

A 21-Year Longitudinal Analysis of the Effects of Prenatal Alcohol Exposure on Young Adult Drinking

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Background: Prenatal alcohol exposure may be a risk factor for the development of alcohol problems in humans.

Methods: We use data beginning with interviews of women in prenatal care at midpregnancy to predict alcohol use and alcohol-related problems in their offspring now aged 21 years. Maternal drinking during pregnancy was assessed from November 4, 1974, through October 2, 1975, along with measures of maternal smoking, use of caffeine and other drugs, and demographic factors. Family history of alcohol problems was assessed from interviews with parents when offspring were 14 years of age and updated when offspring were 21 years of age. Measures of parental use of alcohol and other drugs and many aspects of the family environment were assessed at 7 different ages, prenatally through 21 years. Young adult offspring (age, 21 years [N=433]) provided self-reports of drinking quantity and frequency and

completed the Alcohol Dependence Scale as a measure of alcohol-related problems and dependence.

Results: Univariate, partial least squares, and regression analyses indicate that prenatal alcohol exposure is significantly associated with alcohol problems at 21 years of age. The relationship persists independent of the effects of family history of alcohol problems, nicotine exposure, other prenatal exposures, and postnatal environmental factors including parental use of other drugs. Prenatal nicotine exposure was not associated with alcohol problems by offspring at 21 years of age.

Conclusions: Prenatal alcohol exposure is a risk factor for the development of drinking problems in humans. Potential mechanisms for the role of fetal exposure and the development of alcohol problems deserve study.

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CONTEMPORARY accounts of the etiology of alcoholism typically acknowledge a range of determinants, including genetic, biological, psychological, and social factors.^{1,2} Consistently overlooked in these models is the exposure to teratogenic agents during pregnancy.³ However, fetal exposure to alcohol has been associated specifically with attention problems, memory problems, impulsivity, and deficits in executive cognitive functioning,^{4,5} each of which has been implicated as a risk factor for the development of alcohol use disorders.² Fetal exposure to alcohol may also result in specific drug sensitivity and drug preferences, as has been suggested in animal models.⁶⁻¹⁰ Drug sensitivity has also been included in models of risk for alcohol problems in humans.^{11,12}

Recent evidence has begun to link fetal exposures to adolescent and adult substance use problems in humans. Yates et al¹³ examined a sample of adult adoptees

and reviewed historical adoption records for evidence of maternal drinking during pregnancy. Adult adoptees with fetal exposure to alcohol reported more symptoms of alcohol, nicotine, and other drug dependence compared with those not exposed. Unfortunately, in their study, rates of maternal alcohol use were not available, and the authors could not control for maternal use of nicotine and other drugs. Nevertheless, this study of adoptees suggests that fetal alcohol exposure is a likely confound for models of genetic and environmental influences on substance use disorders. In other studies, prenatal nicotine exposure has been associated with later conduct disorders in adolescents^{14,15} and smoking¹⁶ and drug use among female adolescents.¹⁵

In an earlier study of data from the Seattle Longitudinal Study on Alcohol and Pregnancy,³ the relationship between fetal alcohol exposure and early experiences with alcohol among young adolescents was examined. Maternal drinking,

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as reported by mothers when interviewed during pregnancy, predicted rates of alcohol use and alcohol-related problems in adolescent children undergoing assessment 14 years later. Fetal alcohol exposure was associated with alcohol problems in early adolescence, even after controlling for family history of alcoholism, prenatal nicotine exposure, parenting style, current parental drinking, household stress, and self-esteem.

Alcohol use at 14 years of age is only 1 early risk factor for the development of a range of alcohol use disorders experienced at different periods throughout life. For the present study, we examined drinking as an outcome 7 years later, when this sample was 21 years of age. From 14 to 21 years of age, alcohol use changes markedly. Results of US national surveys report that, in contrast to early adolescence, almost all individuals aged 21 years (90%) have tried alcohol, and heavy drinking, defined as consumption of 5 or more drinks in a row, is common.¹⁷ Problems associated with heavy drinking by young adults include accidental death, injuries, academic failure, vandalism, aggression, and family conflict.¹⁸ Individual differences often associated with the risk for alcohol dependence, such as family history of alcohol problems, are less predictive of drinking rates during this developmental period.¹⁹ Social and environmental factors such as college attendance and residence in large-group housing (eg, barracks, dormitories, fraternities) are strongly associated with heavy drinking for young adults and are likely to be time limited.²⁰ Despite apparently situational and developmental factors that increase heavy drinking during young adulthood, personality factors of impulsivity and disinhibition remain the strongest predictors of negative consequences.¹⁹

In the present study, we tested the hypothesis that prenatal alcohol exposure affects alcohol-related problems in young adults. We studied drinking rates and problems at 21 years of age, by which virtually all subjects have been exposed to alcohol, and negative consequences are not uncommon. Included in our statistical models are variables reflecting a range of demographic indicators, potentially teratogenic agents (eg, nicotine and other drugs), family history of alcohol problems, and family environmental factors including measures of parental postnatal use of alcohol and other drugs.

METHODS

OVERVIEW

From November 4, 1974, through October 2, 1975, 1529 consecutive women presenting at one or the other of 2 Seattle, Wash, prenatal clinics by the fifth month of pregnancy underwent screening via personal interview regarding health habits. Most were married (88.5%) and had graduated from high school (87.5%). Approximately 500 of these generally low-risk families have been followed up as part of a longitudinal prospective study of child development.^{21,22} The follow-up cohort of 500 was chosen to include all of the heaviest drinkers identified from the initial screen and to represent a continuum of lower levels of alcohol use, including abstinence, with stratification on cigarette use. Twenty-two years after the initial prenatal interview, 433 families were again reinterviewed (March 1, 1996, through December 21, 1998). For the present study, we used the original data from the mothers' reports of use of alcohol and other drugs during pregnancy,

together with demographic measures and assessments of the postnatal family environment, to predict alcohol-related outcomes assessed in offspring aged 21 years.

MEASURES

Prenatal Alcohol Exposure

Maternal drinking was assessed midpregnancy by means of self-report in a confidential quantity-frequency-variability interview.^{23,24} Thirteen scores were computed, including an overall 5-point priority scale and 6 pairs of variables. Each pair of variables scored a drinking dimension for the time before pregnancy recognition and the time covering midpregnancy. Two pairs of variables reflected average quantity of alcohol consumption (average absolute ounces per day and occasions per month), whereas the other pairs measured aspects of heavy episodic drinking (average number of drinks per occasion, maximum number of drinks on any occasion, ≥ 5 drinks on an occasion, and a 5-point quantity-frequency-variability scale). **Table 1** presents data on levels of drinking for mothers during pregnancy (statistics based on drinkers only). We found that 79.9% of the sample drank alcohol during pregnancy and in the months before they knew they were pregnant, and 30.9% reported heavy episodic drinking (≥ 5 drinks on an occasion) during pregnancy. Offspring of 2 subjects received a diagnosis of fetal alcohol syndrome at birth.^{25,26} Thirty-one of 433 offspring have been identified as having possible or probable fetal alcohol effects or alcohol-related neurodevelopmental disorder on the basis of results of dysmorphology examinations of subsets of the longitudinal sample at birth,²⁵ 4 years,²⁷ and/or 7 years²⁸ or on a statistical analysis of neurobehavioral deficits through 7 years of age.^{21,26}

Other Prenatal Exposures

Prenatal exposure to a variety of additional ingestants was also measured during pregnancy. Variables reflecting the frequency of use of nicotine, aspirin, caffeine, acetaminophen, antibiotics, diazepam (Valium), marijuana, and other illicit drugs were included in the 1974-1975 prenatal interviews with mothers.²¹

Family History of Alcohol Problems

Family history of alcohol problems was assessed from the parent report on first- and second-degree relatives using a family tree questionnaire²⁹ when offspring were 14 years of age. The determination of alcohol problems for each relative was based on a list of 9 questions reflecting alcohol-related social and marital problems, employment, arrests, physical symptoms, and treatment. When offspring underwent assessment at 21 years of age, parents were asked to update the family history assessment from 14 years of age by a simple indication of alcohol abuse among first- and second-degree relatives. Five binary variables were computed, each an indicator of at least 2 symptoms of alcohol problems reported with respect to the mother, father, grandparents, siblings, and aunts and uncles. By this measure, 93 fathers (21.2%) and 46 mothers (11.0%) were identified as having a history of alcohol problems. Combining binary scores across first- and second-degree relatives, 239 families (57.0%) identified at least 1 member with a history of alcohol problems (26 families [6.2%] were identified via the update at 21 years of age, and 8 families [1.9%] were identified solely on the basis of maternal history of alcohol problems).

Other Postnatal Environment Measures

Postnatal environment measures spanned the 21-year study, from measures of neonatal nursing and early mother-child in-

Table 1. Alcohol Scores for 346 Nonabstinent Mothers by Time of Drinking

Alcohol Scores	No. of Mothers*	Mean (SD)	Minimum	Median	Maximum
Average No. of ounces of absolute alcohol per day†					
Prior to pregnancy recognition	320	0.81 (1.76)	0.01	0.45	25.76‡
During pregnancy	340	0.34 (0.63)	0.01	0.16	8.55
≥5 Drinks on any occasion§					
Prior to pregnancy recognition	320	0.38 (0.49)	0	0	1
During pregnancy	340	0.24 (0.43)	0	0	1
Average No. of drinks per occasion					
Prior to pregnancy recognition	320	2.51 (1.51)	1.50	2.14	13.00
During pregnancy	340	2.21 (1.20)	1.50	1.72	13.00
Maximum No. of drinks reported on any occasion					
Prior to pregnancy recognition	320	4.05 (2.69)	1.50	3.50	13.00
During pregnancy	340	3.62 (2.63)	1.50	3.50	13.00
Monthly occasions of drinking					
Prior to pregnancy recognition	320	17.28 (22.95)	0.30	9.0	240.00
During pregnancy	340	8.72 (13.05)	0.30	4.80	120.00
Quantity-frequency-variability index					
Prior to pregnancy recognition	320	3.52 (1.03)	2	3	5
During pregnancy	340	3.05 (0.95)	2	3	5
Ordered exposure code combining timing, dose, pattern¶	346	2.81 (1.22)	1	3	4

SI conversion factor: To convert ounces to milliliters, multiply by 30.

*Number of represents the women with a positive score on the corresponding alcohol score. In all, 320 reported drinking prior to pregnancy recognition; 340, during pregnancy; 346, in at least 1 of the 2 periods; and 314, during both periods. Prior to pregnancy recognition refers to the month or so before pregnancy or pregnancy recognition; during pregnancy, during pregnancy, assessed at the fifth month of pregnancy.

†Average ounces of absolute alcohol per day is a continuous variable with a score of 1.00, meaning an average of 2 drinks per day of wine, beer, liquor, or any combination.

‡The next highest score was 9.14 oz.

§5 Indicates a dichotomous variable combining the volume variability scores of 5, 8, and 11 (by Cahalan et al²⁴).

||Summarizes 3 dimensions of drinking (Cahalan et al²⁴). The order has been reversed for consistency with the other drinking scales, so that 5 corresponds to the heaviest drinking.

¶Indicates an a priori code developed at the outset of this study to describe the presumed risk to the fetus of different drinking patterns, to enroll women in the follow-up study. Four codes the highest presumed (in 1974) risk and identifies episodic drinkers (≥5 drinks on ≥1 occasion) and those averaging ≥2 drinks/day. For further details see Streissguth et al.²¹

teraction to cumulative indicators of household changes for reasons such as illness, separation, and foster care and later or current measures of family environment.³⁰ From the parent or the caregiver interviews, we also assessed measures of the fraction of the subjects' lives spent with alcohol and/or other drug abusers and the drinking behavior (ie, frequency, maximum quantities) of either parent of the subject.

Offspring Drinking Rates and Associated Problems

Offspring at 21 years of age were asked to rate how often they drank alcohol, how often they drank 5 or more drinks at one time, the usual number of drinks consumed, the most they consume at one time, and the number of drinks consumed on a typical weekend evening during the past month. Summary scores quantified 4 dimensions of drinking behavior (hereafter referred to as *drinking rates*) as follows: monthly frequency of drinking (days), monthly frequency of heavy drinking (days per month with ≥5 drinks), total monthly drinking volume (frequency of usual drinking × average usual quantity plus frequency of heavy drinking × average episode quantity), and average drinks per drinking day (total monthly drinks/monthly frequency of drinking).

Young adult alcohol problems were assessed with the Alcohol Dependence Scale (ADS),³¹ a widely used and reliable assessment for the presence and severity of drinking problems and dependence symptoms. In this 25-item scale, subjects reported the frequency of a range of negative consequences from alcohol use (eg, blackouts) and symptoms of alcohol dependence (eg, tolerance).

SUBJECTS

Subjects for the present study include 433 offspring of mothers who were first studied in 1974-1975. The sample consists

of 227 men (52.4%) and 206 women (47.6%) who ranged in age from 20.8 to 23.4 years. The following racial/ethnic identity generally reflects the population in this geographic area at the time of the initial 1974-1975 study: white, 354 (81.8%); African American, 19 (4.4%); Native American, 3 (0.7%); Asian, 13 (3.0%); and mixed, 44 (10.2%).

ANALYTIC PROCEDURES

Data were analyzed using univariate and multivariate procedures. Univariate analyses provide an initial evaluation of relationships based on common cut scores without attention to covariates. Our multivariate analysis evaluates the contribution of individual predictors and the role of a range of covariates. The multivariate procedure addresses the prediction of 2 blocks of dependent measures from several blocks of independent measures. The 2 outcome blocks consisted of (1) measures of 21-year drinking rates and (2) the 25 items from the ADS. The 2 primary predictor blocks included (1) several measures of prenatal alcohol exposure and (2) the indicators of a family history of alcohol problems. We analyzed the relationship of this pair of predictor blocks with the two 21-year outcome blocks while taking account of the following 4 blocks of variables representing likely covariates: (1) a demographic block including 11 items such as race, maternal age and education, socioeconomic status, and parity; (2) a block of 9 other prenatal exposures also assessed during the prenatal interview, including nicotine, marijuana, caffeine, and prescription and non-prescription drugs; (3) a postnatal alcohol and other drug environment block consisting of 19 indicators reflecting the fraction of life spent in the household with alcohol and/or other drug abusers and measures of the drinking rates of parents; and (4) a postnatal environment block consisting of 40 items reflecting factors such as major life changes in the family (deaths,

Table 2. Drinking Rates and ADS Summary Score for 359 Nonabstinent Offspring at Interview at 21 Years of Age

Drinking Rate Score	Mean (SD)	Minimum	Median	Maximum
Drinking, days/month	5.77 (5.26)	0.50	6.00	30.00
Heavy episodic drinking, days/month*	2.34 (3.98)	0	0.50	30.00
Total No. of drinks consumed per month	23.36 (27.99)	0.75	11.75	199.50
Average drinks per drinking occasion	3.79 (2.23)	1.50	3.75	18.00
ADS summary score	4.06 (3.87)	0	3	24

Abbreviation: ADS, Alcohol Dependence Scale.

*Indicates subset of drinking days per month.

Table 3. Effects of Prenatal Alcohol Exposure vs Family History of Alcohol Problems on 21-Year Alcohol Problems and Drinking Rates

	Family History of Alcohol Problems*		
	No (n = 296)	Yes (n = 123)	Overall (n = 419)
Offspring alcohol problems, %†			
Fetal exposure‡			
No (n = 291)	3.1	9.4	4.5
Yes (n = 128)	15.9	11.9	14.1
Overall (n = 419)	6.1	10.6	7.4
Offspring high drinking rates, %§			
Fetal exposure‡			
No (n = 291)	6.6	7.8	6.9
Yes (n = 128)	13.0	10.2	11.7
Overall (n = 419)	8.1	8.9	8.4

*Indicates first-degree relatives, including parents and siblings.

†Indicates Alcohol Dependence Scale score of at least 10.

‡Indicates prenatal exposure to heavy episodic alcohol.

§Indicates at least 64 drinks per month.

separations etc), mental health problems in the family, religiosity, and family characteristics such as cohesiveness, each assessed at varying times by means of interviews with offspring and parents.

We represent all of these blocks of variables by composite scores (linear combinations). Different methods were used to develop composite scores for outcome blocks, predictor blocks, and covariate blocks. Linear combinations for the 2 outcome blocks (21-year drinking rates and ADS) and the 2 primary predictor blocks (prenatal alcohol exposure and family history) were computed using partial least squares (PLS) analyses^{32,33} performed on matrices of cross correlations between pairs of blocks of variables. These analyses result in sets of saliences (weights for the variables of each block) that provide a simple characterization of the cross-block correlation structure and that serve as coefficients for the computation of latent variable (LV) scores as weighted linear combinations of the elements of each block. The measures of prenatal alcohol exposure first underwent nonlinear transformation on the basis of previously published PLS analyses of other outcomes with this sample.³³ Analyses were then performed relating prenatal alcohol exposure to 21-year drinking rates and ADS scores. Corresponding analyses were performed to relate family history to 21-year drinking rates and ADS scores. Bootstrap analyses³⁴ showed that differences in item saliences were not significantly different between men and women, so the data were pooled across sex. Additional bootstrap analyses showed that the saliences defining the LV summary scores for each of the 4 primary blocks (prenatal alcohol exposure, family history, 21-year drinking rates, and 21-year ADS scores) did not differ significantly according to

the block with which it was paired. Therefore, each block was represented by a single average composite score.

A different computational strategy was used to develop composite scores for the following 4 groups of covariates: demographics, other prenatal exposures, the postnatal alcohol and other drug environment, and other postnatal environment measures. As an alternative to the more conventional stepwise selection of nominally significant covariates, we computed composite scores for each of these 4 covariate blocks by means of univariate PLS regressions³⁵ predicting the 21-year drinking rates and ADS LV scores. In each case, the composites were the predictions of 2- or 3-factor (dimension) PLS regressions. We found that this approach provided a more effective computation of the joint effects of a large group of related variables (ie, it explained more of the variance in the outcome LV scores) than did a collection of individual covariates selected by a stepwise procedure.

A sequence of multiple linear regressions was then completed to assess the relative importance of prenatal alcohol exposure and family history in the prediction of 21-year drinking rates and ADS scores, first alone, then in models adjusting sequentially for different covariate blocks. We used standard graphical diagnostic procedures to assess assumptions such as linearity (in the composite scores) and to look for outliers or potentially influential cases.³⁶

RESULTS

DRINKING HABITS OF OFFSPRING

Of the sample of 433 offspring, 359 (82.9%) reported themselves as current drinkers and 74 (17.1%), as life-long or current alcohol abstainers at the 21-year follow-up. **Table 2** provides descriptive statistics for drinking rates among subjects who considered themselves to be drinkers. Subjects reported drinking, on average, 5.77 times per month, with an average of 3.79 drinks per drinking occasion. Consistent with national survey samples, 36.5% reported drinking 5 or more drinks on at least 1 occasion during the past month. Thirty-five (8.1%) of 433 scored at or above 10 on the ADS, indicating at least mild alcohol dependence on the basis of validity studies using diagnostic interviews.³⁷

DESCRIPTIVE CROSS TABULATIONS

We present in **Table 3** cross tabulations providing a first simple view of the relationships of maternal alcohol consumption and family history of alcohol problems with 21-year alcohol dependency and drinking rates. Approximately 8% of our sample indicated at least mild alcohol dependence symptoms. For descriptive purposes, we simi-

larly identified the 8% scoring highest on total number of drinks per month (a cut point of ≥ 64 drinks per month). To represent fetal exposure, we considered a binary indicator of any episodic drinking (≥ 5 drinks on an occasion) before or during pregnancy. We represented family history of alcohol problems using a binary indicator of any history of problems reported by first-degree relatives (parents, and/or siblings). Logistic regression analyses showed significant main effects of maternal episodic drinking on the 21-year ADS score (14.1% vs 4.5%; $t=2.65$; $P\approx .008$), no significant main effect of family history ($t=1.08$), and nominally a suggestion ($t=1.97$; $P\approx .051$) of an interaction effect. Those with the highest rate of alcohol dependence symptoms (15.9%) were subjects with episodic prenatal alcohol exposure and without first-degree family history of alcohol problems. We found no nominally significant effects in the logistic regression analysis for prediction of 21-year drinking rates. These descriptive analyses were, of course, greatly limited by the a priori binary categorization of prenatal exposure, family history, and outcome scores, and they did not evaluate or control for many possible covariates.

PLS ANALYSES AND COMPOSITE SCORES

The PLS analyses provide a measure of overall association between blocks of variables and provide indices (salience) of the contributions of individual variables for the composite associations. For overall associations, the composite prenatal alcohol exposure LV score had a correlation of 0.28 with the 21-year-old ADS LV score, and 0.18 with the drinking rate LV score. The composite family history LV score had a correlation of 0.22 with the ADS LV score and 0.11 with the drinking rate LV score. Thus, consistent with univariate analyses, prenatal alcohol exposure was related to drinking problems among offspring aged 21 years and less related to drinking rates. Correlations were larger for prenatal exposure than they were for family history of alcoholism.

Salience for the individual prenatal alcohol exposure scores, computed with respect to the ADS items, were evenly weighted across the binge-volume measures and across both time periods reflected in the questions (range, 0.23-0.34). Thus, no specific measure of maternal drinking during pregnancy was specifically identified. The family history of alcohol problems LV score resulting from the PLS analyses with respect to ADS scores weighted maternal and paternal alcohol problems most highly and equally (0.60), with lesser weights for the following other indicators: grandparents (0.33), siblings (0.31), and aunts and uncles (0.29). Because of the relatively weak association of 21-year drinking rate with family history, we used only the drinking rate saliences with respect to prenatal alcohol exposure. The PLS analysis of the drinking rate variables showed drinks per month (0.55) and average drinks per drinking day (0.56) to be slightly more salient than the 2 frequency indicators (0.44).

Table 4 provides endorsement rates and saliences for ADS items as defined in relation to prenatal alcohol exposure, family history of alcohol problems, and their averages. Salience computed for these 2 different predictor blocks were not significantly different according to a boot-

strap analysis. Hence, the average salience was used for the computation of a single composite ADS LV score. Table 4 labels (with a dagger) those average saliences 0.24 and above, as this captures all items of reasonably consistently high salience with respect to both predictor blocks.

Items reflecting negative consequences of specific episodes of heavy drinking (eg, hangovers, blackouts, unclear thinking, passing out, stumbling/staggering, and being physically sick) provided the strongest contribution to correlational relationships. A number of ADS items were endorsed only rarely, and these items tended to contribute little to the composite scores. Nevertheless, the endorsement rate did not completely correspond to salience in these analyses. At least 1 relatively rare item was highly salient (ie, hangovers), and some frequently endorsed items were not salient in these analyses (ie, gulping drinks and feeling hot or sweaty).

REGRESSION ANALYSES

Table 5 presents results of 4 separate regression analyses predicting the ADS LV score at 21 years of age from prenatal alcohol exposure, family history of alcohol problems, and other covariates. Each regression model adds evaluation of covariate blocks of variables. We first evaluated demographics and other prenatal exposures (model 2), next added postnatal alcohol and other drug use in the offspring environment (model 3), and finally added all other postnatal environmental factors (model 4). We provided t statistics only as an indicator of the relative strengths of terms in a model; conventional rules for determining statistical significance (eg, $t>2$ indicates significance at approximately a .05-level) should not be strictly applied, as they do not account for the fact that these predictors were explicitly constructed as composite scores predictive of the ADS LV score.

As can be seen in Table 5, a substantial prenatal exposure term in the simple model ($t=4.97$) was clearly attenuated but remained in the complete model ($t=2.38$). Partial correlations for the prenatal alcohol exposure LV score in these models were 0.23, 0.18, 0.14, and 0.13, respectively (data not shown). Family history of alcohol problems clearly contributed less in the predictive equation than did prenatal alcohol exposure, and its correlation with the postnatal environmental factor lowered its estimated effect essentially to 0 in the multiple regression models. Men had significantly higher ADS scores compared with women in all models. In contrast to univariate cross tabulations, regression analysis showed no evidence of interaction between prenatal alcohol exposure and family history ($t=0.08$ for a multiplicative interaction term added to model 4), and no interaction effects involving sex and prenatal alcohol exposure or family history ($t=-0.14$, $t=1.38$ for interaction terms added to model 4). We found no convincing evidence of other demographic effects or other prenatal exposures in the final model. In particular, we found no evidence of any effect of prenatal nicotine exposure on the ADS LV score marginally (simple correlation, -0.08) or in a multiple regression model. Models 3 and 4 showed that the postnatal environment was an important predictor of the ADS scores (with the highest t statistics), but did not fully account for the effect of prenatal alcohol exposure.

Table 4. Endorsement Rates and Saliences Defining the ADS LV Score With Respect to Prenatal Alcohol Exposure, Family History of Alcohol Problems, and Their Average

ADS Item	Endorsement Rate	Salience*			
		With Regard to Prenatal Alcohol Exposure	With Regard to Family History of Alcohol Problems*	Average	
ADS01	Amount drunk last time†	0.20	0.27	0.27	0.27
ADS02	Hangovers on Sunday-Monday†	0.06	0.23	0.33	0.28
ADS03	Shakes, when sobering up	0.08	0.19	0.06	0.13
ADS04	Physically sick†	0.26	0.31	0.17	0.24
ADS05	Delirium tremens	0.03	-0.07	0.06	-0.01
ADS06	Stumble about and stagger†	0.33	0.26	0.26	0.26
ADS07	Felt overly hot/sweaty	0.21	0.03	0.12	0.08
ADS08	Saw things not there	0.03	0.02	0.27	0.15
ADS09	Fear of not having drink	0	0	0	0
ADS10	Blackout, loss of memory†	0.20	0.32	0.25	0.29
ADS11	Carry a bottle	0.02	-0.18	-0.01	-0.10
ADS12	Heavy drinking postabstinence	0.15	0.12	0.13	0.13
ADS13	Passed out†	0.22	0.36	0.21	0.29
ADS14	Convulsions	0.01	0.07	0.06	0.07
ADS15	Drink throughout the day	0.02	-0.06	-0.04	-0.05
ADS16	Thinking has been unclear†	0.44	0.38	0.22	0.30
ADS17	Heart beating rapidly	0.09	0.22	0.13	0.18
ADS18	Constantly thinking about alcohol	0.01	0.01	0.11	0.06
ADS19	Heard things not there	0.02	-0.01	0.34	0.17
ADS20	Weird sensation	0.08	0.15	0.28	0.22
ADS21	Crawling things not there	0.02	-0.04	-0.11	-0.08
ADS22	Frequency of blackouts†	0.23	0.34	0.27	0.31
ADS23	Tried to cut down, failed	0.04	0.08	0.26	0.17
ADS24	Gulp drinks	0.21	0.20	0.19	0.20
ADS25	Ability to stop drinking once started	0.02	0.03	0.22	0.13

Abbreviations: ADS, Alcoholic Dependence Scale; LV, latent variable.

*Saliences in columns 2 and 3 (with regard to prenatal alcohol exposure and family history of alcohol problems, respectively) are proportional to the correlations of the ADS item scores with the prenatal alcohol exposure LV score (computed using the saliencs in Table 1) and to the correlations of the ADS item scores with respect to the family history LV score (computed using the saliencs reported in the text).

†Average saliencs were 0.24 or greater.

Table 5. Results of 4 Regression Analyses of the ADS LV on Prenatal Alcohol Exposure LV, Family History LV, and Covariate LVs*

	Model 1 $R^2 = 0.126$ (N = 433)		Model 2 $R^2 = 0.144$ (N = 433)		Model 3 $R^2 = 0.200$ (n = 362)		Model 4 $R^2 = 0.262$ (n = 362)	
	Coefficient	t	Coefficient	t	Coefficient	t	Coefficient	t
Prenatal alcohol exposure	0.15	4.97	0.12	3.82	0.09	2.63	0.08	2.38
Family history	0.22	3.16	0.18	2.61	0.05	0.63	-0.01	-0.12
Sex	-0.32	-3.72	-0.32	-3.72	-0.35	-4.05	-0.33	-4.01
Demographics	0.92	1.28	0.81	1.05	0.75	1.01
Other prenatal exposures	1.09	2.66	0.46	1.06	0.32	0.78
Postnatal alcohol and other drug environment	1.28	4.21	1.14	3.89
Postnatal environment	1.46	5.43

Abbreviations: ADS, Alcoholic Dependence Scale; LV, latent variable.

*The t statistics are provided only as an indicator of the relative strengths of terms in a model; conventional rules for determining statistical significance (eg, $t > 2$ indicating significance at approximately a .05 level) should not be applied because of the construction of the predictors as composite scores. Models 1 and 2 are completed on the full sample (N = 433). Because of missing values on measures of postnatal environment, models 3 and 4 are evaluated for 362 subjects.

Religious activity (206 of 378 homes had positive scores, and 55 had missing scores) was the most important component of the postnatal environment composite and had the single highest simple correlation with the ADS LV score at $r = -0.12$.

Similar regression models (not displayed) were completed for the prediction of 21-year drinking rates. In these models, drinking rates were not significantly associated

with prenatal alcohol exposure or family history after adjustment for demographics, other exposures, and the postnatal environment.

COMMENT

Prenatal alcohol exposure is significantly associated with alcohol-related problems assessed in offspring at 21 years

of age. This relationship remains when we account for sex, other demographic factors, family history of alcohol problems, prenatal exposure to nicotine and other drugs, and other aspects of the family environment. With the results from recent studies of adoptees,¹³ this study suggests that prenatal exposure to alcohol should be considered within the matrix of etiologic factors for alcohol use disorders. This conclusion also suggests that fetal exposure to alcohol represents an uncontrolled confound for studies of the heritability of alcoholism.

Our analyses provide additional information about what aspects of young adult drinking might be most related to fetal alcohol exposure. Drinking rates at 21 years of age do not appear to be significantly related to maternal drinking during pregnancy after adjustment for demographics and other prenatal exposures. Consistent with extant etiologic data,^{19,20} rates of drinking in an episodic and heavy manner may be socially mediated and not related to individual-level differences in risk for alcohol-related disorders. The negative consequences associated with heavy drinking, however, are related to prenatal alcohol exposure. When examined with a simple dichotomization of the conventional ADS summary score (≥ 10), maternal heavy episodic drinking during pregnancy, in contrast to all lower (nonepisodic) drinking exposure, approximately triples the odds that an offspring aged 21 years will indicate at least mild alcohol dependence (4.5% vs 14.1%). This relationship is attenuated, but nevertheless remains statistically significant, when the ADS LV scores are evaluated in regression analyses adjusting for a host of other predictive factors, including the substance use of mothers postnatally. The ADS items endorsed at 21 years of age that are most related to prenatal exposure generally reflect negative consequences from episodes of heavy drinking (eg, passing out, blackouts, and being physically sick) rather than symptoms reflecting compulsive patterns of use (eg, carrying a bottle, drinking throughout the day, and inability to stop drinking once started).

With respect to the association with drinking problems in offspring aged 21 years, our measures of maternal prenatal drinking were relatively evenly weighted in PLS analyses, suggesting that no single indicator (eg, average number of drinks per day) accounts for the observed relationship. Descriptively, however, we can characterize, in part, the maternal drinking levels of the top 20% of the prenatal alcohol exposure LV scores by their median prenatal alcohol scores. This top 20% did not report consumption typically associated with alcohol-related problems or alcoholism, but rather reported a pattern that could be described as frequent and moderate, ie, nearly 3.5 drinks per drinking occasion and almost 17 occasions per month prior to pregnancy recognition, and almost 3 drinks per drinking occasion and 9 occasions per month during the first half of pregnancy (approximately 2 drinking days per week). Before and during pregnancy, the median for the maximum drinks consumed on an occasion was 6.

The results reported here both complement and contradict findings from recent studies of prenatal exposures and adolescent psychopathology. We observed no effect of nicotine exposure on 21-year drinking outcomes, a result inconsistent with recent studies report-

ing relationships between fetal nicotine exposure and adolescent smoking and conduct problems.^{14,15,38} We also observed no effects for women only,³⁸ and did not find that family history accounts for the effects of fetal alcohol exposure.³⁹ Our outcome, drinking problems at 21 years of age, may not be strongly related to other psychopathology assessed in younger adolescents in other studies. Predictive relationships between prenatal exposure to alcohol and drinking practices may emerge only after offspring are old enough so that much of the sample has experience with alcohol. However, the method of assessment of prenatal exposures may affect results. To our knowledge, no study of the effects of prenatal nicotine exposure or adolescent psychopathology has assessed the frequency and quantity of maternal drinking during pregnancy. Course dichotomies of maternal drinking limit the power to observe statistical associations. Given that smoking and episodic drinking are highly comorbid, it is conceivable that relationships thought to be associated with prenatal smoking may reflect prenatal alcohol exposure instead, or in combination.

Interpretations about the relative predictive power of several constructs require comparable measurement accuracy. For example, our assessment of prenatal alcohol use may be more reliable than our assessment of family history of alcoholism, which limits longitudinal prediction. Thus, strong conclusions about the relative predictive relationships of these many factors should be cautioned owing to unknown reliability of the assessment of different constructs. In fact, we raise this same concern about the assessment by previous studies of prenatal nicotine and alcohol use.

The results reported herein should be interpreted relative to other strengths and limitations inherent in our method. Its primary methodological strength is the assessment of maternal drinking during pregnancy, more than 21 years before offspring underwent assessment as young adults. This design minimizes problems with retrospective assessment and allows analysis of specific aspects of maternal drinking. Although unwillingness to acknowledge alcohol use during pregnancy may now be a barrier to accurate self-report, the era in which this study began was before general knowledge about the dangers associated with drinking during pregnancy. In fact, this habit was endorsed at midpregnancy by 80% of these primarily middle-class, married, well-educated mothers. In a longitudinal study of 500 consecutive births of children who were for the most part raised in the homes of their genetic parents, we cannot completely separate the effects of genetic, prenatal, and postnatal environments. Our regression analyses, however, show that drinking rates during pregnancy, assessed during pregnancy, retain association with 21-year outcomes, even after controlling for maternal drinking historically and in the years after the offspring were born. Drinking rates and consequences at 21 years of age are based on self-report measures, which could result in inaccurate or socially desirable reporting. Fortunately, self-report measures have been demonstrated as quite reliable and valid where no penalties exist for specific responses.⁴⁰ Finally, our outcomes are limited to rates of alcohol use and associated problems. Measures of other substance use, psychiatric

comorbidity, and adjustment in young adulthood may or may not reflect the patterns of association noted with respect to alcohol use.

Mechanisms accounting for a relationship between prenatal alcohol exposure and later problems with alcohol use deserve study. Prenatal exposure to alcohol at varying levels and at different periods during gestation is known to affect a variety of physical and functional developmental processes, many of which could place an individual at risk for alcohol use disorders. Our data do not suggest that those in this cohort identified as having fetal alcohol effects or alcohol-related neurodevelopmental disorder contributed to the relationships observed. Only 1 of the 24 cases clearly identified as fetal alcohol effects from the results of dysmorphology examinations or facial photographs^{25,27,28} and only 1 of 11 cases identified as a longitudinal pattern of neuropsychological deficits up to 7 years of age consistent with a diagnosis of alcohol-related neurodevelopmental disorder²¹ were among the cases with an ADS score at or above 10 at 21 years of age. Prenatal effects on executive cognitive functioning and temperament could account for observed differences in the management of drinking and drinking-related activities.⁵ Individuals with impaired problem-solving skills or attention deficits⁴¹ or who tend to respond impulsively may make especially risky choices before, during, or after drinking heavily. Prenatal alcohol exposure could also affect adult drinking problems via changes in alcohol preference and sensitivity to alcohol effects. For example, in studies of rats, exposure to ethanol in utero has been found to increase infantile and adult preference for alcohol.^{6,8,9} Such changes could be due to processes involving catecholamines and stimulant effects of ethanol,⁷ enhanced adult pituitary-adrenal and analgesic responsiveness to stress and drugs,^{42,43} or early associative learning with respect to gustatory cues.^{10,44}

The analyses reported herein provide evidence of the relationship, across more than 21 years, between prenatal alcohol exposure and the degree of negative consequences that result from heavy drinking in young adulthood. Most individuals who drink heavily at 21 years of age do not go on to develop alcohol misuse disorders later in adulthood.^{17,45,46} However, those with persistent alcohol problems in midlife typically began drinking in adolescence and young adulthood. Thus, a central challenge for effective prevention with young people is to differentiate those with time-limited problems from those at risk for more persistent problems.^{47,48} Studies of the type reported herein are needed with samples at older ages. Future follow-up with this sample will assess the association of prenatal alcohol exposure with greater chronicity or severity of drinking problems over time.

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