measure of early drug use. The drug section of the interview included two questions about fictitious drugs, which served as validity items. Two subjects, both male, who endorsed taking one or both of these were excluded from analyses of drug use.

### Maximum Consumption

A question on the SAM asks, "What is the largest amount of alcohol you ever consumed in a 24-hr period?" This question, which refers spe-



**Fig. 1.** The distribution of the maximum number of drinks is plotted for fathers with and without a diagnosis of alcohol dependence. The distributions, which are also given in the form of box plots at the top of the figure, were smoothed by means of nonparametric density estimates. ○, observations between the inner and outer "fences," where the inner fences are given by the median  $\pm$  1.5 times the interquartile range and the outer fences are given by the median  $\pm$  three times the interquartile range; ●, observations outside the outer fences.

cifically to the period of one's heaviest use, is asked of all individuals who report ever having had any alcohol. Fathers who never drank, along with their children, were therefore not included in the present sample. This excluded only a small number of families, ranging from one in the younger female cohort to three in both male cohorts. A graphic representation of the distribution of responses on this measure in the whole sample appears in Fig. 1, with separate plots for those with a diagnosis of alcohol dependence and for those without. As Fig. 1 makes clear, the maximum number of drinks consumed was correlated with dependence. The Pearson (point-biserial) correlation was similar for fathers in both age cohorts ( $r = 0.51$  and  $r = 0.47$  for younger and older cohorts, respectively, both  $p < 0.001$ ). The distribution of responses was also highly similar for the two cohorts of fathers as well as positively skewed. We used a log transformation to compensate for the positive skew in the distribution and standardized the log-transformed measures to provide a more straightforward interpretation of odds ratios (ORs) from regression analyses, described next.

### Statistical Analysis

When responses are correlated, as is likely when the sample consists of pairs of biologically related individuals of the same age growing up together in the same family, ordinary logistic regression will tend to underestimate standard errors for time-invariant effects. We therefore used generalized estimating equations (Liang and Zeger, 1986), a quasi-likelihood approach that simultaneously estimates regression parameters for predictor variables and correlations between responses of members of the same twin pair. In essence, generalized estimating equations provide a multivariate generalization of ordinary logistic regression. In this case, paternal status was the independent variable and diagnostic or substance use status of both of the father's twin children was the vector of binary responses.

To assess the validity of paternal maximum consumption (P-MAX) as a risk-related phenotype in the younger age cohort, we examined its associations with the measures of filial externalizing disorders, lifetime substance use, and substance abuse or dependence described above. (To simplify presentation and avoid confusion, particularly when describing alcohol diagnoses in both the father and his offspring, we use acronyms for the paternal, independent variables.) Our analytic strategy consisted of fitting a series of models, the first of which included gender, P-MAX, and the interaction between them as explanatory variables. When the interaction effect was not significant, we dropped it from the model and derived a common effect of P-MAX in the combined gender cohort. In a second

**Table 2.** Association Between P-MAX and Filial Externalizing Diagnoses, Early Substance Use, and Clinical Symptoms of Substance Abuse in the Younger Cohort

Offspring characteristic	Prevalence	P-MAX		P-AD	
		Unadjusted OR (95% CI)	Adjusted for P-AD OR (95% CI)	Unadjusted OR (95% CI)	Adjusted for P-MAX OR (95% CI)
<b>Age-11 behavioral disorders</b>					
Conduct disorder	0.113	1.70 (1.29–2.24)***	1.65 (1.21–2.25)**	1.85 (1.22–2.81)**	1.13 (0.70–1.81)
Oppositional defiant disorder	0.120	1.35 (1.08–1.69)**	1.25 (0.98–1.60)	1.67 (1.12–2.49)*	1.33 (0.86–2.06)
ADHD	0.064	1.28 (0.94–1.73)	1.17 (0.85–1.62)	1.64 (0.97–2.75)	1.39 (0.80–2.42)
Any disruptive disorder	0.207	1.44 (1.18–1.75)***	1.35 (1.09–1.68)**	1.71 (1.23–2.39)**	1.26 (0.87–1.83)
Depression	0.032	0.96 (0.70–1.33)	1.07 (0.71–1.60)	0.68 (0.35–1.35)	0.64 (0.28–1.47)
<b>Age-14 assessment substance use and presence of symptoms of substance use disorders</b>					
Tobacco use	0.331	1.52 (1.27–1.81)***	1.45 (1.18–1.77)***	1.75 (1.26–2.42)***	1.20 (0.83–1.75)
Alcohol use	0.315	1.40 (1.19–1.64)***	1.36 (1.13–1.64)***	1.53 (1.11–2.10)**	1.11 (0.77–1.61)
Illicit drug use	0.157	1.53 (1.21–1.94)***	1.49 (1.14–1.94)**	1.67 (1.11–2.49)*	1.12 (0.71–1.76)
Any use	0.418	1.42 (1.21–1.67)***	1.38 (1.15–1.66)***	1.54 (1.14–2.10)**	1.10 (0.78–1.57)
Ever intoxicated (alcohol)	0.141	1.64 (1.27–2.12)***	1.59 (1.20–2.12)**	1.76 (1.14–2.70)**	1.11 (0.69–1.79)
Nicotine symptoms	0.091	1.79 (1.28–2.51)***	1.69 (1.15–2.49)**	2.05 (1.27–3.31)**	1.24 (0.72–2.15)
Alcohol symptoms	0.044	1.83 (1.16–2.87)**	1.84 (1.13–3.01)*	1.73 (0.90–3.35)	0.96 (0.48–1.94)
Drug symptoms	0.031	2.07 (1.27–3.37)**	2.16 (1.22–3.80)**	1.77 (0.82–3.80)	0.85 (0.35–2.11)
Any substance symptoms	0.102	1.76 (1.28–2.41)***	1.71 (1.20–2.44)**	1.85 (1.18–2.91)**	1.11 (0.66–1.85)

CI, confidence interval.  
\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$ .

Prevalence gives the proportion of subjects with the relevant disorder or responding yes in the case of the substance use variables. OR gives the odds ratio (with the 95% CI around it) of a diagnosis or of having used a given substance for those whose fathers had a diagnosis of dependence or for each SD increase in the log of maximum consumption. Significant ORs are indicated by means of asterisks. Unadjusted ORs are for P-AD or P-MAX when it was the sole predictor variable other than gender; adjusted ORs are derived from a model including both paternal characteristics as predictors.

Tobacco use indicates any lifetime use of tobacco, whether by smoking or chewing. One male subject’s response to questions assessing tobacco use were missing. Alcohol use indicates any lifetime use of alcohol without parental permission. Drug use indicates lifetime use of an illicit substance. Any use refers to having used any one of these substances. Nicotine symptoms represent presence of any symptoms of nicotine dependence, alcohol and drug symptoms indicate at least one symptom of abuse or dependence. Any substance symptoms refers to at least one symptom present for any of these substance use disorders. A response to the question assessing whether one has ever been intoxicated was missing for one female subject.

analysis, we added paternal alcohol dependence (P-AD) as well as its interaction with gender to determine whether any effects of P-MAX might be mediated through a primary effect of alcoholism. As in the first analysis, nonsignificant interaction effects between P-AD and offspring gender were dropped and common effects were derived. We assessed associations between P-AD and the outcome measures in a parallel manner, first considering P-AD alone as a predictor variable and then considering the effect of P-AD when controlling for the effect of P-MAX (derived from the second analysis above). For all analyses, we exponentiated regression coefficients to obtain ORs as measures of effect size for associations between independent and dependent variables.

These analyses allowed us to examine whether P-AD mediated any observed associations between P-MAX and offspring outcomes. To infer a mediating influence of paternal dependence requires that three criteria be met (Baron and Kenny, 1986): (1) P-AD must be significantly associated with the outcome measure in question; (2) any significant associations between P-MAX and filial characteristics should become nonsignificant when adjusted for effects of P-AD; and (3) P-AD should still be significantly associated with the relevant filial characteristics in the presence of P-MAX—that is, there should be significant effects of P-AD that are independent of effects of P-MAX.

RESULTS

*Younger Cohort*

The results for the younger cohort are presented in Table 2. Prevalences of the various offspring disorders and use measures are given in the first column of Table 2, and the results of the statistical analyses are given in the remaining columns. Associations between P-MAX and P-AD, respectively, and offspring measures were somewhat greater in magnitude for the female cohort when conduct disorder

and oppositional defiant disorder were the dependent measures but greater for the male cohort when ADHD was the dependent measure. Nevertheless, none of the interactions between P-MAX or P-AD, respectively, and offspring gender was significant, and ORs for substance-related measures were highly similar for the male and female cohorts. Table 2 therefore presents common ORs for the two gender cohorts combined.

Simple associations between P-MAX and offspring characteristics appear in the column labeled “P-MAX, Unadjusted.” The results indicate that P-MAX was not associated with offspring ADHD or major depression. However, it was associated with diagnoses of conduct disorder, oppositional defiant disorder, and any disruptive behavior disorder at the age-11 assessment as well as with all measures of substance use and with the presence of symptoms of substance-related disorders at the age-14 assessment. For instance, the OR for conduct disorder (1.70) indicates that the odds of having this diagnosis increase 70% for each standard deviation increase in the log of the father’s maximum number of drinks. ORs were homogeneous for lifetime use of various substances, ranging from 1.40 to 1.53. P-MAX was associated with a somewhat greater increase in the odds of ever being intoxicated (1.64) than of simply having used substances. ORs for having any symptoms of a substance use disorder were even greater in magnitude, ranging from 1.79 to 2.07.

Associations between P-MAX and offspring outcomes

**Table 3.** Association Between P-MAX and Externalizing and Substance Use Diagnoses Among 17 Year Olds

Offspring diagnosis	Prevalence	P-MAX		P-AD	
		Unadjusted OR (95% CI)	Adjusted for P-AD OR (95% CI)	Unadjusted OR (95% CI)	Adjusted for P-MAX OR (95% CI)
Behavioral disorders					
Conduct disorder <sup>a</sup>	0.214	1.40 (1.16–1.69)***	1.25 (1.01–1.55)*	(boys) 1.52 (0.98–2.35) (girls) 4.05 (2.09–7.83)***	1.21 (0.74–1.98) 3.32 (1.54–7.19)**
Oppositional defiant disorder	0.179	1.38 (1.12–1.69)**	1.26 (0.99–1.61)	1.80 (1.23–2.63)**	1.44 (0.91–2.27)
ADHD	0.061	1.62 (1.17–2.24)**	1.45 (0.99–2.14)	2.19 (1.23–3.92)**	1.55 (0.77–3.09)
Any disruptive disorder	0.331	1.45 (1.23–1.70)***	1.29 (1.06–1.56)**	2.11 (1.54–2.90)***	1.66 (1.14–2.42)**
Depression	0.125	1.27 (1.02–1.58)*	1.15 (0.91–1.45)	1.76 (1.17–2.67)**	1.55 (0.99–2.41)
Substance use disorders					
Nicotine dependence	0.146	1.59 (1.30–1.94)***	1.55 (1.24–1.94)***	1.66 (1.10–2.51)*	1.11 (0.70–1.78)
Alcohol diagnosis	0.144	1.38 (1.14–1.68)**	1.24 (0.99–1.56)	1.93 (1.29–2.89)**	1.57 (0.97–2.52)
Drug diagnosis	0.061	1.61 (1.22–2.12)***	1.39 (1.01–1.91)*	2.50 (1.38–4.51)**	1.85 (0.94–3.61)
Any substance disorder	0.224	1.48 (1.24–1.76)***	1.43 (1.18–1.74)***	1.60 (1.12–2.30)*	1.14 (0.76–1.73)

\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$ .

<sup>a</sup> Because there was a significant gender by P-AD interaction for conduct disorder, the adjusted OR for P-MAX in this case was derived from a model including this interaction term. ORs for paternal dependence in relation to conduct disorder are given separately for boys (first line) and girls (second line).

Prevalence gives the proportion of subjects with the relevant disorder. OR gives the odds ratio (with the 95% CI around it) of a diagnosis in subjects whose fathers had a diagnosis of dependence or for each SD increase in the log of P-MAX. Significant ORs are indicated by means of asterisks. Unadjusted ORs are for P-AD or P-MAX when it was the sole predictor variable other than gender; adjusted ORs are derived from a model including both paternal characteristics as predictors. Nicotine dependence represents a diagnosis of nicotine dependence, alcohol diagnosis one of alcohol abuse or dependence, and drug diagnosis one of illicit drug abuse or dependence. Any substance disorder is a diagnosis of any of the three.

after controlling for any effect of P-AD appear in the column labeled “P-MAX, Adjusted for P-AD” in Table 2. With the exception of oppositional defiant disorder, which just failed to be significant, the adjusted ORs representing P-MAX’s effect adjusted for any effects of P-AD were significant for all filial characteristics. Even the lack of a significant association with oppositional defiant disorder does not point to a mediating role of P-AD, because dependence itself was not significantly associated with oppositional defiant disorder when adjusted for effects of P-MAX.

The remaining columns of Table 2 describe the results of the analyses for P-AD. Simple associations between P-AD and the offspring outcome measures appear in the column labeled “P-AD, Unadjusted.” These ORs paralleled those for P-MAX. With the exception of the presence of symptoms of alcohol or illicit drug abuse or dependence, all effects that were significant for P-MAX were significant for P-AD.

Associations between P-AD and outcome measures when effects of P-MAX were controlled are given in the column labeled “P-AD, Adjusted for P-MAX.” None of these ORs was significant when adjusted for effects of P-MAX. This stands in marked contrast to the results for P-MAX: ORs for P-MAX were minimally affected by adding P-AD to the model (compare the unadjusted and adjusted ORs for P-MAX). This pattern of results suggests that P-MAX mediated any associations between P-AD and filial characteristics, rather than the opposite.

In summary, P-MAX was significantly associated with externalizing behavioral disorders, especially conduct disorder. It was also associated with early lifetime substance use, having ever been intoxicated, and symptoms of substance abuse. These associations were significant even

when adjusted for effects of P-AD, indicating that they were not mediated by a primary effect of alcoholism in the father.

Prospective studies have found that conduct disorder (Biederman et al., 1997; Boyle et al., 1992; Clark et al., 1998) and persistent delinquency (Loeber et al., 1999; Windle, 1990) predict substance use, perhaps especially use of marijuana and other illicit drugs (Boyle et al., 1992; Clark et al., 1998). Conduct disorder also predicts nicotine dependence (Breslau, 1995). In fact, it is a robust risk factor for substance use and abuse (Robins, 1991; Weinberg and Glantz, 1999). We therefore investigated in a post hoc analysis whether the effect of P-MAX on substance use and abuse at the age-14 assessment might be due to conduct disorder at the intake assessment. For these analyses, we excluded subjects who reported any substance use at their age-11 assessment (25 boys and 11 girls). All characteristics of the twins that had been significantly associated with P-MAX were still significantly associated with it when adjusted for any effects of a diagnosis of conduct disorder.

#### Older Cohort

Table 3 gives results for the older cohort and is organized like Table 2, with prevalences of the offspring disorders in the first column and results of the statistical analyses in the remaining four columns. As in the younger cohort, ORs were very similar for boys and girls with respect to substance measures and somewhat more variable across gender cohorts for disruptive behavioral disorders. Nevertheless, only one interaction between each paternal characteristic (P-MAX and P-AD, respectively) and offspring gender was significant. We therefore combined data from both genders and derived common ORs. The lone

significant interaction involved P-AD and conduct disorder ( $z = 2.51, p = 0.012$ ). The OR of 2.75 (95% confidence interval, 1.25–6.07) indicated greater odds that female offspring of alcohol-dependent men would have a diagnosis of conduct disorder than male offspring. To accommodate this finding, the adjusted OR for P-MAX's effect on conduct disorder was derived from a model including the significant gender by P-AD interaction.

Simple associations between P-MAX and offspring characteristics are given in the first column for P-MAX (labeled "P-MAX, Unadjusted"). These were significant for all disorders. ORs for these disorders ranged from 1.27 (for depression) to 1.62 (for ADHD), with a median increase in risk of 39% for each standard deviation increase in the log of the number of drinks that fathers consumed across the four individual disorders considered. P-MAX was also associated with a 45% increase in the odds of any disruptive disorder in the offspring.

Associations between P-MAX and offspring disorders that control for effects of P-AD appear next to the unadjusted associations, under the heading "P-MAX, Adjusted for P-AD." Five of the nine ORs that had been significant for P-MAX when it was the sole predictor variable remained significant when adjusted for any effects of P-AD, with three becoming marginally nonsignificant.

Simple associations between P-AD and offspring outcome measures, which are given in the first column for P-AD in Table 3 (labeled "P-AD, Unadjusted"), yielded a pattern of results that was similar to that obtained for P-MAX. All associations were significant, although the effect on conduct disorder was significant only for female offspring (the interaction between P-AD and offspring gender described above).

Associations between P-AD and offspring disorders adjusted for effects of P-MAX are given under the heading "P-AD, Adjusted for P-MAX." Only the adjusted common OR for any childhood disruptive disorder was significant, although several others were nearly significant.

As in the younger cohort, then, P-AD's associations with the outcome measures were mostly not significant when effects of P-MAX were controlled. Furthermore, that four adjusted ORs representing P-MAX's effect independent of P-AD were not significant does not suggest that the effects represented by unadjusted ORs in these cases were mediated by P-AD, because P-AD was also not significantly associated with these four outcome measures when its effects were adjusted for those of P-MAX (cf. Baron and Kenny, 1986). These findings support a mediating role of P-MAX for several offspring diagnoses, especially nicotine dependence and any substance disorder, which were strongly associated with P-MAX independent of any effects of P-AD but not with P-AD in the presence of P-MAX. However, they also suggest that P-MAX and P-AD contribute independently to offspring disruptive behavior disorders and that the two paternal characteristics share some-

what more variance in common with offspring measures in the older cohort than in the younger cohort.

### *Mediating Influences of Paternal Nicotine and Drug Diagnoses*

Across the two age cohorts, P-MAX was associated with measures of nicotine use and clinically significant dependence on nicotine and with illicit drug use or abuse not just alcohol use and abuse. The consistency of these findings raises the possibility that these associations might be spurious, a result of other factors correlated with P-MAX and the outcome measures. For instance, to the extent that there are specific genetic or environmental influences on substance use and abuse, associations with tobacco use or nicotine dependence might be due to paternal nicotine dependence rather than to P-MAX. In a similar manner, associations between P-MAX and offspring drug use or abuse might be mediated by paternal drug diagnoses. In fact, P-MAX was correlated with paternal nicotine dependence ( $r = 0.37$  and  $r = 0.33$ ) for younger- and older-cohort fathers, respectively, as well as with paternal drug diagnoses ( $r = 0.24$  in both cohorts of fathers; all correlations were significant with  $p < 0.001$ ).

We therefore conducted two sets of post hoc analyses to investigate whether paternal diagnoses of nicotine dependence and illicit drug abuse or dependence, respectively, might mediate the associations between P-MAX and offspring disorders observed in our primary analyses. The form of these analyses was similar to those for conduct disorder in the younger cohort. None of the interactions between gender and each paternal characteristic (P-MAX and either paternal nicotine dependence or paternal drug diagnoses) was significant. We therefore derived common adjusted ORs for the combined gender cohorts. For both types of substances, P-MAX remained significantly associated with all measures of offspring use after its effects were adjusted for effects of the relevant paternal diagnosis. That is, P-MAX was significantly associated with lifetime tobacco use and the presence of symptoms of nicotine dependence among younger-cohort subjects and with diagnoses of nicotine dependence among older-cohort subjects, independent of any effects of paternal nicotine dependence. P-MAX was similarly associated with lifetime drug use and the presence of symptoms of abuse or dependence among younger-cohort subjects and with diagnoses of drug abuse or dependence among older-cohort subjects, independent of any effects of paternal drug abuse or dependence diagnoses.

When adjusted for effects of P-MAX, paternal nicotine dependence was significantly associated with filial tobacco use (adjusted OR, 2.01; 95% confidence interval, 1.42–2.84) and nicotine dependence symptoms (adjusted OR, 2.07; 95% confidence interval, 1.11–3.84) among younger-cohort subjects at their age-14 assessment. Paternal drug diagnoses, also adjusted for effects of P-MAX, were signif-

icantly associated with illicit drug diagnoses in older-cohort subjects (adjusted OR, 2.62; 95% confidence interval, 1.42–4.85). P-MAX and the relevant paternal diagnosis thus had statistically independent (and significant) effects on measures of offspring substance use and abuse or dependence, although for both paternal diagnostic measures associations were not as consistent across age cohorts.

## DISCUSSION

P-MAX was associated with externalizing behavioral disorders in general, especially conduct disorder, as well as with early substance use in the younger cohort and substance-related problems in both age cohorts. These associations were largely independent of any effects of P-AD. Moreover, the results were consistent across age cohorts, thus providing evidence of replication. The observed associations were not mediated by characteristics of the offspring themselves (i.e., conduct disorder among younger-cohort subjects) or by other characteristics of the fathers (nicotine dependence or drug abuse and dependence). P-MAX thus was uniquely associated with the very characteristics that, across various studies, most reliably differentiate preadolescent and adolescent children of alcoholics from children of nonalcoholic individuals. Taken together with other findings regarding this aspect of drinking history, these results indicate that the maximum number of drinks consumed represents an important phenotype associated with alcohol dependence that might supplement DSM diagnoses in future research.

Results were similar for male and female offspring, and only one interaction between paternal alcohol status and gender was significant. Hence, paternal alcohol-related effects were largely comparable for male and female offspring. In the case of the sole significant interaction, that between gender and paternal alcohol dependence with respect to conduct disorder, odds of a diagnosis were greatest among female offspring of alcoholic fathers. These findings are consistent with previous studies, which have typically not found gender differences in alcoholism risk (Lynskey et al., 1994; Sher, 1991) or have found greater risk among female offspring (Sher et al., 1991).

Consistent with our expectation that a father's status on this measure would relate to externalizing tendencies but not to internalizing ones in his offspring, P-MAX was not associated with major depression in the 11 year olds or in the 17 year olds when adjusted for the effect of P-AD. In addition, neither P-AD nor P-MAX was associated with ADHD diagnoses in the younger cohort. Because early studies were inconsistent with respect to the association between ADHD and alcoholism risk (West and Prinz, 1987) and recent studies have not always found such an association (e.g., Reich et al., 1993), the failure to find consistent associations between P-MAX and ADHD or even between P-AD and ADHD is not particularly surprising.

The more severe form of antisocial behavior (conduct disorder), substance use, and substance-related problems comprised the most consistent correlates of P-MAX. These phenotypes often co-occur, and several investigators have interpreted the comorbidity between antisocial behavior and substance problems in terms of a common tendency toward impulsive and "disinhibited" behavior (Fowles, 1988; Gorenstein and Newman, 1980; Sher and Trull, 1994). Two recent studies of adolescent twins indicated that conduct disorder, substance use and substance disorders share a significant amount of variance with personality traits characterized by a high degree of novelty seeking, sensation seeking, and a relative lack of constraint by social norms. This common variance, conceptualized as a latent dimension reflecting externalizing and disinhibited tendencies, is largely genetically mediated (Krueger et al., 2002; Young et al., 2000). The study by Krueger et al. is especially relevant because it used the same older male twin cohort of the MTFS from which the present study drew. Thus, our findings that P-MAX predicts externalizing disorders, especially conduct disorder, substance use, and substance abuse, are entirely consonant with the findings of Krueger et al. (2002) that these disorders share substantial genetic variance.

Another consistent correlate of P-MAX was offspring tobacco use and nicotine dependence, which was somewhat unexpected. Although tobacco use constituted part of a measure of the breadth of substance experimentation in Young et al. (2000), the latent externalizing dimension in Krueger et al. (2002) did not include symptoms of nicotine dependence as an indicator variable, yet the present results suggest that nicotine dependence might also share important etiologic variance with conduct disorder, alcohol use, and illicit drug use. Indeed, there seems to be substantial shared genetic variance between alcohol use or dependence and tobacco use (Swan et al., 1996) and nicotine dependence (True et al., 1999), respectively. In addition, conduct disorder predicts early tobacco use initiation and later nicotine dependence (Breslau, 1995). The various offspring characteristics that we found were associated with P-MAX thus seem to reflect a more or less coherent constellation. However, it may also be that the associations between P-MAX and both tobacco use and nicotine dependence in the present study reflect a more specific pharmacologic association between alcohol and tobacco use that is independent of externalizing tendencies. Animal studies point to interactions between alcohol and nicotine consumption. For instance, mouse strains bred for sensitivity to alcohol are also sensitive to nicotine (Collins, 1990; de Fiebre et al., 1990). Long-term ethanol exposure can affect nicotinic receptor densities in certain brain regions (Booker and Collins, 1997), and alterations in nicotinic receptors can affect ethanol self-administration in rats (Nadal and Samson, 1999). In addition, alcohol preference in rats is associated with differential nicotinic receptor densities (Tizabi et al., 2001). It is interesting in this regard that Daepfen et

al. (2000) found that the maximum number of drinks consumed was one of several variables that differentiate alcohol-dependent adults who had also been regular smokers but were subsequently able to quit from those who were unable to quit.

It is perhaps surprising that a single variable would account for various filial outcomes so well. However, the question is asked in the context of a clinical interview during which there is ample time to establish rapport and create an environment in which respondents might feel free to answer honestly. In addition, responses at the upper tail of the distribution clearly suggest something more than casual drinking or a single, discrete episode of drinking; one is not likely to consume 30, 40, or more drinks in a single 24-hr period (see Fig. 1) without having consumed large amounts previously and developing a significant degree of tolerance or without possessing unusual insensitivity to the negative effects of alcohol. Although the question asks about a single occasion, that occasion may well reflect a history of excessive drinking or increased risk by virtue of decreased sensitivity to alcohol. Some individuals, too, report an inability to become satiated and may even lack a concept of "having had enough," a failure of self-regulation that might be reflected in this measure.

This study is not, of course, without limitations. Although the sample is representative of the population of individuals who were born in Minnesota at the time, it is not racially or ethnically as diverse as the whole of the U.S. population, and the results of this study might not generalize to other ethnic groups. We also restricted our focus to paternal status as risk indicators. Future work will include maternal status on this variable. In addition, this study adopted a univariate approach to what is essentially a multivariate issue. However, the goal was to assess the construct validity of maximum consumption. The results indicate that maximum consumption has consistent and unique correlates. This does not suggest that maximum consumption should supplant DSM diagnoses of alcohol dependence in future research. It may be that diagnoses of alcohol dependence reflect individual impairment in a fundamental way but do not necessarily predict offspring characteristics as effectively. The results of the present study indicate that maximum consumption might help to quantify severity of alcoholism and alcoholism risk, perhaps especially in population-based samples such as the one used here. This measure might also help researchers to identify missed cases of problematic alcohol use. For instance, some fathers in the present sample who failed to meet DSM criteria for dependence nevertheless reported drinking 48 to 72 drinks in 24 hr (see Fig. 1). Subjects such as these likely represent false negatives. If so, then the measure of maximum number of drinks consumed can clearly help to identify them, to the benefit of genetic studies of risk. Although it is entirely possible that the setting in which this information was obtained and study interviewers' rapport with the father influenced them to at least attempt to respond hon-

estly, given the simplicity of this question, this measure might provide a useful shortcut method of obtaining clinically interesting information. At the very least, we concur with Saccone et al. (2000) that it merits additional attention.

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