Prenatal Smoking and Early Childhood Conduct Problems

Testing Genetic and Environmental Explanations of the Association

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Background: Extensive evidence now supports a statistical association between prenatal smoking and increased risk for antisocial outcomes in offspring. Though this statistical link may signal a causal association, commentators have urged caution in interpreting findings because of the likelihood of confounding.

Methods: We used data from the Environmental Risk Longitudinal Twin Study, a representative British sample of 1116 twin pairs studied at ages 5 and 7 years, to assess associations between prenatal smoking and early childhood conduct problems net of the effects of both heritable and environmental risks for child antisocial outcomes.

Results: Prenatal smoking showed a strong, dose-response relationship with child conduct problems at ages 5 and 7 years. Around half of this association was attributable to correlated genetic effects. Mothers who smoked during pregnancy differed from other mothers in a number of ways. They were more likely to be antisocial, had children with more antisocial men, were bringing up their children in more disadvantaged circumstances, and were more likely to have had depression. Controlling for antisocial behavior in both parents, depression in mothers, family disadvantage, and genetic influences, estimates for the effects of prenatal smoking were reduced by between 75% and the entire initial effects.

Conclusions: Observed associations between prenatal smoking and childhood conduct problems are likely to be heavily confounded with other known risks for children's behavioral development. As a result, tests of any causal influence of prenatal smoking must await findings from experimental studies.

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MATERNAL SMOKING during pregnancy is an established risk for adverse birth, health, and developmental outcomes for children.[1,2] More recently, a growing body of evidence has also highlighted an association between prenatal smoking and aggressive, antisocial behaviors in offspring. Prediction of antisocial outcomes has been reported in both clinical[3] and epidemiologic samples[4]; in offspring ranging in age from preschoolers[5] to adults[6]; and on measures as diverse as behavior rating scales, diagnostic interviews, and crime records. Studies have documented dose-response relationships with prenatal smoking that appear specific to antisocial outcomes and that are possibly specific to males.[7]

Taken together, these findings suggest the possibility of an etiologic role for prenatal smoking in the development of antisocial behavior, argued to operate through influences on early brain development.[7] Although animal studies support the plausibility of such a model,[8] commentators have urged caution in interpreting the human evidence[7,9] because of 3 likely sources of confounding.

First, prenatal smoking is more common among young, less well-educated mothers,[10] among women in adverse social circumstances,[11] and among those who are depressed.[12] All of these factors are known risks for the development of conduct problems in children.[13] In general, past studies have shown that controlling for such risks attenuates, but does not completely erode, links with maternal smoking. If the association between prenatal smoking and children's antisocial behavior is not simply a by-product of other social and parental adversities, it should consistently survive controls for factors of this kind.

Second, smoking is more common among women with antisocial traits,[14] and smoking during pregnancy may be especially so.[15] Antisocial behavior in parents increases the risks of antisocial behavior in children through multiple routes, both genetic (through the transmission of heri-

table traits) and environmental (through effects on the prenatal environment and through later risks of child and partner abuse,[16] harsh and coercive discipline,[17] and co-morbid drug and alcohol problems[18]). As a result, associations between prenatal smoking and child outcomes may be spurious, reflecting instead the operation of these correlated risks. Past studies controlling for parental antisocial behavior have shown mixed results. Most have reported residual effects of prenatal smoking, but 2 studies—the first a small sample of parents with alcohol problems[19] and the second, a large study predicting offspring smoking as well as antisocial behavior[20]—showed that the effects of prenatal smoking were reduced to nonsignificance after controls for parental antisociality. In other studies, however, measures of parental behavior have often been restricted to relatively extreme indicators such as offending or antisocial personality, and by no means have all studies taken into account the antisocial traits of both mothers and fathers. Given the high level of assortative mating on antisocial behaviors,[21,22] this may be an important lack. The presence of 2 antisocial parents may be especially harmful for children, and the joint effects of both parents' characteristics need to be unconfounded from the effects of prenatal smoking. If the association between prenatal smoking and children's antisocial behavior is not spurious, it should survive after controls for both parents' antisocial behavior.

Finally, prenatal smoking may be a proxy measure indexing genetic risk for antisocial behavior. Antisocial behavior is partly heritable,[23] as is women's smoking initiation, nicotine dependence,[24] and prenatal smoking,[25] raising the possibility that children who are exposed to smoking in utero would be at risk for antisocial behavior regardless of whether their mothers smoked during pregnancy. To our knowledge, no study has yet undertaken a direct test of this possibility. But if prenatal smoking is not simply a marker for genetic influences on children's antisocial behavior, its statistical effects must survive after controlling for heritable influences.

In this study, we use data from a nationally representative twin design to assess the effects of prenatal smoking on early childhood conduct problems (assessed at ages 5 and 7 years) after controlling for all 3 types of confounding. Early childhood conduct problems put children at increased risk of later antisocial behavior.[26] In addition, if prenatal smoking influences early brain development, we reasoned that a focus on young children should provide clear evidence of its effects.

METHODS

PARTICIPANTS

Participants were members of the Environmental Risk (E-Risk) Longitudinal Twin Study, which investigates how genetic and environmental factors shape children's development. The study follows an epidemiological sample of families with young twins who were interviewed in the home when the twins were aged 5 and 7 years. The E-Risk study sampling frame was 2 consecutive birth cohorts (1994 and 1995) in the Twins Early Development Study, a birth register of twins born in England and Wales.[27] The full register is administered by the government's Office for National Statistics, which invited parents of all twins born in 1994 and 1995 to enroll. Of the 15 906 twin pairs born in these 2 years, 11 352 (71%) joined the register. Our sampling frame excluded opposite-sex twin pairs and began with the 8298 (73%) register families who had same-sex twins.

The E-Risk study sample was drawn using a high-risk stratification sampling frame. High-risk families were those in which the mother had her first birth when she was aged 20 years or younger. We used this sampling (1) to replace high-risk families selectively lost to the register via nonresponse and (2) to ensure sufficient base rates of problem behaviors in 5-year-old children. Early first childbearing was used as the risk-stratification variable because it was recorded for virtually all families in the register, is relatively free of measurement error, and is a known risk factor for children's problem behaviors.[28,29] The sampling strategy resulted in a final sample in which two thirds of study mothers accurately represent all mothers (aged 15-48 years) in the general population in England and Wales in 1994 and 1995 (estimates derived from the General Household Survey).[30] The other one third of study mothers (younger only) constitute a 160% oversample of mothers who were at high risk based on their young age at first birth (15-20 years). To provide unbiased statistical estimates that can be generalized to the population of British families having children in the 1990s, the data reported in this article were corrected with weighting to represent the proportion of young mothers in that population.[30]

Of the 1203 families from the initial list who were eligible for inclusion, 1116 (93%) participated in the home-visit assessments at age 5 years and form the base sample for the study. Teachers returned questionnaires on the children's behavior for 1049 (94%) of these children. Zygosity was determined using a standard zygosity questionnaire that has been shown to have 95% accuracy.[31] Ambiguous cases were zygosity-typed using DNA. The sample included 622 monozygotic (56%) and 494 dizygotic (44%) twin pairs. Sex was evenly distributed within zygosity (546 male [49.1%]).

A follow-up home visit (which we refer to as the age-7 assessment) was conducted 18 months after the age-5 assessment, when the children were aged 6.5 years on average (range, 6.0-7.0 years). Follow-up data were collected for 1089 (98%) of the 1116 E-Risk study families, and teacher questionnaires were obtained for 2026 (91%) of the 2232 E-Risk study children (93% of those taking part in the follow-up). In both the age-5 and age-7 assessments, families were given shopping vouchers for their participation and children were given coloring books and stickers. All research workers had university degrees in behavioral science and experience in psychology, anthropology, or nursing.

MEASURES

Maternal Smoking

Mothers were contacted 1 year after the twins' birth and asked to provide information about the pregnancy, including the number of cigarettes they had smoked. Around a fifth of mothers (836 [20.8%] of 1055) reported smoking during pregnancy, similar to the 23% rate for England and Wales recorded in a national survey of mothers who gave birth in 1995.[32] Ninety study mothers (8.6%) reported smoking 1 to 9 cigarettes per day, 73 (6.9%) reported smoking 10 to 14 cigarettes per day, and 56 (5.3%) were relatively heavy smokers, smoking 15 or more cigarettes per day during their pregnancy.

Early Childhood Conduct Problems

Children's conduct problems at ages 5 and 7 years were assessed using the Achenbach family of instruments.[33,34] The Con-

duct Problems scale was derived by summing items from mother and teacher reports, including items from the Delinquent Behavior (eg, lying or cheating, swearing or bad language) and Aggressive Behavior (eg, physically attacks people, temper tantrums, or hot temper) scales of the Child Behavior Checklist[33] and the Teacher's Report Form,[34] supplemented with *DSM-IV*[35] items assessing conduct disorder and oppositional defiant disorder (eg, spiteful, tries to get revenge, uses force to take something from another child).

Correlations of mother and teacher reports of conduct problems were 0.29 ($P \leq .001$) and 0.38 ($P \leq .001$) at ages 5 and 7 years, respectively, which is typical of interrater agreement about behavioral problems.[36] At age 5 years, scores ranged from 0 to 130 (mean ± SD, 21.17 ± 16.27) and at age 7 years, scores ranged from 0 to 132 (mean ± SD, 18.48 ± 15.80). The internal consistency of the combined score was 0.94 at age 5 years and 0.95 at age 7 years. The Achenbach instruments have several strengths that make them appropriate for use with children of this age. They have strong and well-documented psychometric properties, have been used in large European and North American epidemiological studies, are highly predictive of *DSM* disorders at later ages, and have been shown to be sensitive to treatment effects.[37] To ease interpretation of the findings, scale scores were standardized to a mean of 0 and an SD of 1.

Covariates

Mothers' and fathers' prior history of antisocial behavior was reported by the mothers at the study contact at age 5 years. Mothers were interviewed using the Young Adult Behavior Checklist,[38] modified to obtain lifetime data and supplemented with questions from the Diagnostic Interview Schedule[39] that assessed the (lifetime) presence of the *DSM-IV*[35] symptoms of antisocial personality disorder. Scores ranged from 0 to 60 (mean ± SD, 11.25 ± 9.71) for mothers and from 0 to 88 (mean ± SD, 14.76 ± 16.29) for fathers. The internal consistency reliabilities of the 2 scales were 0.90 and 0.95, respectively. A methodological study of mother-father agreement about men's antisocial behavior in a representative subset of the sample (67 couples) showed that women can provide reliable information about their children's father's behavior. The correlation between men's and women's reports about men's antisocial behavior was 0.74 (95% confidence interval, 0.53 to 0.95).[40]

Maternal depression since the twins' birth was assessed at each study contact using the Diagnostic Interview Schedule,[39] which provides measures of depressive episodes according to *DSM-IV* criteria.[35] Two hundred ninety (26%) mothers had experienced an episode of depression by the twins' fifth birthday, and 333 (30%) by their seventh birthday.

Family socioeconomic status disadvantage was assessed at each study contact. We created an index summing binary indicators of 7 aspects of socioeconomic status disadvantage: (1) head of household has no educational qualifications; (2) head of household is employed in an unskilled occupation or is not in the labor force; (3) total household gross annual income is less than £10,000; (4) family receives at least 1 government benefit, excluding disability benefit; (5) family housing is government subsidized; (6) family has no access to a vehicle, and (7) family lives in the poorest of 6 neighborhood categories,[41] in an area dominated by government-subsidized housing, low incomes, high unemployment, and single-parent families. At age 5, 600 (45%) families experienced at least 1 socioeconomic status disadvantage.

DATA ANALYSIS

First, we used ordinary least squares regression to test the association between prenatal smoking and children's conduct prob-

lems. We compared women who did not smoke during pregnancy with light (1-9 cigarettes per day), moderate (10-14 cigarettes per day), and heavy (≥15 cigarettes per day) prenatal smokers. Because levels of early childhood conduct problems are higher in boys than in girls, child sex was included as a covariate in this and all subsequent analyses. Regression results are based on the sandwich or Huber/White variance estimator,[42] a method available in Stata 7.0,[43] which adjusts estimated standard errors to account for the dependence in the data due to analyzing sets of twins.

Second, we used DeFries-Fulker (DF) regression analyses to test the hypothesis that passive gene-environment correlations accounted for the association between maternal prenatal smoking and children's conduct problems. DeFries-Fulker analysis uses kinship-pair data (eg, twin data) to separate genetic and environmental influences in a regression framework.[44] The sandwich variance estimator was used to correct for the nonindependence of twin observations.[45] The equation for the basic DF regression model is

$$ASB_{twin1} = \beta_1 + \beta_2(R) + \beta_3(ASB_{twin2}) + \beta_4(R * ASB_{twin2}) + e,$$

where ASB_{twin1} represents the conduct problems score for twin 1, β_1 represents the constant term, R represents the coefficient of genetic relatedness (1.0 for monozygotic twins; 0.5 for dizygotic twins), and ASB_{twin2} represents the conduct problems score for twin 2. β_4 represents the population heritability estimate h^2 because, when it is statistically significant, it demonstrates that twin 1 and twin 2's resemblance for conduct problems is conditioned on their degree of genetic relatedness; β_3 estimates shared environmental variation because it represents the twins' resemblance for conduct problems independent of genetic resemblance.[46]

The hypothesis that genetic transmission accounts for the association between maternal smoking during pregnancy and children's conduct problems predicts that the effect of maternal prenatal smoking will no longer be significant once genetic influences on children's conduct problems are controlled. The basic DF model was expanded to test this prediction. Thus, the effect of maternal smoking was estimated in an augmented model

$$ASB_{twin1} = \beta_1 + \beta_2(R) + \beta_3(ASB_{twin2}) + \beta_4(R * ASB_{twin2}) + \Sigma\beta_{sm}Z_{sm} + e,$$
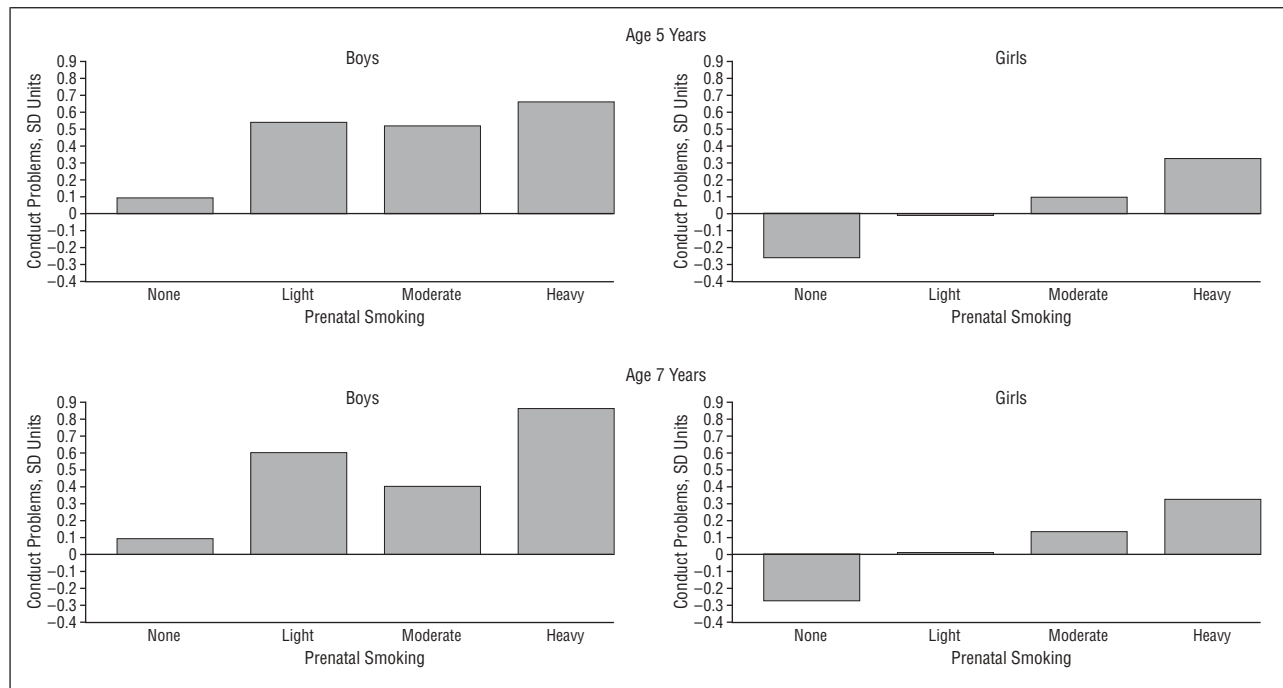
where Z_{sm} represents 3 dummy-coded variables representing light, moderate, and heavy maternal prenatal smoking, respectively, with nonsmoking during pregnancy as the reference category.

Third, we used a series of regression models to test whether the association between maternal smoking during pregnancy and children's conduct problems was accounted for by parents' history of antisocial behavior and by related family adversities. We began by testing the association between maternal smoking during pregnancy and children's conduct problems, using ordinary least squares regression model

$$ASB = \beta_1(\text{light smoker}) + \beta_2(\text{moderate smoker}) + \beta_3(\text{heavy smoker}) + e,$$

where *ASB* represents the child's conduct problems and $\beta1$ through $\beta3$ represent the effects of light, moderate, and heavy maternal smoking during pregnancy compared with mothers who did not smoke during pregnancy (the reference, or contrast, group).

We then tested whether the association between prenatal smoking and children's conduct problems was accounted for by the parents' prior history of antisocial behavior by reesti-

Prenatal smoking and childhood conduct problems, ages 5 and 7 years.

mating model 1 after entering continuous measures indexing the mothers' and fathers' antisocial behavior history

$$ASB = \beta_1(\text{light smoker}) + \beta_2(\text{moderate smoker}) + \beta_3(\text{heavy smoker}) + \beta_4(\text{mother's } ASB) + \beta_5(\text{father's } ASB) + e.$$

Next, we tested whether familywide social adversities that are correlated both with maternal smoking during pregnancy and with children's conduct problems accounted for the effects of maternal prenatal smoking on their children's outcomes. We expanded the regression model,

$$ASB = \beta_1(\text{light smoker}) + \beta_2(\text{moderate smoker}) + \beta_3(\text{heavy smoker}) + \beta_4(\text{maternal } ASB) + \beta_5(\text{paternal } ASB) + \Sigma\beta_j Z_{j,} + e,$$

where Z_j is a set of observed confounding factors (ie, maternal depression and family socioeconomic disadvantage).

Finally, we tested whether the combination of genetic factors, parents' antisocial behavior, and family adversities accounted for the effects of maternal prenatal smoking by expanding the augmented DF regression as

$$ASB_{\text{twin1}} = \beta_1(\text{light smoker}) + \beta_2(\text{moderate smoker}) + \beta_3(\text{heavy smoker}) + \beta_4(P) + \beta_5(ASB_{\text{twin2}}) + \beta_6(R^* \ ASB_{\text{twin2}}) + \beta_7(\text{maternal } ASB) + \beta_8(\text{paternal } ASB) + \Sigma\beta_j Z_{j,} + e.$$

RESULTS

IS THERE AN ASSOCIATION BETWEEN PRENATAL SMOKING AND CHILDREN'S CONDUCT PROBLEMS?

Prenatal smoking predicted children's conduct problems at age 5 years ($F_{3,1054} = 13.75$; $P < .001$) and age 7 years ($F_{3,1030} = 13.92$; $P < .001$). As expected, boys had higher levels of conduct problems than girls at both age 5 years ($t_{1,1115} = 7.18$; $P < .001$) and age 7 years ($t_{1,1088} = 7.40$; $P < .001$). The **Figure** shows a dose-response relation

between the number of cigarettes smoked and the z-transformed measure of conduct problems in both boys and girls. At age 5 years, controlling for sex, children of light, moderate, and heavy prenatal smokers scored 0.33, 0.39, and 0.57 standard deviation units higher, respectively, on the Conduct Problems scale than children of women who did not smoke during pregnancy (**Table 1**, panel A, model 1). These differences persisted at age 7 years, when children of light, moderate, and heavy prenatal smokers scored 0.38, 0.34, and 0.67 standard deviation units higher, respectively, than children of women who did not smoke during pregnancy (Table 1, panel B, model 1). As the Figure suggests, these associations were as powerful for girls as for boys. Tests for interactions with child sex were nonsignificant at both age 5 years ($F_{3,1054} = 0.25$; $P = .86$) and age 7 years ($F_{3,1030} = 0.52$; $P = .67$).

IS THE ASSOCIATION BETWEEN PRENATAL SMOKING AND CHILDREN'S CONDUCT PROBLEMS ACCOUNTED FOR BY GENETIC RISKS?

The results of the DF regression analyses are presented in Table 1 (model 2). Three findings are highlighted. First, approximately two thirds of the variation in children's conduct problems at age 5 years (68%) and at age 7 years (73%) was accounted for by genetic factors. Second, prenatal smoking continued to predict children's conduct problems even after controlling for genetic effects. Third, genetic factors accounted for approximately 50% of the effect of maternal prenatal smoking on child outcomes at both age 5 and 7 years (Table 1, model 1 vs model 2 in panel A and panel B). The shared environment parameter was nonsignificant at both ages and is therefore not included in the models presented in Table 1. These findings provide partial support for the genetic trans-

Table 1. Results of Regression Analysis of the Effects of Maternal Smoking During Pregnancy on Early Childhood Conduct Problems*

	Model 1: Baseline	Model 2: Controlling for Genetic Risk	Model 3: Controlling for Parental Antisocial Behavior	Model 4: Controlling for Parental Antisocial Behavior and Family Adversities	Model 5: Controlling for Genetic Risk, Parental Antisocial Behavior, and Family Adversities
A. Predicting Children's Conduct Problems at Age 5 Years (N = 2084)					
Sex	0.36 (0.26 to 0.47)†	0.18 (0.13 to 0.23)†	0.36 (0.27 to 0.46)†	0.36 (0.26 to 0.45)†	0.20 (0.15 to 0.26)†
Maternal smoking in pregnancy‡					
Light smoker	0.33 (0.10 to 0.56)§	0.15 (0.05 to 0.25)§	0.05 (−0.18 to 0.29)	0.02 (−0.22 to 0.27)	0.01 (−0.11 to 0.13)
Moderate smoker	0.39 (0.22 to 0.56)†	0.19 (0.10 to 0.28)†	0.15 (−0.01 to 0.31)‖	0.10 (−0.06 to 0.26)	0.06 (−0.03 to 0.15)
Heavy smoker	0.57 (0.30 to 0.84)†	0.29 (0.15 to 0.44)†	0.17 (−0.04 to 0.38)‖	0.12 (−0.09 to 0.33)	0.09 (−0.03 to 0.21)
Confounding variables					
Maternal antisocial behavior	NA	NA	0.03 (0.02 to 0.04)†	0.03 (0.02 to 0.04)†	0.02 (0.01 to 0.02)†
Paternal antisocial behavior	NA	NA	0.008 (0.005 to 0.012)†	0.006 (0.003 to 0.010)§	0.003 (0.001 to 0.005)§
Maternal depression	NA	NA	NA	0.09 (0.02 to 0.17)¶	0.05 (0.01 to 0.09)¶
SES disadvantage	NA	NA	NA	0.04 (0.01 to 0.07)¶	0.020 (0.002 to 0.037)¶
Genetic transmission					
R	NA	0.03 (−0.07 to 0.14)	NA	NA	0.05 (−0.05 to 0.16)
R × ASB (h²)	NA	0.68 (0.62 to 0.74)†	NA	NA	0.59 (0.51 to 0.66)†
Constant	−0.28 (−0.35 to −0.21)†	−0.16 (−0.26 to −0.07)†	−0.68 (−0.76 to −0.60)†	−0.69 (−0.77 to −0.61)†	−0.42 (−0.52 to −0.32)†
B. Predicting Children's Conduct Problems at Age 7 Years (N = 2036)					
Sex	0.37 (0.26 to 0.47)†	0.16 (0.11 to 0.21)†	0.36 (0.26 to 0.46)†	0.36 (0.26 to 0.46)†	0.18 (0.12 to 0.23)†
Maternal smoking in pregnancy‡					
Light smoker	0.38 (0.13 to 0.64)§	0.16 (0.06 to 0.26)¶	0.15 (−0.10 to 0.40)	0.10 (−0.15 to 0.36)	0.05 (−0.07 to 0.16)
Moderate smoker	0.34 (0.17 to 0.51)†	0.14 (0.06 to 0.22)§	0.15 (−0.03 to 0.33)‖	0.05 (−0.13 to 0.23)	0.03 (−0.06 to 0.12)
Heavy smoker	0.67 (0.37 to 0.97)†	0.33 (0.17 to 0.49)†	0.33 (0.07 to 0.59)¶	0.258 (−0.002 to 0.519)‖	0.17 (0.02 to 0.32)¶
Confounding variables					
Maternal antisocial behavior	NA	NA	0.03 (0.02 to 0.04)†	0.02 (0.01 to 0.03)†	0.01 (0.01 to 0.02)†
Paternal antisocial behavior	NA	NA	0.007 (0.002 to 0.011)§	0.003 (−0.002 to 0.008)	0.002 (−0.001 to 0.004)
Maternal depression	NA	NA	NA	0.12 (0.04 to 0.20)§	0.06 (0.02 to 0.10)§
SES disadvantage	NA	NA	NA	0.09 (0.04 to 0.14)†	0.04 (0.02 to 0.06)§
Genetic transmission					
R	NA	0.05 (−0.05 to 0.15)	NA	NA	0.07 (−0.03 to 0.17)
R × ASB (h²)	NA	0.73 (0.66 to 0.79)†	NA	NA	0.65 (0.58 to 0.73)†
Constant	−0.29 (−0.35 to −0.22)†	−0.16 (−0.26 to −0.07)§	−0.63 (−0.72 to −0.55)†	−0.66 (−0.74 to −0.57)†	−0.38 (−0.48 to −0.28)†

Abbreviations: ASB, child's conduct problems; h², population heritability estimate; NA, not applicable; R, coefficient of genetic relatedness (1.0 for monozygotic twins; 0.5 for dizygotic twins); SES, socioeconomic status.

*Values are expressed as β (95% confidence interval).

†$P<.001$.

‡The dependent variable of early childhood conduct problems is standardized to a mean ± SD of 0 ± 1. The effects of smoking in the Table thus represent standard deviation unit differences between smokers and nonsmokers during pregnancy.

§$P<.01$.

‖$P\leq.10$.

¶$P\leq.05$.

mission hypothesis, but they also document that prenatal smoking is associated with environmentally mediated effects on children's conduct problems beyond genetic transmission.

IS THE ASSOCIATION BETWEEN PRENATAL SMOKING AND CHILDREN'S CONDUCT PROBLEMS CONFOUNDED BY THE MOTHERS' (AND FATHERS') ANTISOCIAL BEHAVIOR HISTORY?

Women who smoked during pregnancy were likely to engage in higher levels of antisocial behavior than nonsmokers (**Table 2**). To illustrate, high levels of maternal antisocial behavior (the top quartile of the maternal antisocial behavior distribution) were associated with a 3-fold increase in the odds of prenatal smoking (odds ratio, 3.1 [95% confidence interval, 2.3 to 4.3]). In addition, women who smoked during pregnancy were sig-

nificantly more likely to have children with antisocial men (Table 2). Moreover, there was significant assortative mating for antisocial behavior; antisocial women were significantly more likely to reproduce children with antisocial men ($r=0.53$; $P<.001$).

Prior antisocial behavior of both mothers and fathers predicted children's conduct problems (Table 1, model 3). Moreover, comparing model 3 with model 1 showed that parental antisocial behavior accounted for more than 50% of the effect of prenatal smoking on children's behavioral outcomes. At age 5 years, controls for parental antisocial behavior reduced the effects of light smoking during pregnancy to nonsignificance and those of moderate and heavy smoking during pregnancy to just below conventional (5%) levels of statistical significance. At age 7 years, the effects of light smoking during pregnancy became nonsignificant and the effects of moderate smoking during pregnancy became marginally significant, but the effects of heavy maternal smoking dur-

Table 2. Maternal Smoking in Pregnancy Is Associated With Parental Antisocial Behavior and With Family Adversities*

	Maternal Smoking During Pregnancy				Test Score	P Value
	None (n = 782)	Light (n = 104)	Moderate (n = 93)	Heavy (n = 76)		
Mother's antisocial behavior	9.76 (8.44)	16.25 (12.11)	14.63 (10.42)	19.02 (12.36)	$F_{3,1048} = 24.02$	<.001
Father's antisocial behavior	12.37 (14.43)	21.32 (19.32)	22.23 (19.40)	26.53 (22.12)	$F_{3,1044} = 19.46$	<.001
Maternal depression, %	22.3	36.4	41.1	35.5	$\chi^2_3 = 20.66$	<.001
SES disadvantage	0.88 (1.50)	1.89 (1.88)	2.28 (1.99)	2.70 (2.03)	$F_{3,1051} = 32.86$	<.001

Abbreviation: SES, socioeconomic status.
*Values are expressed as mean (SD) unless otherwise specified.

ing pregnancy remained significant when parental antisocial behavior was controlled.

IS THE ASSOCIATION BETWEEN PRENATAL SMOKING AND CHILDREN'S CONDUCT PROBLEMS CONFOUNDED BY SOCIAL DEPRIVATION AND MATERNAL DEPRESSION?

Women who smoked during pregnancy were also more likely to have been depressed during their children's lifetime than other mothers, and their households were significantly more socioeconomically disadvantaged (Table 2). Both of these risks were associated with higher levels of child conduct problems. Maternal depression was significantly linked to children's conduct problems at ages 5 years ($F_{2,1108} = 30.33$; $P<.001$) and 7 years ($F_{2,1081} = 31.03$; $P<.001$), as was social disadvantage. The more severe the family's socioeconomic deprivation, the more conduct problems the children had at ages 5 years ($F_{1,1115} = 78.88$; $P<.001$) and 7 years ($F_{1,1088} = 79.12$; $P<.001$). Controlling for these adversities further reduced the association between prenatal smoking and children's behavioral outcomes. On average, three quarters of the association between prenatal smoking and children's conduct problems was accounted for by parental antisocial behavior and other maternal and family adversities (Table 1, model 4). Controlling for all of these factors, no reliable effects of prenatal smoking on child outcomes could be detected.

DOES PRENATAL SMOKING HAVE AN EFFECT ON CHILDREN'S CONDUCT PROBLEMS AFTER CONTROLLING FOR GENETIC AND ENVIRONMENTAL RISKS?

The final models (Table 1, model 5 in panel A and panel B) present results of augmented DF regression analyses that control for parental antisocial behavior, maternal depression, and social deprivation while also controlling for genetic risk. Coefficients for the effects of prenatal smoking were further reduced in these models; together, the genetic and environmental risks accounted for between 75% and the entire initial effect of prenatal smoking on children's conduct problems. To test the robustness of these findings, we repeated the analyses with maternal smoking treated as a scalar rather than a categorical variable and using other indicators of early childhood conduct problems (the separate Child Behavior Checklist aggression and delinquency subscales and a measure drawing on teacher reports only). (Results of these additional analyses are available from the corresponding author on request.) In each case, strong initial effects of prenatal smoking were reduced by at least 75% by controlling for both genetic and environmental risks. No reliable effects of prenatal smoking could be detected in any of these models on child outcomes at age 5 years. On outcomes at age 7 years, effects of all levels of prenatal smoking were reduced to nonsignificance on the Child Behavior Checklist aggression subscale and the teacher-only reports. On the Child Behavior Checklist delinquency subscale and in analyses treating maternal smoking as a scalar variable, the effects of light and moderate prenatal smoking were reduced to nonsignificance; the effects associated with heavy smoking during pregnancy could still be detected, though they were small in magnitude.

COMMENT

Childhood conduct problems arise in the context of multiple and often overlapping risks. We used data from a large representative twin sample to test the extent to which associations with 1 specific risk factor—prenatal smoking—were robust to controls for genetic and environmental confounds.

Like past investigators, we found a strong, dose-response relationship between prenatal smoking and childhood conduct problems, replicated at 2 ages and as powerful for girls as for boys. Controlling for possible confounds of this relationship, our findings yield 2 main conclusions. First, to our knowledge, the present study provides the most direct test yet of the possibility that prenatal smoking may be a proxy measure indexing genetic risk for antisocial behavior. Our twin analysis, which controlled for the heritability of conduct problems, confirmed that genetic confounds are important. Around half of the observed association between prenatal smoking and young children's conduct problems was attributable to correlated genetic effects. But the results were also clear in showing that, even after controlling for genetic influences, prenatal smoking continued to be significantly linked to children's behavioral outcomes.

Second, our results documented that women who smoke during pregnancy are different from those who do not. They are more antisocial, they bear children with more antisocial men, they are more likely to rear their children in disadvantaged environments, and they are

more likely to be depressed. With these factors and genetic risk controlled, estimates of the effects of prenatal smoking were greatly reduced. In tandem, these 2 sets of findings suggest that (1) prenatal smoking is not simply a proxy indexing genetic risk for antisocial behavior but that (2) it is also unlikely to be a unique cause of early childhood behavior problems.

These findings must be interpreted in light of 4 potential limitations. First, like most other studies in this field, our measures of prenatal smoking relied on maternal reports. Although these have adequate reliability, direct assessment of maternal cotinine levels would undoubtedly have been desirable.[47] Second, the main measures of child outcomes and parental antisocial behavior also came from maternal interviews, raising queries over the possibility of reporter effects. Analyses of teacher-only reports of child behavior, however, were clear cut. Using these independent reports of early childhood behavior problems, no significant effects of prenatal smoking were detectable once genetic and environmental confounds were controlled.

Third, though our study was based on a twin sample, we assume that our findings can be generalized to the population of singletons. This assumption is probably defensible because twin-singleton comparisons find no notable differences in rates of children's behavior problems,[48-52] because the rate of smoking during pregnancy in our sample is comparable with national rates of smoking among pregnant women[32] and because the association between prenatal smoking and children's behavioral outcomes is similar to that reported in samples of singletons.[7] Finally, though nationally representative, our sample was confined to young children and to 1 historical period. If prenatal smoking influences early brain development, we reasoned that effects should be most evident early in childhood; it remains possible, however, that older samples would highlight different patterns of effects. Our study also focused on a recent cohort, whereas some past research has used data from cohorts established many years ago. Historically, rates of prenatal smoking have fallen in many Western countries in recent decades.[10,32] As a result, prenatal smoking may have become more concentrated in families with other adversities, and the extent of confounding with other risks may have become more marked. Past cohorts may not have experienced this level of confounding. For the future, however, our findings should provide a good guide to the extent of overlapping risk.

Given these caveats, the core conclusion of our analyses is that observed associations between prenatal smoking and early childhood conduct problems are highly confounded with other known risks for children's behavioral development. With few exceptions, past studies have found residual effects of prenatal smoking after controls for other risks. We suspect that much of the power of our analyses lay in our assessments of parental antisocial traits. Whereas many past studies have focused on criminality or diagnosed psychiatric/personality disorders in parents, our dimensional measures of parental antisociality included a broad spectrum of markers of antisocial behaviors that showed associations with prenatal smoking and with risks for childhood conduct problems across the range. Whereas some past studies have controlled for antisocial behavior in just 1 parent, we found that both maternal and paternal characteristics accounted for independent variance in child outcomes. Because parents' antisocial behavior indexes both heritable and environmental risks for children's behavioral development and because of the high degree of assortative mating for antisocial behavior,[21,22] we conclude that comprehensive assessments of parental traits are key to evaluating the independent effect of other postulated risks.

Though our findings do not preclude an independent causal role for prenatal smoking in the genesis of child conduct problems, they do imply that strategies other than observational studies will be needed to detect it. Interventions to reduce prenatal smoking offer perhaps the best tests here, though these are known to face challenges. "Best practice" current programs are only successful with some 20% of pregnant smokers and least effective with those who smoke heavily.[53] Studies of pregnant smokers[15] concur with our findings to suggest that for many of these women, prenatal smoking forms part of a wider spectrum of adjustment problems that may put both mothers and their children at risk. Reducing levels of prenatal smoking remains a key target for public policy because of the damaging effects of smoking during pregnancy on other aspects of fetal and early child development.[1,2] For child behavioral outcomes, our findings argue that while we await further evidence on the causal role of prenatal smoking, the many other risks faced by women who smoke during pregnancy constitute equally important targets for intervention and research.

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