

Causal Inferences Regarding Prenatal Alcohol Exposure and Childhood Externalizing Problems

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Context: Existing research on the neurobehavioral consequences of prenatal alcohol exposure (PAE) has not adequately accounted for genetic and environmental confounds.

Objective: To examine the association between PAE and offspring externalizing problems in a large representative sample of families in the United States using measured covariates and a quasi-experimental design to account for unmeasured genetic and environmental confounds.

Design: This study combines information from the National Longitudinal Survey of Youth and the Children of the National Longitudinal Survey of Youth. The analyses statistically controlled for measured characteristics of the mothers and families and exposure to other prenatal psychoactive substances. In the primary analyses, siblings differentially exposed to prenatal alcohol were compared.

Setting and Participants: Women were recruited from the community using a stratified and clustered probability sample and were followed longitudinally. The sample included 8621 offspring of 4912 mothers.

Main Outcome Measures: Maternal report of conduct problems (CPs) and attention/impulsivity problems (AIPs) during childhood (ages 4-11 years) using standardized assessments related to psychiatric diagnoses.

Results: There was an association between PAE and offspring CPs that was independent of confounded genetic and fixed environmental effects and the measured covariates. The CPs in children of mothers who drank daily during pregnancy were 0.35 SD greater than those in children whose mothers never drank during pregnancy. Although AIPs were associated with PAE when comparing unrelated offspring, children whose mothers drank more frequently during pregnancy did not have more AIPs than siblings who were less exposed to alcohol in utero. Additional subsample analyses suggested that maternal polysubstance use during pregnancy may account for the associations between PAE and AIPs.

Conclusion: These results are consistent with PAE exerting an environmentally mediated causal effect on childhood CPs, but the relation between PAE and AIPs is more likely to be caused by other factors correlated with maternal drinking during pregnancy.

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PRENATAL ALCOHOL EXPOSURE (PAE) has been associated with offspring externalizing problems, such as conduct problems (CPs),¹ criminality,² attention/impulsivity problems (AIPs),^{3,4} and alcohol disorders.⁵⁻⁸ A recent review of the literature⁹ and a meta-analysis,¹⁰ however, have raised questions about the strength of some of the associations. Given the current state of research on prenatal drug exposure, Huizink and Mulder¹¹ recently highlighted important challenges for the research community. In particular, they noted the need to document deleterious outcomes associated with moderate levels of alcohol exposure, explore the adjustment of off-

spring across time, and delineate the effects of exposure to multiple drugs. Research also needs to adequately control for covariates that may confound the effects of PAE, such as family processes (eg, problematic parenting or family conflict) and parental characteristics, especially maternal substance use.^{11,12} Researchers also need to account for genetic liabilities that are shared by parents and offspring.^{13,14} A woman's genetic risk of substance use could be passed down to her children and subsequently affect their behavior.¹⁵ Research on the consequences of PAE, therefore, needs studies with large samples, with sufficient statistical power to detect small effects, using analytical methods and designs that can account for potential con-

finds, including factors that are not measured. Such studies could complement smaller, more intensive studies^{6,7,13} and provide the opportunity to find convergent evidence from multiple research approaches.¹⁶

Because of the myriad of variables associated with prenatal substance exposure, quasi-experimental designs are useful because they can test alternative causal inferences.¹⁶ Quasi-experimental designs rely on natural experiments that can pull apart processes that are typically confounded. Genetically informed approaches, one class of quasi-experimental designs, are important because they can separate the co-occurring genetic and environmental processes. The use of quasi-experimental designs, therefore, can help the study of putative environments, such as PAE, move from merely identifying risk factors to highlighting the underlying causal mechanisms of externalizing problems.¹⁷

Recently, a variety of quasi-experimental and genetically informed studies related to prenatal substance exposure have been reported. Two studies used the children-of-twins design¹⁸⁻²⁰ to explore smoking during pregnancy (SDP), finding an independent association between SDP and birth weight²¹ and attention-deficit/hyperactivity disorder (ADHD)¹⁴ when shared genetic and environmental liability were taken into account. Sibling comparison studies have also been used to study SDP. The approach contrasts children exposed to more prenatal nicotine to their siblings exposed to less, a design that controls for characteristics of the mothers, including genetic risk associated with SDP. The results suggest that independent associations between SDP and psychosocial adjustment are either greatly reduced or absent.^{22,23} Only 1 quasi-experimental study, however, has been conducted on the consequences of PAE. Knopik et al¹⁴ found that PAE was not independently associated with offspring ADHD in a children-of-twins study.

Given the somewhat contradictory findings of the association between PAE and offspring attention problems⁹ and the results of the 1 genetically informed study,¹⁴ a quasi-experimental study of the consequences of PAE on offspring externalizing problems is of critical importance. Inferences about PAE affect public health campaigns and prevention efforts²⁴ in addition to informing theories about the etiology of CPs.¹⁷ The need for more rigorous studies of PAE is further supported by recent prevalence estimates that indicate that alcohol use during pregnancy is still relatively common.²⁵

The overall aim of the present article is to explore whether PAE is related to offspring externalizing behaviors and, if so, whether the exposure is consistent with a causal association. The present study has 6 goals. First, these analyses explore the relation between PAE and characteristics of the mothers and families. Second, the study documents the statistical relation between PAE and child externalizing problems. Third, the analyses explore whether measured covariates account for associations with PAE. Fourth, the analyses compare siblings and cousins differentially exposed to prenatal alcohol to account for unmeasured confounds, including genetic and environmental factors. If PAE causes externalizing problems, the association will be found at all levels, especially within mothers (ie, siblings exposed to higher levels of prena-

tal alcohol would have more problems than their siblings exposed to lower levels).²⁶ The comparison of siblings explicitly controls for maternal genetic confounds because PAE is not correlated with genetic risk within mothers. Fifth, the analyses investigate whether the relation was robust to the quasi-experimental approach and statistical controls. Finally, an analysis of a subsample of the children that includes measures of prenatal exposure to marijuana and cocaine further explores maternal polysubstance use. Ultimately, an environmentally mediated causal effect of PAE on childhood externalizing behaviors—a causal inference—would be supported if the relation remained robust to the measured covariates and quasi-experimental methods because these approaches account for many of the alternative explanations for the association between PAE and externalizing problems. This research was approved by the institutional review board at Indiana University.

METHODS

SAMPLE

Mother Generation Sample

The National Longitudinal Survey of Youth (NLSY79) is a longitudinal study of adolescents and young adults funded by the Bureau of Labor Statistics. The initial NLSY79 sample included a nationally representative sample of 6111 youths and an oversample of 3652 African American and Hispanic youth. The initial sample of youth used a stratified and clustered probability sample, which included all siblings in each household in the age range. The present study was conducted using 4912 females from the combined sample who had a child who was at least 4 years old by the 2004 survey. The initial NLSY79 assessment had a response rate of 90%. Participants were assessed annually between 1979 and 1994 and biennially since then. Retention rates were 90% or better during the first 16 waves of data collection. Probability weights for the sample are available for the sample of mothers, so the analyses could be weighted to produce population-based estimates. More details concerning the NLSY79 are available elsewhere.²⁷ The characteristics of the females with children are given in **Table 1**. The sample was racially diverse; based on mothers' self-reports, 17.1% were Hispanic, 25.9% were African American, and 57.1% were non-Hispanic white.

Offspring Generation Sample

Starting in 1986, biennial assessments of the offspring of the women in the NLSY79 sample were performed, referred to as the Children of the National Longitudinal Survey of Youth (CNLSY) sample.²⁸ The initial response rate was 95%, with subsequent assessments averaging 90%. Although 3 types of interviews are available on the offspring, the present project uses maternal report of the children's characteristics assessed between ages 4 and 11 years (n=8621 children with reports of PAE). Studies using the offspring of the NLSY79 mothers have been plagued by selection bias because until all childbearing of the mothers is complete, offspring available for assessment were necessarily born to the younger mothers. Given that the overwhelming majority of the childbearing was completed by the 2004 survey and we use assessments of young children, the selection bias for the present analyses is relatively small (B.M.D., J. A. Goodnight, MA, C.A.V.H., I.D.W., J.L.R., P.J.R., and B.B.L., unpublished data, August 2007).

Table 1. Sample Characteristics of Mothers From the National Longitudinal Survey of Youth

Maternal Variable	Mothers, No.	Mean (SD)	Range
Intellectual ability, %	4659	37.40 (27.25)	1.00 to 99.00
Education, y	4911	12.95 (2.41)	0.00 to 20.00
Yearly net income (at age 30 y), \$	3947	34 127 (78 200)	14 to 977 585
Delinquency (reported in 1980) ^a	4631	0.00 (1.48)	-1.50 to 9.00
Age at first birth, y	4765	23.30 (5.39)	11.67 to 43.44
Alcohol frequency, d/mo	3737	2.71 (5.16)	0.00 to 31.00
Alcohol quantity, drinks/d	3737	1.13 (1.50)	0.00 to 6.00
Binging (ever in the past month)	3740	0.16 (0.37)	0.00 to 1.00
Alcohol abuse/dependence items	3741	0.17 (0.41)	0.00 to 2.00

^aThe number of delinquent activities during the previous year residualized after regression on mother's age when she completed the Self-Reported Delinquency Interview.

Table 2. Prenatal Alcohol Exposure in Offspring From the National Longitudinal Survey of Youth

Alcohol Response	Calculated d/wk	Offspring, No. (%)	
		Entire Sample	Sibling Comparison Sample
Never	0.00	5958 (63.7)	1497 (43.4)
<1/mo	0.12	1287 (13.8)	862 (25.0)
1/mo	0.23	625 (6.7)	492 (14.3)
3-4 d/mo	0.82	353 (3.8)	276 (8.0)
1-2 d/wk	1.50	301 (3.2)	233 (6.8)
3-4 d/wk	3.50	59 (0.6)	54 (1.6)
Nearly every day	5.50	17 (0.2)	12 (0.4)
Every day	5.50	21 (0.2)	21 (0.6)
Missing ^a	NA	728 (7.8)	0

Abbreviation: NA, not applicable.

^aMissing values were almost exclusively due to an incorrect skip in the interview. Because sensitivity analyses revealed that the missing data did not affect the results of the hierarchical linear models, the subsequent models did not include offspring with missing values for prenatal alcohol exposure.

MEASURES

Prenatal Exposure to Psychoactive Substances

Beginning in 1983, the NLSY79 females reported their prenatal substance use, including alcohol consumption and cigarette use, during each of their pregnancies. Most of the assessments of prenatal substance use reports were completed when the children were young, mostly within 2 years of birth.²² **Table 2** includes the response categories for alcohol and conversions to days per week for the sample of offspring with information on externalizing problems. A previous article²² analyzed the consequences of SDP. Owing to the small number of pregnancies during which the mothers reported drinking every day, the last 2 categories were collapsed. There are missing data for the prenatal substance use section. Most of the missing PAE data (92%) were due to an incorrect skip in the assessment protocol. Sensitivity analyses (replacing the missing values with zeros, the mean PAE for the mothers, or estimates

based on multiple imputation) revealed that the missing values for PAE did not alter the results presented herein, which are based only on offspring with reports of PAE.

The maternal assessment started to measure marijuana and cocaine use during pregnancy in the 1986 assessment. Therefore, the variables were available only for 3977 offspring with data on externalizing behaviors. Because of the low prevalence, exposure was coded as exposed or not for each drug. In the subsample, 1.6% of children were exposed to prenatal marijuana and 0.6% to cocaine.

Maternal and Familial Characteristics

Available characteristics of the mothers and families that could confound the effects of PAE were included in the analyses. Table 1 provides the distribution of the items. When the eventual mothers of the CNLSY sample were aged 15 to 22 years they were asked about their participation in 12 delinquent behaviors using the Self-Reported Delinquency Interview,²⁹ a reliable and valid measure used in contemporary delinquency research.³⁰⁻³² Symptom counts were regressed on the mother's age at which she completed the survey and were converted to a z score for ease of interpretability. Maternal age at the birth of her first child was also obtained, a variable that predicts offspring delinquency in the CNLSY (B.M.D., J. A. Goodnight, MA, C.A.V.H., I.D.W., J.L.R., P.J.R., and B.B.L., unpublished data, August 2007).³³ Net family income was reported for mothers at age 30 years in 1986 inflation-adjusted dollars, a measure that includes income from all adults in the household at that time. Total number of years of schooling was also assessed for each mother. A composite score of the Armed Services Vocational Aptitude Battery was used as a measure of the mother's intellectual ability, which was converted to a z score. The 1994 assessment included an extensive assessment of the mother's alcohol use and alcohol problems (during her lifetime and not limited to her pregnancies). These questions assessed alcohol frequency (days per month), quantity (drinks per day), and the number of binge episodes in the past month, and 25 items assessed lifetime symptoms of alcohol abuse and dependence. A total of 32% of the women also reported having children by more than 1 man.

Offspring Childhood Externalizing Problems

Mothers rated their 4- to 11-year-old children on the Behavior Problem Index at each wave of assessment. The Behavior Problem Index included 13 items from the Child Behavior Checklist³⁴ that had the strongest associations with Child Behavior Checklist factor scores.³⁵ Mothers rated each child using a 3-point scale. Standard diagnostic approaches³⁶ and previous factor analyses²² revealed that the items load on 3 factors: CPs, oppositional problems, and AIPs. The association between PAE and CPs and AIPs is explored herein. Trajectory analyses on the CNLSY sample³⁶ indicated that the average number of CPs during ages 4 to 11 years was stable and represents a good measure of severity of externalizing problems reported by adolescents. Therefore, mean CP scores across ages 4 to 11 years were calculated by taking the mean of z scores for CPs at each assessed year of age, standardized within each age. The CPs at each age were highly correlated with the mean across ages 4 to 11 years ($r=0.74-0.80$). The items assessing CPs used in the CNLSY also overlap substantially with those used in previous population-based longitudinal studies.^{32,37} The mean of z scores for AIPs was also stable and exhibited good external validity. The AIP scores at each age were highly correlated with the mean score across ages 4 to 11 years ($r>0.80$ for each). Mean AIPs were also strongly related to standardized assessments of aca-

ademic achievement performed at age 10 years, even controlling for CPs ($\beta_{\text{math}} = -.17, P < .001$; $\beta_{\text{reading}} = -.17, P < .001$; and $\beta_{\text{word recognition}} = -.19, P < .001$). Moreover, the AIP items are similar to those used in several studies that yielded results similar to studies that used full measures of ADHD consistent with the DSM-III-R.³⁸

STATISTICAL ANALYSES

Correlations were calculated among the maternal covariates to estimate the associations among PAE and maternal and familial characteristics to explore what factors predicted or were associated with PAE. All of the analyses in the present article were weighted to produce estimates from a representative sample of women in the United States.

Hierarchical linear models (HLMs) were used to explore and characterize the associations between PAE and offspring externalizing behaviors because of the nested nature of the data.³⁹ When the NLSY79 and CNLSY samples are combined, there are 3 levels of analysis: the offspring, maternal, and NLSY79 household levels.²² Five primary HLMs were fit to the associations between PAE and each measure of offspring externalizing problems.

Model 1 calculated the unadjusted relation between alcohol exposure, measured in mean number of days exposed per week, and each dimension of externalizing behavior, controlling for offspring sex. The analyses included 8621 offspring of 4912 mothers. Although previous analyses suggested that offspring sex,^{6,40} maternal SDP,⁴¹ and family race/ethnicity⁴² may moderate the associations, the factors did not affect the magnitude of the relations between PAE and CPs or AIPs in the present sample. The analyses also revealed that linear models provided the best fit for CPs and AIPs because the parameters associated with a quadratic effect were small and statistically nonsignificant.

Model 2 was fit to the relation between PAE and offspring externalizing behaviors controlling for measured covariates that could confound the association (listed in the "Measures" subsection of the "Methods" section).

Model 3 compared siblings differentially exposed to prenatal alcohol (ie, the mother drank alcohol during one pregnancy and not another or drank more during one pregnancy than another). The within-mother association (ie, comparisons of the different offspring of each mother) provides a more stringent test of causality because the comparison controls for unmeasured genetic and environmental confounds that vary between unrelated mothers. The analyses were based on a subset of the families that included children with differing amounts of exposure (3447 offspring from 1258 mothers). Siblings were compared using contrast codes. Each offspring was assigned a value equal to the deviation of the individual measure of PAE from the mean PAE of all the children from the same mother. The contrast codes, therefore, reflect the amount of PAE relative (more or less) to the mean PAE of all the children in the family. The model also included comparisons of cousins born to NLSY79 mothers who are sisters. Although the comparison of cousins is not as strong as a within-mother approach, it can help provide converging evidence concerning causal processes.⁴³ Cousins were also compared using contrast codes; cousins with more PAE, on average, were compared with their cousins with less PAE, on average. The model also compared unrelated individuals (mean PAE in all cousins from one extended family compared with mean PAE in cousins in a separate extended family). More details about how the contrast codes were calculated,^{22,43} and the statistical justification for their use,⁴⁴ can be found elsewhere.

Model 4 combined the use of measured covariates and the sibling and cousin comparisons, thus using statistical and methodologic controls for potential confounds.

Model 5 tested whether PAE was associated with externalizing problems in the subsample of children that included information on prenatal exposure to marijuana and cocaine. The HLMs included prenatal exposure to alcohol, nicotine, marijuana, and cocaine and the sex of the offspring. Because the assessment of all the substances was available only on a subset of the sample, sibling comparisons could not be completed.

Multiple imputation was used for all of the HLMs that included maternal and familial covariates to account for missing values. The analyses, therefore, use all available data rather than relying on families with complete maternal data. Given the assumption that the missing values are missing at random or completely at random, multiple imputation yields standard errors that account for uncertainty due to missing values and avoids bias arising from complete-record analysis.⁴⁵ Unstandardized regression parameters were used because of the difficulty comparing standardized coefficients when exploring causal processes,⁴⁶ and measurement of PAE is in meaningful units (days per week).

RESULTS

ASSOCIATIONS AMONG MEAN ALCOHOL USE DURING PREGNANCY AND MATERNAL AND FAMILIAL CHARACTERISTICS

Table 3 provides the associations among mean alcohol use during pregnancy and maternal and familial characteristics. Mean PAE across all pregnancies was slightly correlated with maternal delinquency and age at first childbirth. Mean PAE was more strongly related to substance use measures, including mean levels of SDP, alcohol frequency and quantity, and alcohol abuse and dependence items. Binge drinking $\Delta(M_{\text{binge}} - M_{\text{no binge}}) = 0.20$, where M represents the mean; $P < .001$) and having children with different biological fathers $\Delta(M_{\text{not blended}} - M_{\text{blended}}) = 0.08$; $P < .001$) were also associated with PAE.

ASSOCIATION BETWEEN PAE AND OFFSPRING CPs

The results of the HLMs exploring the association between PAE and offspring CPs are given in **Table 4**. Model 1 indicates that for each additional day of PAE per week, offspring had an increase of 0.09 SD in CPs ($P < .001$). Model 2 explored the association of PAE and CPs controlling for the main effects of race/ethnicity, prenatal nicotine exposure, and maternal covariates. Including the measured covariates slightly reduced the association between PAE and offspring CPs ($b = 0.06$, where b represents unstandardized regression weight; $P < .001$) compared with model 1, but the model still revealed a positive and statistically significant relation. The **Figure** presents the unadjusted and adjusted means for CPs at each level of PAE. The adjusted means are based on least squares estimates after controlling for the measured covariates. The **Figure** illustrates a positive association between PAE and CPs for the entire sample; children exposed to more prenatal alcohol had more CPs than unrelated children with less PAE, even after controlling for the measured covariates.

Table 3. Correlations Among Maternal Characteristics^a

Variable	1	2	3	4	5	6	7	8	9	10
1. Mean prenatal alcohol exposure	1 [Reference]
2. Mean SDP	0.15 ^b	1 [Reference]
3. Intellectual abilities	0.02	-0.20 ^b	1 [Reference]
4. Highest grade	-0.03 ^b	-0.30 ^b	0.59 ^b	1 [Reference]
5. Income	-0.01	-0.09 ^b	0.20 ^b	0.19 ^b	1 [Reference]
6. History of delinquency	0.11 ^b	0.21 ^b	-0.10 ^b	-0.11 ^b	-0.04 ^b	1 [Reference]
7. Age at first birth	-0.02	-0.21 ^b	0.41 ^b	0.46 ^b	0.18 ^b	-0.06 ^b	1 [Reference]
8. Alcohol frequency	0.26 ^b	0.04 ^b	0.11 ^b	0.02	0.04 ^b	0.15 ^b	0.08 ^b	1 [Reference]
9. Alcohol quantity	0.21 ^b	0.20 ^b	-0.06 ^b	-0.11 ^b	-0.01	0.17 ^b	-0.05 ^b	0.45 ^b	1 [Reference]	...
10. Alcohol abuse/dependence	0.15 ^b	0.13 ^b	0.03	-0.02	0.01	0.16 ^b	0.03 ^b	0.36 ^b	0.44 ^b	1 [Reference]

Abbreviation: SDP, smoking during pregnancy (packs per day).

^aData are weighted.

^b $P < .05$. Values are for individuals with data for both variables ($n = 3424-4819$). Estimates of the correlations based on 5 multiply imputed data sets⁴⁵ ($n = 4912$ each) did not differ from the correlations presented herein by more than 0.01.

Model 3 provided a statistical comparison of siblings differentially exposed to prenatal alcohol. The within-mother association with PAE was still significant ($b=0.05$; $P=.03$) and was commensurate with findings from the comparison of cousins and unrelated individuals in the model. The last model included the measured covariates, and the statistical relation with PAE remained within mothers ($b=0.05$; $P=.04$). The cousin comparisons in models 3 and 4 also suggests that PAE is independently associated with offspring CPs. The Figure also provides an estimate of the association between PAE and CPs based on the parameters from model 4. Children with more PAE have more CPs than their siblings with less PAE while controlling for the measured factors. The results of all the models are consequently consistent with a causal association between PAE and offspring CPs.

ASSOCIATION BETWEEN PAE AND AIPs

The results of the HLMs for AIPs are given in **Table 5**. Model 1 found an association between PAE and AIPs ($b=0.09$ SD per days exposed per week). Model 2 controlled for measured covariates, and the statistical association with PAE remained ($b=0.06$; $P=.001$). The results of model 3, the comparison of siblings ($b=0.03$; $P=.18$), and model 4, the comparison of siblings controlling for measured covariates ($b=0.02$; $P=.24$), revealed greatly reduced and statistically nonsignificant associations. The comparison of cousins in model 4 also revealed no association, further suggesting that the statistical association between PAE and AIPs is not causal. The association between PAE and AIPs, therefore, seems to be due primarily to characteristics related to PAE that were not included in the previous analytical models.

ANALYSIS OF PAE CONTROLLING FOR MATERNAL POLYSUBSTANCE USE DURING PREGNANCY

Additional HLMs of the sample of children with data on exposure to prenatal alcohol, nicotine, cocaine, and marijuana were conducted. The results suggested that PAE was independently associated with CPs; the magnitude of the estimate ($b \pm SE = 0.04 \pm 0.03$; $P=.16$) was commensurate with the results of the full sample, but the parameter could not be precisely estimated in the smaller subsample. Consistent with the sibling comparisons, statistically controlling for all of the measures of prenatal substance exposure resulted in no association between PAE and AIPs ($b \pm SE = -0.01 \pm 0.15$; $P=.93$).

COMMENT

The structure of relationships within families in this sample provides a powerful natural laboratory for quasi-experimental designs of environmental risk factors.^{16,26} The results of the present study indicate that there is an association between PAE and CPs that was not due to genetic factors related to maternal alcohol consumption during pregnancy, to environmental factors correlated with PAE that vary between unrelated mothers, or to a variety of measured covariates, including maternal and familial characteristics and exposure to multiple drugs in utero. The findings thus support a strong inference that PAE causes an increased risk of offspring CPs through environmental processes.

Compared with children who were not exposed to any alcohol in utero, the results suggest that offspring ex-

Table 4. Parameter Estimates From HLMs for Conduct Problems^a

Variable	Model							
	1		2		3		4 ^b	
	b	SE	b	SE	b	SE	b	SE
Prenatal alcohol exposure								
Phenotypic	0.09 ^{c,d}	0.02	0.06 ^d	0.02
Sibling comparison	0.05 ^d	.02	0.05 ^d	0.02
Cousin comparison	0.14 ^d	.07	0.14 ^d	0.06
Unrelated comparison	0.15 ^d	.03	0.08 ^d	0.03
Child's sex	-0.32 ^d	0.02	-0.32 ^d	0.02	-0.32 ^d	.03	-0.32 ^d	0.03
Family race/ethnicity								
Non-Hispanic white	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Hispanic	0	0.04	0.01	0.04
African American	0.14 ^d	0.04	0.12 ^d	0.04
Prenatal nicotine exposure	0.13 ^d	0.02	0.13 ^d	0.02
Maternal characteristics								
Intellectual abilities	0.02	0.02	0.02	0.02
Years of education	-0.02 ^d	0.01	-0.02 ^d	0.01
Income ^e	-0.05 ^d	0.01	-0.05 ^d	0.01
Delinquency	0.05 ^d	0.01	0.05 ^d	0.01
Age at first birth	-0.01 ^d	0.00	-0.01 ^d	0.01
Blended family	0.15 ^d	0.03	0.15 ^d	0.03
Alcohol frequency	-0.01	0.01	-0.01	0.01
Alcohol quantity	0.01	0.01	0.01	0.01
Alcohol abuse/dependence	0.05	0.04	0.05	0.03
Binge drinking	-0.05	0.05	-0.05	0.05

Abbreviation: HLM, hierarchical linear model.

^aAll the parameters are unstandardized. Model 1 estimated the unadjusted relation between prenatal alcohol exposure and the externalizing behavior. Model 2 estimated the relation controlling for measured covariates. Model 3 compared siblings, cousins, and unrelated individuals who were differentially exposed to prenatal alcohol. Model 4 provided the various comparison and controlled for the measured covariates. The HLMs indicated that offspring sex, maternal smoking during pregnancy, and family race/ethnicity did not moderate the association between prenatal alcohol exposure and each measure of externalizing behavior. The analyses also revealed that linear models, as opposed to nonlinear (quadratic) models, provided the best fit for each offspring measure. Including parity, family size, and a variable representing the oldest age of the offspring assessed in the HLMs did not alter the findings.

^bThe sibling comparison in model 4 for the sample of children and families with no missing maternal data (n=6562) was comparable (b±SE=0.04±0.02; P=.11).

^cb±SE=0.05±0.01.

^dSignificant at P<.05. Child sex was coded male=0 and female=1.

^eIncome was converted to a z score so that the parameter could be accurately estimated in standard units.

posed to prenatal alcohol every day of the week had an increase of 0.35 SD in CPs (the parameter estimate in model 4 reflecting each additional day of exposure multiplied by 7 days). This finding is consistent with the previous research that found robust associations between PAE and offspring externalizing problems, including studies that controlled for characteristics of both parents^{7,8,13} and included more precise measures of PAE.⁶ In addition, the present causal inference regarding PAE and child CPs is consistent with experimental animal studies,¹¹ including research in monkeys⁴⁷ and mice,⁴⁸ that found teratogenic effects of PAE. Therefore, prevention efforts should continue to target alcohol consumption during pregnancy.²⁴

Although AIPs were statistically associated with PAE and the association remained robust to the use of maternal covariates, PAE does not seem to be a causal risk factor for AIPs. The comparison of siblings and cousins differentially exposed to prenatal alcohol while controlling for measured characteristics revealed no (or a very limited) association. If the present analyses relied only on the use of maternal covariates, we would have wrongly inferred that PAE was a causal risk factor for AIPs. The analysis of the subsample of children with information on prenatal expo-

sure to multiple drugs further provides converging evidence in the study and suggests that maternal polysubstance use during pregnancy may account for the unadjusted associations between PAE and AIPs. The finding that PAE does not cause AIPs is also consistent with a recent review⁹ and 1 extant behavior genetic study on PAE.¹⁴

The contrasting findings for CPs and AIPs underscore the findings from imaging studies that different brain regions may be more vulnerable to PAE. Structures such as the basal ganglia, corpus callosum, and parietal cortex seem to be particularly susceptible to the effects of PAE.^{49,50} The brain imaging results and studies comparing children with high levels of PAE with those with ADHD⁵¹ highlight the importance of exploring the specific neuroanatomical processes that mediate or account for associations between each neurobehavioral problem associated with PAE.

The present study has many advantages. Most important, the study used a quasi-experimental design that controlled for genetic and environmental liability shared by mothers and their offspring. The results also accounted for measured maternal and familial characteristics and maternal polysubstance use during pregnancy, a major limitation of many existing studies.¹¹ The results of the

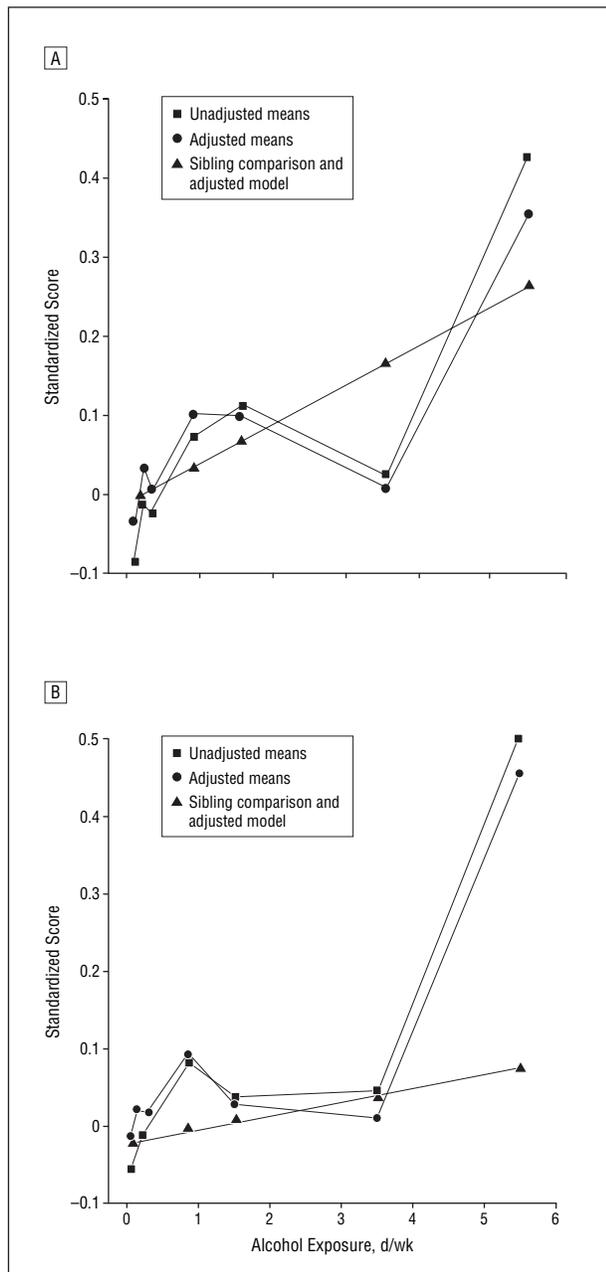


Figure. Mean numbers of offspring externalizing problems by level of prenatal alcohol exposure. A, Results for conduct problems. B, Results for attention/impulsivity problems. The adjusted means (controlling for measured covariates) are based on model 3. The best-fitting estimates of the sibling control and statistical covariate model are based on parameter estimates from model 4. The line presents the estimated means of model 4 for each measure: the comparison of siblings differentially exposed to prenatal alcohol controlling for maternal and familial characteristics. The models are defined in the "Statistical Analyses" subsection.

study are also more highly generalizable than those of many previous studies because the present results are based on a sample of offspring of women in a large national study, which was weighted to be representative of all women in the United States.

The present study has limitations that must be considered. First, quasi-experimental designs cannot prove causality.¹⁶ The analyses do not account for every possible variable that could confound the relation. The only plausible

alternative explanation for the present findings is that an unmeasured factor that varied between siblings and was highly correlated with variations in PAE is the actual environmental causal factor. This might include variations in maternal depression at the time of each pregnancy. It could also include characteristics of different fathers when they differed across siblings (I.D.W., B.M.D., C.A.V.H., J.L.R., P.J.R., and B.B.L., unpublished data, August 2007),⁷ but the analyses at least partially ruled out that explanation by controlling for being in a blended family. A full exploration of the variation in alcohol use during pregnancy within mothers is beyond the scope of the present analyses, although some of the variation is related to the historical reduction that has occurred during the longitudinal NLSY79 study.⁵² Future studies will need to explore additional risks that covary with PAE within mothers. Second, the frequency measure of drinking during each pregnancy may not precisely measure PAE. The assessment of maternal alcohol use during pregnancy was based on reported frequency of alcohol consumption, which did not include the amount of consumption per day or the timing.⁶ The assessment was also completed retrospectively. However, the magnitude of the unadjusted associations is consistent with previous research,¹¹ and there is evidence that retrospective reports of prenatal substance use are reliable^{53,54} and are perhaps even more valid than concurrent assessments.⁵⁵

Third, the present design is based on variations in alcohol consumption across pregnancies.²² The present findings are relevant to the general population only if women who vary their consumption of alcohol across pregnancies are not different from mothers who consistently drank the same amount during each pregnancy. This assumption may be warranted in the present analyses, as most women (88%) who (1) ever drank during 1 pregnancy and (2) had more than 1 child reported variation in their alcohol use among their pregnancies. The difficulties in accurately reporting alcohol consumption for different children in a family by a mother could have affected the sibling comparison analyses. The fact that the sibling and cousin comparisons were comparable, however, suggests that inaccurate measurement of PAE within mothers cannot fully account for the findings.

Fourth, the present analyses explored moderators (offspring sex, maternal SDP, and family race/ethnicity) that have been found to influence the effects of prenatal substance exposure,⁴⁰⁻⁴² but other characteristics, including genetic factors⁵⁶ and stressful events,⁴⁷ may also moderate the effects of PAE.

Fifth, the present analyses could not determine whether the confounding factors for AIPs were genetic or environmental in origin. Use of the NLSY79 and the CNLSY provides the opportunity to nest the sibling comparison approach within a children-of-twins/siblings design, but not all kinship relations are unambiguous.²² The most recent wave of assessments in the NLSY79 (2006) obtained more precise measures of genetic relatedness, so future analyses will explore the nature of the confounding factors with the full adult and offspring sample.

Sixth, the results are limited to externalizing problems during childhood reported by the mothers. Future analyses will need to explore substance use outcomes or

Table 5. Parameter Estimates From HLMs for Attention/Impulsivity Problems^a

Variable	Model							
	1		2		3		4 ^b	
	b	SE	b	SE	b	SE	b	SE
Prenatal alcohol exposure								
Phenotypic	0.09 ^{c,d}	0.02	0.06 ^d	0.02
Sibling-comparison	0.03	0.02	0.02	0.02
Cousin-comparison	0.10	0.07	0.03	0.07
Unrelated-comparison	0.15 ^d	0.03	0.11 ^d	0.03
Child, sex	-0.40 ^d	0.02	-0.40 ^d	.02	-0.41 ^d	0.03	-0.40 ^d	0.03
Family race/ethnicity								
Non-Hispanic white	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Hispanic	-0.07	0.04	-0.06	0.04
African American	-0.02	0.04	-0.02	0.04
Prenatal nicotine exposure	0.12 ^d	0.03	0.12 ^d	0.03
Maternal characteristics								
Intellectual abilities	-0.02	0.02	-0.02	0.02
Years of education	-0.03 ^d	0.01	-0.03 ^d	0.01
Income ^e	-0.03 ^d	0.01	-0.03 ^d	0.01
Delinquency	0.03 ^d	0.01	0.03 ^d	0.01
Age at first birth	-0.01 ^d	0	-0.01 ^d	0.00
Blended family	0.15 ^d	0.03	0.15 ^d	0.03
Alcohol frequency	-0.01 ^d	0	-0.01 ^d	0
Alcohol quantity	0.01	0.01	0.01	0.01
Alcohol abuse/depend	0.04	0.03	0.04	0.03
Binge drinking	-0.02	0.05	-0.02	0.05

Abbreviation: HLM, hierarchical linear model.

^aSee Table 4.

^bThe sibling comparison in model 4 for the sample of children and families with no missing maternal data (n=6562) was comparable (b±SE=0.02±0.03; P=.45).

^cb±SE=0.05±0.01.

^dSignificant at P<.05. Child sex was coded male=0 and female=1.

^eIncome was converted to a z score so that the parameter could be accurately estimated in standard units.

other characteristics of adolescents.^{5,8} Seventh, the study was conducted on a nationally representative sample in which the prevalence of children with extremely high levels of PAE was low. The finding of a linear association between PAE and offspring externalizing problems is consistent with previous research,⁴⁹ but the sample may not have included enough children exposed to high levels of prenatal alcohol to explore whether there is a critical threshold. Likewise, the results exploring the effects of maternal polysubstance use during pregnancy must be viewed cautiously because of the low prevalence of exposure to cocaine and marijuana.

Finally, smaller studies of PAE can conduct more extensive assessments of PAE, offspring mental health problems, and potential confounds. Thus, the present large-scale study complements but does not replace more focused and intensive studies.

The present study, which was based on a representative sample, a rigorous design, and a sophisticated analytical approach to identify possible confounds, strengthens the inference that PAE has a causal effect on the risk of CPs in offspring. In contrast, the finding that unmeasured confounds related to PAE may be responsible for greater AIPs in offspring suggests that the research community needs to focus on putative environmental risk factors that are correlated with maternal substance use during pregnancy, particularly ones that vary across siblings. The results are con-

sistent with research using different methods but further emphasize the need for additional quasi-experimental studies of prenatal substance exposure.

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