

Maternal Smoking During Pregnancy and Psychopathology in Offspring Followed to Adulthood

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ABSTRACT

Objective: To extend findings from several independent reports of an association between maternal smoking during pregnancy and attention-deficit hyperactivity disorder, conduct disorder, and substance abuse in the offspring. **Method:** This is a 10-year longitudinal study of offspring assessed at 3 points in time into adulthood. Fifty offspring of mothers who reported smoking at least 10 cigarettes almost daily during pregnancy and 97 offspring of mothers who reported never smoking during pregnancy were studied. Psychiatric diagnosis in offspring was assessed blind to parental diagnosis. **Results:** There was a greater than 4-fold increased risk of prepubertal-onset conduct disorder in boys and a greater than 5-fold increased risk of adolescent-onset drug dependence in girls whose mothers smoked 10 or more cigarettes almost daily during pregnancy. These findings could not be explained by maternal substance abuse during pregnancy, parental psychiatric diagnosis, family risk factors, prenatal and early developmental history of offspring, postnatal maternal smoking, or smoking in the offspring. **Conclusions:** Maternal smoking during pregnancy may have a long-term effect on specific psychopathology in offspring. The underlying pathophysiology of nicotine on the fetus requires study. The findings suggest the importance of programs aimed at smoking prevention and cessation in women during pregnancy. *J. Am. Acad. Child Adolesc. Psychiatry*, 1999, 38(7):892-899. **Key Words:** maternal smoking, pregnancy, offspring psychopathology, conduct disorder, substance abuse.

Maternal smoking during pregnancy has been associated with offspring physiological deficits in infancy (Abel, 1980) and cognitive deficits and behavioral and attentional problems in childhood (Denson et al., 1975; Fergusson et al., 1993, 1998; Fried, 1989; Kristjansson et al., 1989; McGee and Stanton, 1994; Naeye and Peters, 1984; Nichols and Chen, 1981; Orlebeke et al., 1997; Tong and McMichael, 1992; Weitzman et al., 1992).

Animal studies have corroborated a pattern of nicotine-induced hyperactivity (Ajarem and Ahmad, 1998; Johns et al., 1982; Richardson and Tizabi, 1994). Three studies (Fergusson et al., 1998; Orlebeke et al., 1997; Rantakallio et al., 1992) have obtained the mother's smoking history while she was pregnant and are not subject to problems of retrospective recall of smoking or quality of prenatal medical records.

Five recent studies have extensive diagnostic assessment or criminal records on the offspring but have few or no data on both parents' psychiatric diagnoses, which could have explained the findings. Milberger et al. (1996) examined 140 clinically referred boys aged 6 to 12 years with attention-deficit hyperactivity disorder (ADHD) and 120 normal controls. They found an increased frequency of maternal smoking during pregnancy in the mothers of boys with ADHD (22%) compared with controls (8%), which remained significant after they controlled for socioeconomic status (SES), parental IQ, and parental ADHD. Information was not available on other psychiatric disorders in the boys. The only parental psychiatric diagnostic data presented are for ADHD.

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Wakschlag et al. (1997) used annual diagnostic interviews to follow 177 clinically referred boys, aged 6 to 12 years, over a period of 6 years. Mothers who smoked more than half a pack of cigarettes per day during pregnancy were significantly more likely to have a son with conduct disorder (CD). This association remained significant after the authors controlled for SES, maternal age, substance use during pregnancy, problematic parenting, and parental antisocial personality. Wakschlag et al. concluded that maternal smoking was an independent risk factor for CD in male offspring. CD has been shown to be one possible adolescent outcome of ADHD (Klein and Mannuzza, 1991), suggesting the connection between these disorders. Data on mothers' lifetime history of psychopathology were obtained by direct interview. Similar paternal data were obtained by family history only from the mothers.

Landgren et al. (1998) in Sweden studied 62 six-year-olds with ADHD and a healthy control group and found that twice as many of the children with ADHD and deficits in attention, motor control, and perceptions had mothers who smoked during pregnancy. No data on parental diagnosis were presented.

Fergusson et al. (1998) presented data from the follow-up of a New Zealand birth cohort of 1,265 subjects aged 16 to 18 years. Children exposed, compared with those not exposed to maternal smoking during pregnancy, had higher symptom rates of CD, substance abuse, and depression. The effects remained after the authors controlled for socioeconomic disadvantage, impaired child-rearing behavior, and parental and family problems. The effect was stronger in male than female adolescents. No data on parental diagnosis were reported.

Rantakallio et al. (1992), in a study of 5,966 male members of a 1966 Northern Finland birth cohort, found by age 22 years a 10.3% rate of delinquency (as determined by criminal record) in offspring of mothers who smoked during pregnancy, compared with 4.6% in offspring of mothers who did not. These effects remained after the authors controlled for marital status, social class, place of residence, maternal age at birth, parental employment, number of siblings, and desirability of pregnancy. Although no psychiatric diagnosis was obtained on the parents, the authors note that alcohol abuse among Finnish women in 1966 was a fairly minor problem.

None of these studies on maternal smoking have followed the offspring through the age of risk for substance abuse. Limited data were available on the psychiatric

and substance abuse disorder of both parents. This article reports findings from a 10-year longitudinal study of offspring at high risk for depression and preliminary results on the third generation (the grandchildren). These analyses were undertaken to confirm findings on the association between maternal smoking during pregnancy and prepubertal-onset ADHD or CD in boys. This study also extends previous ones in that psychiatric diagnoses were available for both parents and the hypothesis about their effect in explaining the association between maternal smoking and offspring psychopathology could be tested. Moreover, the offspring in this study have been followed into adulthood through the period of risk for substance abuse.

METHOD

Sample

The analyses were based on 147 offspring and mother pairs who were interviewed 3 times over a period of 10 years. Offspring were initially selected for the presence or absence of a lifetime history of major depression (MDD) in their parents (Weissman et al., 1997). The depressed probands came from treatment clinics. The normal controls came from a community survey and had no history of psychiatric illness, based on at least 3 direct interviews during a 10-year period. All probands and controls were white and group-matched for age.

At the initial interview (time 1), the sample of offspring who had information on maternal smoking during pregnancy consisted of 194 offspring between ages 6 and 23 years (mean age 16.4 years) from 83 mothers. Two years after the initial interview (time 2), 94% of the offspring and mothers were reinterviewed. Approximately 10 years after the initiation of the study (time 10), families were recontacted when the offspring ranged between ages 17 and 36 years (mean age 27 years). Among the 194 offspring interviewed at time 1, one had died and 85% ($n = 164$) were interviewed. There were 5 deaths among the mothers eligible to be interviewed. Of the remaining 78 living mothers, 65 (83%) were interviewed. There were no significant differences ($p < .05$) in attrition rate of mothers or offspring by parental diagnosis or smoking history during pregnancy; by psychiatric diagnoses, age, or sex of the offspring; or by social class of the family.

The analytical sample included 147 of the 164 offspring whose mothers reported either never having smoked during pregnancy (97 offspring) or who reported having smoked more than 10 cigarettes almost daily (50 offspring). The 17 offspring whose mothers reported they smoked during pregnancy only briefly were excluded from the analysis.

Prenatal and Postnatal Smoking and Birth History

Mothers provided self-administered reports about each offspring at times 1 and 2, including questions about prenatal, developmental, and general medical history; birth complications; and the use of substances during pregnancy. Mothers were asked whether they had ever smoked more than 10 cigarettes per day during the pregnancy of each child. If the mother responded yes to the question, she was asked how often she had smoked 10 or more cigarettes per day during the pregnancy: 1 to 2 times, 3 to 5 times, 6 to 10 times, every 2 weeks, weekly, and almost daily. The same criteria were used for categorizing

smoking during pregnancy in the offspring who had children. Information on postnatal exposure was also obtained at time 1, 2, and 10, and the effect on diagnosis in offspring was examined.

Parent and Offspring Psychiatric Diagnostic Assessments

Probands, spouses of probands, and offspring were independently interviewed at each interview with the Schedule for Affective Disorders and Schizophrenia-Lifetime version (SADS-LA), which covers information on lifetime history of major psychiatric disorders including substance abuse and smoking (Mannuzza et al., 1986). The child version was used at time 1 and 2 if the offspring were younger than age 19 years and in the grandchildren at time 10 (Weissman et al., 1992). A separate parent informant diagnostic interview about the offspring was also administered. Offspring interviews were conducted blind to the parents' status and the offspring's previous assessments. Offspring verbal intelligence assessed at time 1 was based on the Peabody Picture Vocabulary Test (PPVT) (Dunn and Dunn, 1981).

Interviewers were doctoral- and master's-level experienced mental health professionals, who underwent four 8-hour group training sessions. Individual trainee interviews were observed during the training period by the supervisor as well as periodically throughout the study to limit interviewer drift. Interrater reliability studies found excellent agreement between interviewers (Weissman et al., 1997).

Final diagnoses of offspring were based on the best-estimate procedure (Leckman et al., 1982). To derive best-estimate diagnoses, an experienced clinician, who was not involved in the interviewing and was blind to the diagnostic and smoking status of the parent and the diagnostic results from previous assessments, independently reviewed all available information including parent informant, offspring interview, and medical records at each interview and assigned a diagnosis for each offspring. A similar procedure was completed for parents, independent and blind to offspring data. Results of interrater reliability of best-estimate diagnosis are reported elsewhere (Weissman et al., 1997).

Assessment of Family Environmental Factors

Six family environmental factors were assessed at time 1: two measures reported by the parent (poor marital adjustment and parent-child discord); two measures reported by the offspring (parental affectionless control and low cohesion); and two measures assessing family structure (divorce and number of offspring in the family). See Fendrich et al. (1990) for coding and validity of cutoff points chosen for the factors. All measures, except number of offspring in the family, were coded 1 if the offspring was considered exposed to the factor and 0 if the offspring was considered not exposed to the factor.

Poor marital adjustment was based on the Short Marital Adjustment Test (Locke and Wallace, 1976). To be consistent with our previous analysis, we coded families as having poor marital adjustment if either parent reported a score below the median score in the sample (Fendrich et al., 1990). Offspring were recorded as being exposed to parent-child discord if the mother reported on the life events inventory that there had been a great deal of fighting between either parent and at least one offspring in the family. Affectionless control was based on the offspring reporting at least one parent as expressing low care and high overprotection on the 25-item 4-point scale of the Parental Bonding Instrument (Parker et al., 1979). Low cohesion was based on a score below the sample median of the 5-item Cohesion subscale of the Family Adaptability and Cohesion Scale (Olson et al., 1979). History of parental divorce, the number of offspring in the family, and SES (Hollingshead and Redlich, 1975) were collected by

direct interview with the parent. All other measures were by self-report. The risk factors assessed at time 1 were used because these were the most likely to precede the onset of disorder in offspring. Informed written consent was obtained from parents and their offspring aged 18 years and older. Assent was obtained when offspring were younger than age 18 years.

Data Analysis

We initially used proportional hazards regression models to examine the association between maternal smoking during pregnancy and offspring psychopathology. Time to first onset of the specific psychiatric disorder was the outcome variable, and maternal smoking the independent variable. Following the suggestions of Wakschlag et al. (1997), we selected potential confounding and mediating variables of this association from 4 categories of previously identified risk factors for offspring psychopathology, i.e., demographic factors, parental psychopathological conditions, pregnancy risk factors, and family (parenting) risk factors. We screened these potential risk factors for their association with maternal smoking during pregnancy by comparing group differences by maternal smoking status, using *t* tests for continuous variables and χ^2 tests for dichotomous variables. Upon completion of this initial screening process, variables that were significantly associated with maternal smoking ($p < .05$) or were considered a priori to be confounders were selected for inclusion in a final series of analyses using the Cox proportional hazards model. In the final series of analyses, as suggested by (Rothman and Greenland, 1998), we first identified those potential confounders that were significantly associated ($p < .05$) with the outcome variable and in addition were associated with a 10% or more change in the regression coefficient associated with maternal smoking during pregnancy. The relative risk of psychopathology due to maternal smoking, controlling for all potential confounders selected by this process, was estimated by fitting a model with offspring psychopathology as the outcome and maternal smoking status and the potential confounding variables included simultaneously as independent variables. Age of offspring and maternal MDD were always included in the model as a priori confounders. Important potential interactions between maternal smoking, alcohol consumption, and coffee consumption during pregnancy were examined. Models with interaction terms were considered to fit the data better if the 2 log likelihood ratio test was significant (Hosmer and Lemeshow, 1989). The analyses were performed separately for boys and girls to replicate findings from some of the previous studies which had examined boys only.

Previous studies (Fergusson et al., 1998) have investigated the association between maternal smoking and offspring psychopathology occurring during a specific developmental phase such as prepubescence and/or adolescence, and one of our goals is to replicate these findings in our study. Consequently we also examined the association between maternal smoking and offspring psychopathology for specific developmental phases (prepubertal phase, adolescence, and adulthood). The manner in which this was performed is described briefly in the following section (see Wickramaratne and Weissman, 1998, for further details): for the prepubescent phase, Cox proportional hazards regression models were fitted where the incidence of the disorder in offspring occurring before age 13 years was considered to be the outcome; offspring who had not developed the disorder under study during the entire study period or who developed the disorder after age 13 years were considered censored (Cox and Oakes, 1984). Similar analyses were conducted for the other 2 developmental phases. For adolescence, incidence of disorder between ages 13 and 17 years was

considered as the outcome variable, while offspring who had not developed the disorder in this age interval were considered censored. Offspring who had an incidence of disorder before age 13 years were not considered at risk for adolescent-onset depression. For the adult phase the outcome variable was considered to be incidence of disorder after age 18 years. The relative risk (ratio of hazards) corresponding to the maternal smoking variable indicates the association between maternal smoking and offspring psychopathology and can be obtained for each of the 3 developmental phases of the offspring (in the manner described above). Comparison of these 3 relative risks indicates the variation of the association between maternal smoking and offspring psychopathology by developmental phase of offspring.

Because the disorder status of offspring from the same family may not be independent, the assumption of independence of the outcome variable implicit in the use of the proportional hazard may be violated. To overcome this problem we used the methods of Binder (1992), who extended the methods of Lin and Wey (1989), who proposed a method for estimating the covariance matrix of the estimated parameters when the model is misspecified, to those situations in which there is correlation among sample units. SUDAAN was used to obtain the appropriate adjusted variance for the relevant parameters (Shah et al., 1996).

RESULTS

Demographic Characteristics of Mothers and Offspring

Maternal smoking during pregnancy, defined as more than 10 cigarettes nearly every day, did not vary significantly by age, education, marital status, and social class of the mother, or age, sex, and PPVT score of the offspring (Table 1). There were significantly more Catholics among the smokers.

Offspring Diagnosis

In analyses adjusted for maternal MDD and child age at interview and based on fitting Cox proportional hazards models, we found that male offspring of mothers who smoked during pregnancy had more than a 3-fold lifetime risk of CD (relative risk [RR] = 3.17, 95% confidence interval [CI] = 1.46, 6.91, $p < .05$) and female

TABLE 1
Demographics of Mothers (Time 1) and Offspring (Time 10) by Maternal Smoking

	Mother Smoked During Pregnancy		Statistics		
	No	10 Cigarettes Almost Daily	<i>t</i> or χ^2 ^a	<i>df</i>	<i>p</i>
No. of mothers	44	21			
No. of offspring	97	50			
Age of mother, mean (SD)	43.7 (6.5)	44.3 (5.8)	-0.563	138.0	.57
Education, <i>n</i> (%)					
Graduate school or college	11 (12.0)	11 (22.9)			
Partial college	20 (21.7)	14 (29.2)			
High school	44 (47.8)	18 (37.5)			
<High school	17 (18.5)	5 (10.4)	5.19	3	.16
Religion, <i>n</i> (%)					
Catholic	64 (69.6)	39 (81.2)			
Protestant	22 (23.9)	2 (4.2)			
Jewish	2 (2.2)	3 (6.2)			
Other/not affiliated	4 (4.4)	4 (8.3)	10.10	3	.02 ^b
Current marital status, <i>n</i> (%)					
Not married	0 (0.0)	0 (0.0)			
Married/remarried	77 (83.7)	40 (83.3)			
Separated or divorced	12 (13.0)	8 (16.7)			
Widowed	3 (3.3)	0 (0.0)	1.86	2	.40 ^b
Ever divorced/separated, <i>n</i> (%)	20 (21.7)	8 (16.7)	0.507	1	.48
Family SES, <i>n</i> (%)					
I	10 (10.4)	4 (8.2)			
II	13 (13.5)	9 (18.3)			
III	19 (19.8)	14 (28.6)			
IV	45 (46.9)	16 (32.6)			
V	9 (9.4)	6 (12.2)	3.58	4	.46
Offspring female, <i>n</i> (%)	48 (49.5)	29 (58.0)	0.959	1	.33
Age (time 10), mean (SD)	27.2 (4.7)	27.4 (5.1)	-0.213	92.7	.83
IQ, mean (SD)	99.7 (15.7)	103.7 (14.7)	-1.39	83.1	.17

Note: SES = socioeconomic status.

^a *t* statistic for continuous variables, χ^2 for dichotomous except where otherwise specified.

^b Fisher exact test, 2-tailed.

offspring had more than a 5-fold risk of drug abuse/dependence (RR = 5.21, CI = 1.61, 16.81, $p < .05$). Rates of MDD, anxiety disorder, ADHD, and alcohol dependence/abuse did not vary in offspring by maternal prenatal smoking status for either sex.

Effects of Parental Diagnosis

Risk factors for offspring psychiatric disorders of interest were examined for their association with maternal prenatal smoking and their ability to explain the association with offspring diagnosis. Of the maternal and paternal psychiatric diagnoses assessed (i.e., any anxiety, MDD, alcohol abuse/dependence, drug abuse/dependence, antisocial personality), only paternal diagnoses were associated with maternal smoking during pregnancy. Offspring whose mothers smoked during pregnancy were more likely to have fathers who had a history of alcohol abuse (RR = 1.94, CI = 1.18, 3.20, $p < .01$) and/or anxiety disorders (RR = 1.82, CI = 1.25, 2.64, $p < .01$) and less likely to have fathers with drug abuse (0% versus 8%; $\chi^2 = 4.36$, $p = .04$). There was no association between maternal prenatal smoking and history of maternal psychiatric diagnosis. When added to the proportional hazards model, paternal diagnosis did not explain the association of maternal smoking during pregnancy with early-onset CD in boys or the association of maternal smoking in pregnancy with drug abuse in girls.

Effects of Family Risk Factors and Postnatal Maternal Smoking

Family risk factors (divorce, affectionless control, parent-child discord, poor marital adjustment, low family cohesion, and number of children), as well as current maternal smoking, were examined. Maternal smoking was assessed by direct interview with the SADS-LA; offspring of mothers who smoked during pregnancy compared with offspring of mothers who did not smoke during pregnancy were more likely to have mothers who smoked postnatally (56% versus 30%; $\chi^2 = 9.47$, $p = .002$). Offspring exposed to maternal smoking during pregnancy were 1.75 times more likely to have their parents divorce (RR = 1.75, CI = 1.02, 2.99, $p < .04$) and 2 times more likely to be exposed to parent-child discord in the family (RR = 2.03, CI = 1.26, 3.26, $p < .004$). When added to the proportional hazards model, none of these risk factors explained the association of smoking with CD or drug abuse or dependence in the offspring.

Effects of Pregnancy, Birth, and Early Developmental History

A variety of pregnancy, birth, and developmental history variables were examined with regard to maternal smoking during pregnancy. Pregnancy smoking history was not significantly associated with age of mother or father at offspring's birth; prior pregnancies or miscarriages; premature deliveries; increased maternal problems during pregnancy such as nausea and vomiting, bleeding, rubella, anemia, urinary tract infection, prescription medication use, or weight gain; or increased maternal and child problems around labor or delivery, such as induced labor, cesarean section, forceps delivery, prolapsed cord, delayed infant breathing, weak cry, or fetal distress. However, mothers who smoked during pregnancy had babies with significantly lower birth weight. Nearly 21% of the offspring of mothers who smoked during pregnancy compared with 7% of the offspring of mothers who did not smoke were reported to weigh less than 5.5 lb at birth ($\chi^2 = 5.75$, $df = 1$, $p = .02$). The smoking mothers also were significantly more likely to drink 2 or more cups of coffee (RR = 1.43, CI = 1.20, 1.71, $p < .001$) or 2 or more drinks of alcohol per day (RR = 3.07, CI = 1.62, 5.81, $p < .0001$) during pregnancy and report having shorter labor (mean 5.3 versus 7.7; $t = -2.68$, $df = 123.2$, $p = .008$). Maternal age at birth of child, drinking alcohol or coffee during pregnancy, and length of labor did not explain the significant association between prenatal maternal smoking and CD or drug abuse or dependence in the offspring.

Offspring Diagnosis by Developmental Phase

When these psychiatric outcomes were examined by sex and age at onset of childhood disorders, based on fitting Cox proportional hazards models, the significant findings were clarified (Table 2). The risk was increased in offspring of mothers who smoked during pregnancy as follows: for males the increased risk of CD was significant for prepubertal onset (RR = 5.67, CI = 2.07, 15.54), and for female offspring the increased risk of drug abuse/dependence was significant for adolescent onset (RR = 4.68, CI = 1.43, 15.32). The most frequently abused drug was cannabis and for multiple drugs, the most frequent combination was cannabis and cocaine. Of the females who abused drugs, 70% abused more than one drug. In the final model (see data analysis), each of the potential confounders was first entered into the model

TABLE 2
Adjusted Relative Risks for Offspring *DSM-III-R* Diagnoses Given Maternal Smoking 10 Cigarettes or More
Almost Daily During Pregnancy by Offspring Sex and Age at Onset of Disorder

Age at Onset (yr)	MDD	Anxiety Disorder	Conduct Disorder	ADHD	Drug Abuse/Dependence	Alcohol Abuse/Dependence
Male offspring						
<13	1.22 (0.267, 5.61)	1.02 (0.403, 2.60)	4.10 ^a (1.56, 10.78)**	0.444 (0.094, 2.09)	— ^b	— ^b
13–17	1.71 (0.282, 10.37)	— ^b	1.70 (0.483, 5.96)	— ^b	— ^b	— ^b
18+	0.778 (0.210, 2.88)	— ^b	— ^b	— ^b	1.21 (0.216, 6.76)	0.638 (0.133, 3.06)
Female offspring						
<13	0.721 (0.185, 2.80)	0.480 (0.215, 1.07)	1.72 (0.238, 12.40)	2.16 (0.135, 34.71)	— ^b	— ^b
13–17	0.980 (0.420, 2.28)	1.08 (0.067, 17.61)	1.00 (0.354, 2.86)	— ^b	5.36 ^c (1.43, 20.17)*	0.810 (0.071, 9.27)
18+	0.865 (0.201, 3.72)	— ^b	— ^b	— ^b	— ^b	1.76 (0.411, 7.50)

Note: Values represent relative risk (95% confidence interval), based on Cox proportional hazards models. MDD = major depression; ADHD = attention-deficit hyperactivity disorder.

^a Adjusted for maternal MDD, age of offspring, and divorce.

^b Not sufficient cases to estimate.

^c Estimated for all cases with onset after age 13 years. Adjusted for offspring current smoking in addition to maternal MDD and age of offspring.

* $p < .05$; ** $p < .01$.

(containing maternal MDD and age) individually, and subsequently those that were significant were added into the model simultaneously. In the model with male prepubertal-onset CD as the outcome, only parental divorce was associated with CD and appreciably decreased the β for maternal smoking. In analyses controlled for divorce, males who were exposed to maternal smoking during pregnancy remained at increased risk for prepubertal-onset CD (RR = 4.1, CI = 1.56, 10.78). After adjustment for offspring smoking, female offspring exposed to maternal smoking during pregnancy remained at increased risk for adolescent-onset drug abuse/dependence (RR = 5.36, CI = 1.43, 20.17). Controlling for parental drug abuse/dependence in the model with drug abuse/dependence in girls as the outcome increased the β for maternal smoking from 1.54 to 1.75 or 14%. Parental antisocial personality disorder was considered to be an a priori confounder of the association between maternal smoking and CD. Entering parental antisocial personality disorder into the model decreased the β for maternal smoking from 1.57 to 1.49 or 5%. In addition, models for CD and drug abuse/dependence were fit with interaction terms between maternal smoking, alcohol consumption, and coffee consumption during pregnancy. None of the interaction terms significantly improved the fit of the models as mea-

sured by the 2 log likelihood ratio test. The final model was also rerun with adjustment for possible nonindependence of offspring, using the methods of Binder (1992). The significant levels remained unchanged when compared with the levels of significance assuming independence, and consequently we have presented only results from the model assuming independence.

DISCUSSION

Given the limitations of using data collected from a high-risk, not a population sample, we have replicated previous findings of an association between prenatal maternal smoking and CD in boys (Wakschlag et al., 1997). By extending the observation through offspring adolescence and early adulthood, we have shown that this effect occurs prepubertally. Our findings could not be explained by the potential confounders studied, were specific to CD and drug dependence/abuse, and were not a general effect on childhood psychopathology. We did not replicate the association with ADHD reported by Milberger et al. (1996). However, our sample of offspring with ADHD was small. The relative risk for ADHD was 2.2, although not significant, possibly due to the sample size. Milberger et al. (1996) reported only on children with ADHD. Finally, longitudinal studies

by Gittelman et al. (1985), Klein and Mannuzza (1991), and Mannuzza et al. (1991, 1993) have found that CD was an adolescent outcome and drug abuse the young adult outcome of ADHD, suggesting an overlap and relationship between the disorders.

Our findings are also consistent with Kandel and colleagues' (1994) hypothesis of an increased risk for adolescent-onset drug dependence/abuse in girls. Their analysis of 2 longitudinal data sets found that maternal smoking during pregnancy increased the probability that female but not male adolescent offspring would smoke and would persist in smoking. They hypothesized that nicotine input to the dopaminergic motivational system could predispose the brain, in a critical period of its development, to subsequent addictive influences and that because of its potential effect on the dopamine system (Collins, 1990–1991; Corrigan, 1991; Koob, 1992; Mereu et al., 1987; Nestler, 1992), in utero exposure to nicotine might be related to an increased risk of substance abuse as the offspring matures. Their hypothesis has not been clinically examined. Why the effect should appear for female and not male offspring remains to be understood. There are several possible explanations. The sex difference may reflect the distinctive sexual dimorphism of the brain, including hormonal and structural factors, which emerge during fetal development. The release of androgens may protect the male against the priming effect of nicotine. Prenatal exposure also could potentiate different genetic vulnerabilities for girls and boys. Maternal modeling of addictive behavior could have a differential effect on daughters, or *DSM-III* diagnosis may underestimate the prevalence of CD in girls.

As with some of the previous studies, our findings are limited by the retrospective nature of maternal reports of smoking in pregnancy. However, they are consistent with findings of other studies which directly assessed smoking during pregnancy (Fergusson et al., 1998; Orlebeke et al., 1997; Rantakallio et al., 1992). Because of the small sample size, we could not examine the effect of combinations of confounders. However, we were able to test the effects of parental Axis I diagnosis. It is possible that some unmeasured genetic or personality factor, and not the smoking per se, that leads mothers to smoke during pregnancy might be causal in the offspring's psychopathology. Several of our findings are consistent with those of direct studies of pregnant women, e.g., lower birth weight of offspring and increased maternal coffee and alcohol use during pregnancy for mothers who reported smoking

during pregnancy (Cnattingius and Haglund, 1997). The proportions of mothers who stopped smoking in pregnancy paralleled those reported in studies in which cigarette use was assessed directly during pregnancy (Fried, 1989; Fried et al., 1984, 1985). We attempted to deal with the retrospective reporting bias by including only women in the extreme groups (those who reported that they smoked at least 10 cigarettes nearly every day during pregnancy and those who said they never smoked during pregnancy). If the women who denied smoking actually included some smokers, this would have served to weaken our findings. Finally, it is possible that the smoking effect on offspring is due to secondary smoke and exposure through breast-feeding. We do not have the data to determine this precisely.

Clinical Implications

While the available data from several groups must be evaluated within their limitations, the convergence of results across studies with different designs should not be ignored. Maternal smoking during pregnancy appears to have long-term effects on offspring's behavior and health that cannot be explained by the measured confounding factors. Until the pathophysiology of nicotine is understood, from a public health perspective, the findings suggest the importance of programs aimed at smoking prevention and cessation in women during pregnancy. Clinicians treating boys with CD or girls with drug abuse might inquire about maternal smoking history during pregnancy. In addition, clinicians treating women who have smoked heavily during pregnancy should inquire about behavioral problems in their offspring.

Addendum

Since this paper was submitted, a study was published reporting findings from a birth cohort (1959–1961) of 4,169 males in Copenhagen (Brennan et al., 1999). During the third trimester of pregnancy, mothers reported the number of cigarettes they smoked daily. When the male offspring were 34 years old, arrest histories were checked in the Danish Criminal Register. Additional information was collected on maternal rejection, socioeconomic status, maternal age, pregnancy and delivery complications, use of drugs during pregnancy, paternal criminal history, and parental psychiatric hospitalization. Results showed a dose-response relationship between amounts of maternal prenatal smoking and arrests for nonviolent and violent crimes. Maternal prenatal smok-

ing was related to persistent criminal behavior in males rather than to arrests confined to adolescence. These relationships remained significant after controlling for potential demographic, parental, and prenatal risk confounds. Because the study was restricted to males, the outcome in females could not be examined.

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