Maternal Smoking and Drinking during Pregnancy and the Risk for Child and Adolescent Psychiatric Disorders*

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ABSTRACT. *Objective:* To examine the relative importance of prenatal exposure to cigarettes and alcohol and familial/genetic susceptibility for alcohol dependence in the etiology of childhood psychopathology. *Method:* A longitudinal prospective study of 150 children/adolescents (51.3% male), who were at either high or low risk for developing alcohol dependence because of their familial loading for alcoholism, provided multiple diagnostic assessments (N = 318) of these subjects. High-risk families were identified through the presence of two adult alcoholic sisters; low-risk control families were selected from the community. Annual assessments of offspring from these families included an in-depth psychiatric interview of each child and his/her parent to determine the presence or absence of childhood disorders. Mothers were interviewed concerning their prenatal use of substances, and information was gathered concerning their personal and familial loading for psychiatric disorders. *Results:* Using conventional logistic regression analyses, internalizing and externalizing disorders were found to be associated with familial loading for alcoholism and prenatal exposure to cigarettes and alcohol. In addition, a specialized statistical analysis, a multivariate confounder score approach, was conducted using familial risk status and the child's exposure to maternal prenatal use of alcohol and cigarettes. This analysis demonstrated that only one relationship between a single variable and a childhood disorder was significant while controlling for the other two variables: Oppositional disorder remained significant in association with familial risk status. Three additional analyses were performed to evaluate the effects of familial risk status, prenatal alcohol exposure and prenatal cigarette exposure on childhood psychopathology while controlling for two known risk factors (SES and parental ASPD) for externalizing disorders. Results of these analyses revealed that the only childhood disorder that was elevated was ADHD, and that this was the result of the familial risk variable only. *Conclusions:* Familial loading for alcohol dependence is an important risk factor for the development of childhood psychopathology and may account for the previously reported associations between prenatal exposure to nicotine and alcohol. Studies of substance abuse/dependence etiology and childhood psychopathology need to include consideration of both prenatal exposures and familial loading for alcohol dependence and other psychiatric disorders. (*J. Stud. Alcohol* **61:** 661-668, 2000)

FETAL ALCOHOL SYNDROME (FAS) was first identified in 1973 as a birth defect in children whose mothers were chronic alcoholics who drank during pregnancy. Since that time, it has become recognized that alcohol consumption in doses not generally associated with alcohol problems can produce a variety of neurocognitive deficits in the absence of effects on growth and morphology (Baer et al., 1998). Offspring of women who drink during pregnancy appear to have a continuum of neurobehavioral, morphological and developmental effects.

There is now clear evidence that children of alcoholics have significantly higher rates of child/adolescent psychopathology (Earls et al., 1988; Hill and Hruska, 1992; Hill and Muka, 1996; Hill et al., 1999; Reich et al., 1993). However, only a few studies (Hill and Muka, 1996; Hill et al., 1999) have been concerned about possible effects of prenatal exposure as an explanatory factor in the observed differences. Most studies have presumed that a familial/genetic diathesis for alcoholism is responsible for elevated rates of psychopathology in offspring. As recently noted by Baer et al. (1998), this may be a shortcoming of much of the research that assesses neuropsychological, neurophysiological and psychopathological characteristics of children of alcoholics.

Three recent studies have suggested an important relationship between prenatal exposure to alcohol and cigarette smoking and adverse behavioral outcomes in adolescence and young adulthood (Baer et al., 1998; Brennan et al., 1999; Griesler and Kandel, 1998). Baer and colleagues have reported that 14-year-old adolescents who had been exposed to alcohol during their mother's pregnancy consumed greater quantities of alcohol than did adolescents without such a history. In addition, a regression analysis combining prenatal alcohol use and family history of alcoholism revealed that prenatal alcohol exposure retained a greater effect after adjustment for family history than did family history after adjusting for alcohol exposure. Griesler and Kandel (1998) found that mothers' self-reported moderate to heavy drinking during pregnancy was associated with their adolescent daughters' current drinking. Although several potentially confounding variables were controlled in that study, measures of familial loading for alcoholism or other psychiatric conditions in parents and other relatives were not assessed.

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Maternal delinquency in young adulthood was assessed but found to have only a minimal effect on the overall finding that prenatal maternal drinking was associated with their daughters' use of alcohol in adolescence (Griesler and Kandel, 1998).

Prenatal use of nicotine has also been investigated with respect to the psychopathological characteristics of offspring. Several studies have reported finding an association between maternal prenatal smoking and such externalizing behaviors as truancy, conduct disorder, attentional problems and impulsivity (Brennan et al., 1999; Fergusson et al., 1998; Wakschlag et al., 1997). Follow-up of a birth cohort of 4,169 males born in Denmark revealed evidence for a dose-response relationship between the amount of maternal prenatal smoking and persistent criminal behavior seen in 34-year-old offspring (Brennan et al., 1999). Although several potentially confounding variables were controlled for in the analysis, the investigators did not control for genetic risk. However, the offspring of mothers who smoke during pregnancy may be those who are most likely to inherit genotypes for antisocial behavior from their mothers. It might be argued that, because of public health campaigns, women are usually informed regarding the risks to unborn children due to smoking and other drug or alcohol use; therefore, those who continue to smoke may be the most behaviorally disinhibited and prone to develop externalizing behavior problems including antisocial and criminal behaviors.

Several risk factors for the development of childhood/adolescent externalizing disorders have been identified, including lower socioeconomic status (SES) and parental antisociality. Lower SES has been reported as a significant predictor of conduct disorder (Wakschlag et al., 1997) and criminality (Brennan et al., 1999). In one study, lower SES was found to be highly associated with the likelihood of smoking during pregnancy (Fergusson et al., 1998) which, in turn, was found to predict later development of externalizing disorders. Parental antisocial personality disorder (ASPD) (Wakschlag et al., 1997) and parental criminality (Brennan et al., 1999) have also been shown to be associated with conduct disorder in offspring.

The purpose of the present analysis is to determine if familial risk, smoking during pregnancy and prenatal alcohol use would significantly elevate the risk for specific psychopathology in offspring. Extensive information on familial/genetic risk for alcohol dependence was available along with information regarding maternal use of alcohol, cigarettes and other drugs; therefore, it was possible to assess the relative contribution of all of these factors within the same sample of individuals.

Studies evaluating maternal use of alcohol and cigarettes and other confounding factors (e.g., SES and ASPD) on childhood psychopathology have typically used logistic regression to assess the effect of these variables. However, as noted by Rantakallio and colleagues (1992), conventional logistic regression models may not be the most appropriate method for estimating the odds of developing a disorder in association with specific variables when the confounding variables included in the analysis are correlated. Thus, Rantakallio et al. (1992) estimated the effect of maternal smoking on the likelihood that offspring would develop delinquency by using the confounder score approach (Miettinen, 1976) rather than the conventional logistic regression method. Collinearity was seen among variables in the present analysis; therefore, we reasoned that logistic regression analyses might present statistical limitations (Miettinen, 1976; Robins and Greenland, 1986). In conventional logistic regression analysis, Type I errors can occur because variables that appear to be significantly related to outcome are, in fact, not significant. The apparent statistical significance is the result of the variable in question being highly correlated with a variable that is truly significant. Similarly, Type II errors can occur when a major variable of interest, which is truly significant, appears to be nonsignificant because the variable is highly correlated with other variables under study that are not significant. The confounder score approach, in contrast, adjusts for correlations between variables, thereby reducing the likelihood that Type I and II errors due to collinearity of variables will occur. Therefore, a multivariate confounder score approach was used in a separate analysis to estimate the odds of developing the childhood diagnoses of interest in association with familial risk for alcohol dependence, prenatal use of alcohol and prenatal use of cigarettes. Results of logistic regression and log-linear analyses are presented along with the confounder score approach for comparison.

Method

Subjects

A total of 150 children/adolescents (ages 8 to 18), who were at either high or low risk for developing alcoholism, were assessed. The high-risk children averaged (SD) 11.4 (2.9) years and the low-risk children averaged 11.1 (2.5) years of age at entry into the study. Approximately equal numbers of male and female children were in each group. The high-risk children ($n = 89$) were drawn from families selected to be part of a larger family study of alcoholism based on the presence of two adult alcoholic sisters. These sisters are the mothers or aunts of the high-risk children upon which the present analysis is based. Selection of families using a two proband method (two alcoholic sisters) results in a high density of alcohol dependence within families and increases the likelihood of finding genes or biological markers associated with alcohol dependence (Hill and Neiswanger, 1997). Additional inclusion criteria required that all adult first-

degree relatives of the affected proband pair of sisters be free of DSM-III (Axis I) (American Psychiatric Association, 1980) disorders other than alcohol dependence. Antisocial personality disorder was free to vary and was determined along with Axis I disorders using an in-person structured interview (Diagnostic Interview Schedule; Robins et al., 1981) with all available adult relatives. (Interviews were performed by trained, M.A.-level interviewers.) All other first-degree relatives were diagnosed using a minimum of two family-history reports. Exclusion criteria for potential families were the presence of recurrent major depression, bipolar disorder, primary drug dependence (i.e., drug dependence preceded alcohol dependence by 1 or more years) or schizophrenia in any first-degree relative. Therefore, the children of the proband pair or their siblings came from families with a high density of alcoholism and a minimum of Axis I comorbidity. The low-risk children (n = 61) were also part of the larger family study. They were members of families selected from volunteers and screened for an absence of Axis I disorders, including alcohol and drug dependence, in the child's first- or second-degree relatives.

The ongoing longitudinal study evaluates children at approximately annual intervals until the age of 18. Because families continue to be recruited into the study and children enter the study at various ages, not all children have completed the same number of assessments (some children have completed their fourth annual evaluation). Analyses were based on the maximum number of repeated data assessments for each child. On average, 2.1 assessments per child have been conducted.

Prenatal alcohol exposure

Each mother was administered a structured interview concerning prenatal drinking, to determine the quantity and frequency of alcohol consumed (family history report from the father was used in approximately 5% of the cases). Thus, drinking histories were available from the mother of each child, permitting the calculation of the total number of drinks consumed throughout the pregnancy. Most mothers reported that they decreased their ethanol intake by the second and third trimesters (Table 1). The median consumption of ethanol during the entire pregnancy was 2.7 drinks per week for all of the women who reported any drinking during pregnancy. The range of drinking was 3 to 2,160 drinks over the entire pregnancy (median = 108). Drinking was more common among mothers from the high-risk families; 62.9% of these mothers reported drinking during pregnancy whereas 31.1% of mothers of the low-risk children reported drinking at least one drink during pregnancy. Some mothers reported drinking only a minimal amount of alcohol during their pregnancies (one or two drinks during the entire pregnancy). In order to provide equal numbers of cases in each group, log-linear and regression analyses were performed, based on a median split of the consumption seen for all the mothers interviewed who reported any use. Confounder score analyses were based on continuous data, however.

TABLE 1. Prenatal substance use by trimester

	First trimester	Second trimester	Third trimester
Number of drinks per day, mean (SD)			
High-risk mothers	1.70 (2.9)	0.40 (1.3)	0.30 (1.3)
Low-risk mothers	0.03 (0.1)	0.01 (0.1)	0.01 (0.1)
Number of cigarettes per day, mean (SD)[a]			
High-risk mothers	10.0 (13.3)	8.5 (12.1)	8.1 (12.1)
Low-risk mothers	0.4 (1.7)	0.3 (1.3)	0.1 (0.4)
Children with prenatal alcohol exposure (%)			
High-risk	61.8	33.7	30.3
Low-risk	27.9	8.2	8.2
Children with prenatal cigarette exposure(%)[a]			
High-risk	61.8	52.9	50.0
Low-risk	7.3	7.3	4.8

[a]Cigarette and drug use information was unavailable for 41 cases.
Note: Information on drug use is not presented since drug use was reported in 30.9% of high-risk mothers only.

Prenatal cigarette and drug use

Interview data were available for a majority of mothers concerning their cigarette and drug use (marijuana, amphetamines, barbiturates, cocaine, opiates, psychedelics, tranquilizers) during pregnancy. Although this procedure was not in place at the onset of the study, complete data were available for 109 mothers. Log-linear and regression analyses of the smoking data were based on a dichotomous split (any smoking [n = 47] during pregnancy vs none [n = 62]), whereas the confounder score analysis used the continuous data. Log-linear analyses of drug-use data were also based on a dichotomous split of the data (yes/no). Those mothers who smoked during pregnancy reported quite varying quantities. Some mothers reported smoking less than a pack per month while many smoked more than a pack a day (range = 9 packs throughout the pregnancy to 3 packs per day).

Clinical assessment of children/adolescents

All children were administered the Schedule for Affective Disorders and Schizophrenia for School-Aged Children (K-SADS) (Chambers et al., 1985) by trained clinical interviewers (M.A. in psychology) at each annual evaluation. K-SADS interviewers had diagnostic reliability of 90% or greater with interviewers trained by the authors of the instrument. The parent who accompanied the child to the testing session (usually the mother) also participated in the

K-SADS, answering the same questions asked of the child, in a separate interview. A third- or fourth-year resident, specializing in child psychiatry in an integrated general and child psychiatry program, conducted an unstructured interview independently with both the child and the parent. Both the interviewer and the psychiatrist were blind to the risk status of the subject's family. The presence of the following selected disorders was determined through a "best-estimate" consensus diagnosis between the interviewer and the psychiatrist: depression (major depression and dysthymia); phobia; anxiety disorders (panic disorder, separation anxiety, overanxious disorder); attention deficit hyperactivity disorder (ADHD); conduct disorder; substance abuse/dependence disorders; and oppositional disorder. Any discrepancies were resolved in the presence of a third clinician.

Data analyses

The log-linear regression (BMDP 4F) analysis included testing the association between four independent variables (familial risk for alcohol dependence and maternal use of cigarettes, drugs and alcohol during pregnancy) and the outcome variable (childhood diagnoses). The cell counts in each two-way contingency table were modeled to test for possible associations among the variables. Log-linear models were fitted to frequency tables in order to describe the relationship between childhood psychopathology diagnosed at any evaluation (presence or absence of a particular disorder) and the factors of interest: familial risk (high or low); prenatal cigarette use (yes/no); prenatal alcohol use (median split); and prenatal drug use (yes/no). Analyses were conducted separately for each K-SADS diagnosis and separately for each factor.

Logistic regression analyses were then performed on the data to obtain odds ratios describing the odds of incurring a particular diagnosis in association with each of the major variables of interest (familial risk for alcoholism, prenatal use of alcohol, prenatal use of cigarettes; drug use was not included as it was not found to be significantly associated with any of the K-SADS diagnoses). The confounder score approach (Miettinen, 1976) was subsequently used to calculate odds ratios for particular disorders in association with a specific risk variable, controlling for the other two risk variables. This method was included after it was determined that confounding variables were highly correlated. Previous studies of prenatal smoking have reported strong associations between smoking and specific childhood disorders, using a variety of statistical analyses. Logistic regression was used by Milberger et al. (1996) in their study of smoking and ADHD. Others have reported significant effects of prenatal smoking on risk for offspring developing conduct disorder, using log-linear and logistic regression techniques (Brennan et al., 1999; Fergusson et al., 1998; Wakschlag et al., 1997) as well as the confounder score methodology (Rantakallio et al., 1992). Therefore, it appeared useful to analyze the present data set using all three techniques, in order to provide a comparison across studies.

Results

A log-linear regression was performed to test the bivariate relationships between each childhood diagnosis and familial risk and prenatal use of alcohol, cigarettes and drugs. Significant associations between the presence of a K-SADS diagnosis in the offspring and familial risk for alcoholism were found using the log-linear approach. Only one childhood disorder, phobia, was not associated with familial risk. In addition to the important impact of familial risk for alcoholism on the likelihood of developing a childhood disorder, prenatal use of alcohol or cigarettes was also associated with the presence of specific diagnoses in these offspring. Prenatal use of either alcohol or cigarettes was associated with increased risk for conduct disorder ($\chi^2 = 8.80$, 1 df, $p = .003$; $\chi^2 = 5.94$, 1 df , $p = .015$, respectively) and oppositional disorder ($\chi^2 = 6.89$, 1 df, $p = .009$; $\chi^2 = 4.21$, 1 df, $p = .041$, respectively) as well as depression ($\chi^2 = 9.78$, 1 df, $p = .002$; $\chi^2 = 4.42$, 1 df, $p = .036$, respectively). Prenatal use of alcohol was associated with the presence of anxiety disorders ($\chi^2 = 6.51$, 1 df, $p = .011$) and ADHD ($\chi^2 = 8.55$, 1 df, $p = .004$). Familial risk for alcohol dependence ($\chi^2 = 18.49$, 1 df, $p = .001$) and maternal prenatal alcohol use ($\chi^2 = 18.47$, 1 df, $p = .001$) significantly increased the risk of developing a diagnosis (none vs one or more diagnoses). Drug use was not found to be significantly associated with any of the K-SADS diagnoses; only a small number reported using drugs other than alcohol or nicotine during their pregnancies (21 high-risk mothers).

Logistic regression analyses were first performed to evaluate the effects of the three main variables of interest (familial risk, prenatal alcohol use, prenatal cigarette use). Next, two other variables, parental antisocial personality disorder and socioeconomic status, were tested because of reported associations between these variables and the likelihood that offspring will develop externalizing disorders. In addition, analyses using all five variables were performed. No significant effects were detected; however, this analysis was largely uninformative because of the small number of cases within cells. Therefore, a series of logistic regression analyses were conducted using subsets of variables.

The odds of developing specific disorders in association with the specific factors of interest (familial risk, prenatal alcohol use, prenatal cigarette use) may be seen in Table 2. Odds were first calculated using the independent effect of each variable. As may be seen, the risk of developing an externalizing disorder (conduct, ADHD, oppositional) was elevated as a result of familial risk for alcoholism and maternal prenatal alcohol use. Also, prenatal use of cigarettes increased the odds that the offspring would develop conduct

TABLE 2. Odds ratios (OR) of K-SADS diagnoses for the effects of familial risk, alcohol use and cigarette use

	Familial risk			Prenatal alcohol use[a]			Prenatal cigarette use		
Disorder	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Depression	15.21	5.70-40.45	< .0001	4.48	1.45-13.83	.009	3.43	1.06-11.09	.039
Conduct	13.15	4.76-36.57	< .0001	4.42	1.35-14.33	.014	4.66	1.38-15.72	.013
Anxiety	3.62	1.43-9.04	.006	3.27	1.13-9.38	.028	2.06	0.76-5.58	NS
Phobia	2.09	0.78-5.53	NS	2.05	0.67-6.28	NS	1.91	0.61-5.97	NS
ADHD	4.56	1.75-11.95	.002	4.00	1.34-12.04	.014	1.38	0.47-4.09	NS
Oppositional[b]	6.21	2.76-13.79	< .0001	3.01	1.20-7.55	.019	2.44	0.99-6.00	.053
Any diagnosis	4.72	2.42-9.00	.001	5.77	2.68-12.36	.0001	2.14	1.00-4.59	.050

[a]Alcohol use was determined using a median split.
[b]The effect of familial risk adjusting for alcohol and cigarette use was also significant (odds ratio = 4.64; 95% CI: 1.08-19.9; $p = .018$).

disorder. The risk for developing specific internalizing disorders (depression and anxiety) was also elevated in association with familial risk for alcoholism. The mothers' prenatal use of alcohol was associated with increased odds that their offspring would have a childhood/adolescent anxiety disorder (separation anxiety, panic disorder or overanxious disorder). Prenatal cigarette use increased the odds that the offspring would have a depressive disorder (major depression or dysthymia). The mothers' prenatal use of alcohol also increased the risk of their offspring having a depressive disorder.

Next, confounder score analyses were conducted to evaluate the effect of each variable while adjusting for the effects of the other two variables. This analysis demonstrated that only one relationship between a single variable (familial risk, prenatal exposure to alcohol, prenatal exposure to cigarettes) and a childhood disorder remained significant while controlling for the other two variables. Controlling for prenatal use of cigarettes and alcohol, familial risk for developing alcohol dependence increased the risk to offspring for developing oppositional disorder (odds = 4.54; 95% CI: 1.38-14.97; $p = 0.014$). We cannot confirm the association between prenatal cigarette use and conduct disorder previously reported by Brennan et al. (1999), Fergusson et al. (1998) and Wakschlag et al. (1997) or the reported association between cigarette use and ADHD reported by Milberger et al. (1996) when confounding variables (prenatal use of alcohol and familial risk for developing alcoholism) are controlled.

Because of the previously reported association between lower SES and/or parental ASPD and conduct disorder (Brennan et al., 1999; Fergusson et al., 1998; Wakschlag et al., 1997), these variables had been included in the analysis plan. (Due to sample size limitations, these variables could not be addressed within the same analyses that included familial risk and prenatal exposure to alcohol and cigarettes.) The present data set included information concerning SES of both parents along with parental psychiatric diagnoses including presence or absence of ASPD. The associations between each of the externalizing disorders and these two risk factors (SES and parental ASPD) were tested in separate analyses (Table 3). Socioeconomic status was determined using the Four Factor Index of Socioeconomic Status (Hollingshead, 1975). Each child's score was calculated using the average of each parent's SES score. As may be seen in Table 3, SES scores were significantly lower in children with conduct disorder, oppositional disorder or ADHD. In addition, a significantly greater proportion of children of parents with ASPD had oppositional disorder than those whose parents were without ASPD. Because significant associations between the presence of these externalizing disorders and these two variables were found, further analyses were performed. Familial risk for alcoholism and prenatal use of alcohol and cigarettes were analyzed along with ASPD and SES, using logistic regression analysis. The only significant odds ratio that was seen was for ADHD, and this was the result of the familial risk variable when controlling for SES and ASPD (the odds ratio was 5.95; 95% CI: 1.02-30.4; $p = .02$).

Comparison of the results obtained using the three statistical methodologies (log-linear analysis, logistic regression and confounder score approach) suggests that the collinearity of the three main variables of interest (familial risk, prenatal exposure to alcohol, prenatal exposure to cigarettes) is an important consideration in the results obtained. Collinearity makes it difficult to determine which factors are independently associated with the childhood disorders studied. As

TABLE 3. Risk factors associated with childhood externalizing disorders

	Without conduct	With conduct	Test statistic
SES (mean)	42.3	23.4	$t = 9.8$, 4 df, $p < .0001$
Parental ASPD (%)	20.9	35.3	$\chi^2 = 1.8$, 1 df, $p =$ NS
	Without oppositional	**With oppositional**	**Test statistic**
SES (mean)	43.1	29.1	$t = 5.5$, 4 df, $p < .0001$
Parental ASPD (%)	16.5	45.2	$\chi^2 = 11.4$, 1 df, $p = .0007$
	Without ADHD	**With ADHD**	**Test statistic**
SES (mean)	41.9	29.8	$t = 3.8$, 2 df, $p = .001$
Parental ASPD (%)	21.4	30.0	$\chi^2 = 0.7$, 1 df, $p =$ NS

might be expected, prenatal substance use was higher among mothers from the high-risk families. Familial risk and prenatal drinking were found to be significantly collinear (φ = -.312, p = .0001) as were familial risk and prenatal smoking (φ = -.510, $p < .0001$). (The values are negative because risk status for high and low risk was coded as 1 and 2, respectively.) Mothers who smoked during pregnancy were also more likely to drink during pregnancy (φ = .237, p = .0135).

Because of the collinearity found among variables, the multivariate confounder score approach (Miettinen, 1976) was used to estimate the odds of developing a childhood diagnosis in association with familial risk for alcohol dependence and maternal prenatal use of alcohol and cigarettes. Unlike the conventional logistic regression procedure, in which all of the confounding variables are entered into the model, in the multivariate confounder-score method, the confounding factors to be controlled are summarized in terms of a single multivariate score for each subject. The first step in the present confounder score analysis was to enter all of the independent variables into the model in order to predict the logit for the nonexposed individuals (those without familial risk or prenatal exposure to alcohol or cigarettes). A few strata are formed on the basis of this confounder score for the whole sample, providing the comparison for exposed and nonexposed children. The observed odds ratio is then calculated in each stratum, and the adjusted odds ratio and its 95% confidence interval are estimated from the stratum-specific estimates by the method of weighted least squares. This analysis revealed only one significant result: the odds of developing oppositional disorder were increased in association with familial risk for alcohol dependence.

Discussion

This study examined the relationships between familial risk for alcohol dependence and maternal smoking and alcohol use during pregnancy, and psychiatric symptoms in childhood/adolescence. Using a log-linear test of association and a logistic regression analysis, we found strong and significant positive associations (increased odds) between specific externalizing disorders (conduct disorder, oppositional disorder) and maternal smoking. These analyses, in finding increased odds for developing externalizing pathology as a result of prenatal smoking, are in agreement with several reports that indicate a relationship between externalizing psychopathology and prenatal use of nicotine (Brennan et al., 1999; Fergusson et al., 1993, 1998; Milberger et al., 1996; Rantakallio et al., 1992; Wakschlag et al., 1997; Weitzman et al., 1992). In addition, we found a significant association between maternal use of cigarettes and increased risk for developing depression among offspring.

However, a subsequent analysis, using a confounder score approach that adjusts for the collinearity among the major variables of interest (familial risk, prenatal smoking and drinking), did not, for the most part, support these associations. Whether these apparent associations are real or are secondary to other characteristics women who smoke or drink during pregnancy may possess has been suggested by others (Rantakallio et al., 1992; Wakschlag et al., 1997; Weitzman et al., 1992). In the present study, correlational analyses showed that maternal smoking during pregnancy was significantly collinear with drinking during pregnancy. The familial risk variable and prenatal drinking were also collinear. Therefore, the principal concern was that any associations found between smoking and specific diagnoses might be the result of either familial substance dependence or prenatal use of alcohol or both. Logistic regression analyses were performed to assess the independent effects of each major variable alone and when each of the other variables was controlled. These analyses revealed significantly increased odds for developing conduct disorder and oppositional disorder as a result of maternal prenatal cigarette smoking. The odds of developing conduct disorder, oppositional disorder or ADHD were also elevated as a result of maternal prenatal use of alcohol. In addition, the odds of developing these disorders were increased as a result of having a family history of alcohol dependence. However, when each effect was evaluated holding the other two major variables constant in the confounder score analysis, only oppositional disorder proved to be elevated and this was due to the familial risk factor increasing the odds of the offspring developing the disorder.

Several other confounding factors have been included in previous studies relating prenatal maternal smoking and conduct disorder (Brennan et al., 1999; Fergusson et al., 1993, 1998; Milberger et al., 1996; Rantakallio et al., 1992; Wakschlag et al., 1997; Weitzman et al., 1992). Among the risk factors for externalizing disorder that have been investigated are socioeconomic status, parental substance abuse, parental antisocial personality disorder, maternal age, and pregnancy and delivery complications. Most of the studies (Brennan et al., 1999; Fergusson et al., 1998) have found support for a relationship between prenatal smoking and conduct disorder even when selected confounding risk factors have been controlled.

In the present study, two of the known risk factors for conduct disorder, lower socioeconomic status and parental antisocial personality disorder, were evaluated with respect to conduct disorder and other externalizing psychopathology. Results of that analysis revealed a significant effect of SES for all three externalizing disorders evaluated. Parental ASPD was found to be a significant predictor for oppositional disorder. When the potential confounding effects of both ASPD and SES were evaluated, only the relationship between familial risk for alcohol dependence and ADHD in offspring remained significant.

The present set of analyses were undertaken to evaluate the role of prenatal smoking and ethanol use on externalizing psychopathology in children/adolescents who are being fol-

lowed as part of a long-term, longitudinal study of families at high and low risk for alcohol dependence. The strength of the present analyses is that extensive information on the familial/genetic background of the children/adolescents was available as part of the ongoing study. Previous studies (Brennan et al., 1999) have been criticized (Fergusson et al., 1998) for not having adequately controlled for the familial/genetic loading for substance dependence in analyses designed to assess the role of maternal prenatal smoking on conduct disorder in offspring.

Supplementing the more conventional statistical analyses (log-linear associations and logistic regression) with the confounding score approach made it possible to test the effect of the main variables of interest while controlling for the effects of other variables. As a result, the present analysis demonstrates that significant associations between prenatal smoking and externalizing disorders in offspring are most likely not causally related. The observed association is probably secondary to having a familial risk for alcohol dependence that results in family members engaging in a number of behaviors highly correlated with familial risk status. Such behaviors include the greater likelihood that high-risk women with a family history of alcohol dependence will use alcohol, cigarettes and other drugs during pregnancy. Similar conclusions may be drawn with respect to the observation that prenatal use of alcohol was significantly associated with increased risk for externalizing behavior (conduct disorder, oppositional disorder and ADHD) in offspring. When appropriate confounding variables were controlled, no relationship between prenatal use of alcohol and conduct disorder, oppositional disorder or ADHD was found.

Several limitations of this study should be mentioned. The sample of children/adolescents available for analysis was not large enough to simultaneously evaluate more than a few variables in one analysis. Therefore, separate analyses were conducted to address subsets of variables and their influence on child/adolescent psychopathology. Also, although the children were not part of a clinical sample (none had been included because of referred status), their parents and/or multiple relatives had been selected for study because of problems with substance dependence. Therefore, the sample was not a representative one. (Note that sacrifice of representativeness may be necessary for gene finding or conducting searches for biological markers in which more severe phenotypes are most useful.) Also, there is some indication that maternal smoking during pregnancy may have greater effects on boys than on girls (Streissguth, 1986). The mixed-gender sample used in the present analysis might have reduced the power to detect differences.

The data analyses concerning the prenatal period were based on maternal retrospective reports. This, clearly, is a limitation of the analysis; pregnancies and births had occurred 8-17 years earlier. The data could be flawed by recall of behavior occurring years before and might also be flawed as a result of underreporting. However, women in the present study reported retrospectively that they used less alcohol each subsequent trimester. This pattern of change in consumption across trimesters reported by the mothers concerning their drinking during pregnancy parallels that reported by mothers who were assessed during their pregnancy (Fried et al., 1985; Robles and Day, 1990). Comparison of prospective and retrospective data for drinking during pregnancy has shown retrospective data to be valid (Griesler and Kandel, 1998). Moreover, follow-up of women for 4 and 5 years following their pregnancies has shown substantial reliability (r = 0.53 and 0.67, respectively) between reports obtained during pregnancy and those obtained following the pregnancy (Ernhart et al., 1988; Jacobson et al., 1991).

The present self-report data appear to be reasonably valid, and the number of cases studied (N = 150) is comparable to that of studies reporting positive associations between maternal prenatal smoking and conduct disorder (N = 177; Wakschlag et al., 1997) or ADHD (N = 140; Milberger et al., 1996). Nevertheless, our results and those of others who have addressed the effects of prenatal smoking or alcohol use on childhood psychopathology should not be viewed as conclusive. Collinearity of the variables studied limits the generalizability of the results obtained. Availability of large samples, in which some of the variables can be dissociated on a case-by-case basis, would be useful. For example, availability of higher SES women who smoked during pregnancy, and who did not have either a personal or family history of drinking-related problems, would aid in clarifying whether smoking is causally related to the development of externalizing disorders or is simply correlated with a currently unidentified causative factor. Conclusions concerning the effects of prenatal alcohol use on the risk to offspring for childhood disorders may, also, be limited by the failure to incorporate relevant confounding factors. Only the present study and one by Baer et al. (1998) have investigated familial risk and prenatal exposures within the same analysis. Baer et al. (1998) investigated prenatal use of alcohol and adolescent alcohol problems, carefully assessing family history of alcohol problems in conjunction with prenatal use of alcohol. In that study, prenatal use of alcohol appeared to be more important than family history of alcoholism in determining outcome. The present study found significant associations between prenatal alcohol use and a number of childhood disorders. However, these associations did not remain significant when confounding variables (familial risk, SES and ASPD) were controlled. The implications of the present results are that studies designed to evaluate the effects of prenatal exposure to alcohol, cigarettes and other drugs should incorporate evaluations of the familial/genetic risk of the exposed children. As well, studies that focus on familial/genetic precursors of childhood psychopathology should incorporate questions concerning prenatal exposures. It is important to have in place statistical plans that allow for

controlling for the highly collinear nature of the variables under study. Women who are alcoholic, and continue to drink and/or use cigarettes or drugs during pregnancy, often have, as well, substantial familial/genetic risk for alcohol/drug dependence and ASPD. This may be manifest in offspring as an elevated risk for particular childhood disorders (e.g., parental ASPD increases offspring risk for childhood conduct disorder).

In conclusion, the present results suggest the need for further study to carefully address, within the same analysis, familial loading for alcohol and drug dependence as well as cigarette and alcohol exposure. In this way, familial/genetic diatheses may be evaluated along with quantified estimates of prenatal use and may be related to childhood behavioral outcomes. This strategy could best inform us as to which childhood disorders are most related to familial/genetic diatheses and which are most related to prenatal exposure. In addition, this strategy could provide the opportunity for uncovering potentially important Gene × Environment interactions.

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