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Maternal smoking during pregnancy and conduct problems in high-risk youth: A developmental framework

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Abstract
Smoking during pregnancy is associated with adverse consequences for children. Most recently, it has been established as a risk factor for developmental psychopathology, specifically Conduct Disorder (CD). Although this association has been shown to be robust, developmental pathways from exposure to CD have not been established. We examined how prenatal exposure to cigarettes interacts with child and family factors to increase risk of CD symptoms in a longitudinal study of 10-year-old urban, African-American youth ($N = 77$). The effects of prenatal exposure at school age were moderated by child sex. Boys whose mothers smoked during pregnancy were significantly more likely to develop CD symptoms, but exposure did not increase risk in girls. A similar trend was found during infancy: prenatal smoking was associated with low sociability/negative emotionality only for boys. The effects of smoking during pregnancy were also moderated by the quality of the early caregiving environment. Exposed boys whose mothers were unresponsive during infancy were at increased risk of CD symptoms, but exposed boys with early responsive mothers were not. Prospective studies, with developmentally based measures of behavior across time, are critical for further elucidating pathways from prenatal exposure to cigarettes to the development of clinical disorder. The identification of a potentially modifiable, prenatal risk factor for early onset developmental psychopathology has important implications for prevention.

There is increasing evidence that insults during the prenatal and infancy periods play a role in trajectories to developmental psychopathology (Cicchetti & Cannon, 1999; Nelson, 2000; Neugebauer, Hoek, & Susser, 1999; Watson, Mednick, Huttenen, & Wang, 1999). However, many of the risk factors identified (e.g., birth complications, exposure to influenza) are nonspecific, often not preventable, and difficult to quantify (Olson, 2000). Recently, an emerging body of research has demonstrated that youth who are prenatally exposed to cigarettes are at increased risk for

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Conduct Disorder (CD; Wakschlag, Leventhal, Cook, & Pickett, 2000). Smoking during pregnancy is a preventable, potentially modifiable risk factor, which is easily quantified with well-developed measurement methods (Benowitz, 1999). Although this is also true of illicit drugs, studies to date have not yielded a systematic and consistent pattern of behavioral effects in offspring (Frank, Augustyn, Grant, Pell, & Zuckerman, 2001; Hans, 1996). Thus, the study of developmental pathways from prenatal exposure to cigarettes to CD is uniquely suited to shed light on brain: behavior relationships in the development of psychopathology.

The present paper examines the relation of prenatal exposure to cigarettes to conduct problems in a sample of urban youth. Using a transactional framework (Cicchetti & Toth, 1997), we examine developmental pathways in exposed youth, including testing hypothesized moderational factors, examining whether a consistent pattern is present across developmental periods, and exploring whether early exposure-related neurobehavioral vulnerabilities mediate this association.

Despite growing awareness of the public health risks of smoking, more than half a million infants per year are exposed to cigarette smoke prenatally (Smith, Martin, & Ventura, 1999).[1] Smoking during pregnancy has long been established as a risk factor for low birth weight and other perinatal problems (Cotton, 1994). More recently, however, maternal smoking has been identified as a risk factor for long-term developmental problems (Ernst, Moolchan, & Robinson, 2001; Olds, 1997). In particular, smoking during pregnancy has been associated with serious antisocial behavior in offspring, including CD and delinquency (Wakschlag, Pickett, Cook, Benowitz, & Leventhal, 2001).

Table 1 summarizes studies of smoking during pregnancy and conduct problems (i.e., clinically significant disruptive behavior and/or delinquency).[2] As Table 1 indicates, the association of smoking during pregnancy and CD is robust to a range of potential confounds and appears to be unique to disruptive behavior problems rather than to developmental psychopathology more broadly (e.g., internalizing problems).[3]

The consistency of these findings, however, should not be considered proof that smoking during pregnancy plays an etiologic role in the onset of conduct problems in youth. In fact, these data should be interpreted with caution due to the methodologic constraints of studies to date, including limitations of (a) exposure measurement (e.g., retrospective), (b) measurement of potential confounders (e.g., parenting concurrently with conduct problems), and (c) the absence of data on developmental pathways that would provide a coherent explanatory model. Although potential error in exposure, risk factor, and outcome measurement in existing studies limits our ability to draw conclusions about the nature of this association, the cumulative evidence is sufficiently compelling to warrant further investigation of developmental pathways.

Research on developmental psychopathology has demonstrated that relations between

1. There has been a notable decline in the prevalence of smoking during pregnancy as a result of public health efforts (from an average of 16.3% in 1987 to 12.3% in 1999; Matthews, 2001). However, this appears to be the result of a decline of overall smoking *initiation* rates by women rather than an increase in *cessation* rates during pregnancy. Approximately 50% of pregnant smokers continue to smoke throughout their pregnancies (Ebrahim, Floyd, Merritt, Decoufle, & Holtzma, 2000).

2. A number of studies have also demonstrated an association to milder forms of behavior problems, utilizing parent checklist ratings. These studies are generally consistent with those of more severe antisocial behavior and have been reviewed elsewhere (Ernst et al., 2001; Olds, 1997).

3. An association to ADHD has also been reported (Milberger, Biederman, Faraone, Chen, & Jones, 1996). These findings are discrepant with data from several other studies that have examined the association of exposure to multiple disorders and have found a significant association to CD and not ADHD (Wakschlag et al., 1997; Weissman et al., 1999). The apparent association to ADHD in the Milberger et al. study may be due to the high rates of comorbidity between ADHD and CD (Hinshaw, Lahey, & Hart, 1993) because the association to other disruptive behavior disorders was not examined in this study.

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risk factors, vulnerabilities, and the development of psychopathology are rarely linear and often involve a complex set of interactions between biologic vulnerabilities, family environment, and social context (Cicchetti & Cannon, 1999; Kraemer, Stice, Kazdin, Offord, & Kupfer, 2001; Wakschlag, Pickett, Cook, et al., 2001). Yet, research establishing increased risk of CD in the children of mothers who smoked during pregnancy has generally not had a developmental focus. As a result, we know little about *for whom, under what circumstances*, and *how* the increased risk of CD in the children of mothers who smoked occurs. The present study brings a developmental psychopathology perspective to bear on this question in order to shed light on the developmental processes by which smoking during pregnancy and CD are linked.

Moderational Effects

A few studies have examined whether smoking during pregnancy interacts with other risks in trajectories to offspring conduct problems. Significant interactions have been demonstrated with perinatal complications and father absence in studies of offspring delinquency (Brennan, Grekin, & Mednick, 1999; Gibson & Tibbetts, 1998, 2000). Although these studies provide preliminary evidence suggesting that exposure-related vulnerabilities interact with other risks in pathways to adverse behavioral outcomes, more in-depth research guided by developmental theory is needed for the identification and systematic testing of factors that modify risk in exposed children.

Both child and environmental factors may moderate the effects of prenatal exposure to cigarettes. One child characteristic that is emerging as a potential moderator is child sex. Boys are more vulnerable to developmental problems, in general (Gualitieri & Hicks, 1985), and to disruptive behavior problems, in particular (Loeber & Keeman, 1994). As illustrated in Table 1, there is some evidence that the increased risk of CD in exposed youth is stronger for boys.

However, there are a number of issues that remain to be addressed in order to establish whether sex moderates the behavioral effects of prenatal exposure to cigarettes. First, only a few studies have included girls. In addition, sex differences in behavioral effects of exposure have not been examined in younger children. As a result, it is not clear whether sex differences in exposure-related effects are present from early in development or whether they are specific to later emerging and more serious conduct problems. Examining sex differences in behavioral effects of exposure at different developmental periods is important for shedding light on this issue.

Postnatal environmental factors may also modify the effect of prenatal exposure. As has been suggested (Raine, Brennan, & Mednick, 1994), in order for early biologic vulnerability to lead to violent behavior, it may need to be "potentiated" by a problematic early social environment. Of particular importance is identifying the role that parenting plays in trajectories from exposure to child problem behavior. "Vulnerability is not destiny" (Weinberg & Glantz, 1999, p. 291) and adverse events that increase risk are associated with a diversity of outcomes (Cicchetti & Rogosch, 1996). The interaction of biologic vulnerability with environmental risk, in general, and parenting, in particular, has long been seen as a critical factor in determining outcomes of exposed children (Lester, Boukydis, & Twomey, 2000). In particular, early responsive parenting appears to be a uniquely important influence on the developing nervous system (Rogeness & McClure, 1996) and on trajectories to later disruptive behavior disorder (Shaw & Bell, 1993; Wakschlag & Hans, 1999). Whether a positive early parenting environment can modify the adverse behavioral effects of prenatal exposure to cigarettes has not been tested.

Developmental Patterning and Timing of Effects

Infants are not born with CD. Identifying pathways from exposure to CD is a complex endeavor because it requires delineation of developmental models that identify age-specific manifestations of vulnerability and dys-

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Table 1. *Review of studies of maternal smoking during pregnancy and severe antisocial behavior in offspring*

Study[a]	Design/Sample	Developmental Domains Controlled[b]			Main Outcomes (Adjusted)	
		Parenting/Home Environment[c]	Perinatal/Child	Parent Psychopathology[d]	Associated With/Strength of Association	Lack of Association With[e]
Studies of CD						
Wakschlag et al. (1997), United States	Clinic-based case control 177 males (7–17 years)	• Discipline, communication, supervision	• Exposure to illicit drugs/alcohol • Pregnancy/birth complications • Low birth weight	• Antisocial personality • Substance abuse	Diagnosis of CD OR = 3.3	ADHD
Fergusson et al. (1998), New Zealand	Population-based prospective cohort 1,265 males/females (18 years)	• Responsiveness (age 3 years) • Physical discipline • History of child abuse • Parental conflict	• Exposure to illicit drugs/alcohol • Unplanned pregnancy	• Offending • Substance abuse	CD symptoms Linear increase in boys' mean CD score increased as exposure increased	In boys and girls: depression, anxiety, substance abuse In girls: CD
Weissman et al. (1999), United States	Offspring of case-control study of maternal depression 147 males/females (17–36 years)	• Family cohesion • Parental conflict • Marital adjustment	• Exposure to alcohol/caffeine • Pregnancy/birth complications • Low birth weight • ETS	• Antisocial personality • Substance abuse • Depression • Anxiety	Diagnosis of CD RR of early onset CD in boys = 4.1 In girls: drug abuse/dependence RR = 5.4	In boys: ADHD, depression, anxiety, substance abuse In girls: CD, ADHD, depression, anxiety, alcohol abuse
Wakschlag & Keenan (2001), United States	Clinic-based case control 129 males/females (2–5 years)	• Observed responsiveness • Harsh discipline • Parenting stress/support	• Low birth weight • IQ	• Maternal antisocial personality • Offending • Maternal depression	Disruptive behavior (ODD/CD) symptoms Mean symptom score was 1.54 higher for exposed children	—

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Studies of criminal offending						
Brennan et al. (1999), Denmark	Population-based prospective cohort 4,169 males (34 years)	• Rejection (age 1 year)	• Exposure to illicit drugs/alcohol • Pregnancy/birth complications	• Paternal offending • Psychiatric hospitalization	Violent, nonviolent, and persistent offending OR of persistent offending = 1.5 OR of violent offending = 1.7	Adolescence-limited offending
Rasanan et al. (1999; see also Rantakallio, Laara, Isohanni, & Moilanen, 1992), Finland	Population-based prospective cohort 3,883 males (16 years)	—	• Exposure to illicit drugs/alcohol • Pregnancy/birth complications • Unplanned pregnancy • Infant developmental status	• Maternal depression	Violent and persistent offending OR of persistent offending = 2.4 OR of violent offending = 2.1	Nonviolent offending
Gibson et al. (2000; see also Gibson & Tibbets, 1998, 2000), United States	Population-based prospective cohort 200 males/females (17 years)	Unstable home environment	• Pregnancy/birth complications • Low birth weight • IQ	—	Early-onset offending OR for early-onset offending for boys = 2.6, for girls = 3.5	Late-onset offending

Note: CD, conduct disorder; OR, odds ratio; RR, relative risk; ETS, environmental tobacco exposure.
[a]Related findings from the same cohort that have been reported in multiple papers are represented only once in this review.
[b]All studies also controlled for sociodemographic factors.
[c]Measured concurrently with outcome and by self-report unless noted.
[d]Measured for both parents, unless noted.
[e]Reported for those studies in which association to multiple outcomes was examined.

function, an area of science that is just emerging (Cannon, Rosso, Bearden, Sanchez, & Hadley, 1999; Keenan, 2000). If smoking during pregnancy does contribute to pathways to conduct problems in youth, it is likely that this occurs via exposure-related neurobehavioral vulnerabilities that increase susceptibility to other risks. The challenge that this presents from a measurement perspective is that the types of neurobehavioral outcomes typically measured during infancy and early childhood are qualitatively different from antisocial behavior. In addition, early vulnerabilities increase, but do not linearly determine, risk of later disorder (Sroufe, 1990), making it difficult to identify coherent behavioral patterns over time. These limitations of current knowledge notwithstanding, efforts to determine how exposure-related behavioral difficulties are linked to the development of clinically significant conduct problems are critically important for informing understanding of pathways to developmental psychopathology.

There is some evidence of exposure-related neurobehavioral vulnerabilities from both human and animal studies. These include increased tremulousness, poor autonomic regulation, heightened negativity, and developmental lags in humans (Brook, Brook, & Whiteman, 2000; Franco, Groswasser, Hassid, Lanquart, Scaillet, & Kahn, 1999; Fried, 1993; Fried & Makin, 1987; Jacobson, Fein, Jacobson, Schwartz, & Dowler, 1984; Schuetze & Zeskind, 2001) and hyperactivity and impairments in arousal modulation, learning, and attention in animals (Ajarem & Ahmad, 1998; DiGiovanni, Cagiano, DeSalvia, Giustino, & Lacomba, 1993; Hafstrom, Milerad, Asokan, Poole, & Sundell, 2000; Tizabi, Popke, Rahman, Nespor, & Grunberg, 1997). Two prospective studies have examined prenatal smoking and behavior at multiple time points and have provided evidence of smoking-related behavioral difficulties across developmental periods from infancy to middle childhood (Fergusson, Horwood, & Lynskey, 1993; Fergusson, Woodward, & Horwood, 1998; Fried, 1993; Fried, Watkinson, & Gray, 1992, 1997). The relationship of these early neurobehavioral vulnerabilities to later conduct problems has not been examined, however.

Another aspect of establishing developmental pathways is establishing the developmental timing of effects. Childhood-onset conduct problems are more likely to have origins in early neurobehavioral vulnerability and to manifest in persistent behavior problems over time (Lahey, Waldman, & McBurnett, 1999; Moffitt, Caspi, Dickson, Silva, & Stanton, 1996).[4] In contrast, late onset conduct problems are generally limited to adolescence, often occur in the context of association with deviant peers rather than early vulnerability, and are less likely to reflect pervasive and chronic maladaptation (Moffitt et al., 1996). Based on the different pathways and origins of these two forms of conduct problems, we would hypothesize that prenatal exposure to cigarettes would be more strongly associated with early onset conduct problems. As Table 1 indicates, emerging evidence is consistent with this hypothesis. However, the majority of studies that have established an association to early onset antisocial behavior have utilized developmentally heterogeneous (e.g., ages ranging from 6 to 23 years) and/or adult samples. Examining the relationship of smoking during pregnancy to early onset CD in a homogeneous school-age cohort is important for studying this issue in developmental context.

Establishing Generalizability Across Contexts

The generalizability of this association across psychosocial contexts has also not been fully established. To date, studies of the behavioral effects of prenatal exposure to cigarettes have been in predominantly Caucasian, middle class, and/or socioeconomically diverse samples. Recently, the association of maternal smoking during pregnancy and conduct problems has been reported in two African-American inner-city samples (Gibson, Piquero, &

4. In DSM-IV, the cutoff for childhood onset CD is age 10 years (APA, 1994). Others have defined it as prior to midadolescence (Gibson et al., 2000; Moffitt et al., 1996).

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Tibbets, 2000; Wakschlag & Keenan, 2001). Children in high-risk environments may be especially vulnerable to the behavioral effects of exposure because chronic stress may exacerbate biologic vulnerabilities (Post & Weiss, 1997). Conversely, effects of exposure may be less salient because of the strength of other risk factors. In examining whether maternal smoking increases risk of conduct problems for children with many other risk factors for CD, robust measurement of other salient risk factors is especially critical to establishing that this association is not a spurious one. One primary alternative explanation for the maternal smoking to offspring conduct problems association is that it is spurious to the poorer quality care that women who smoke during pregnancy are likely to provide (Chassin, Presson, Todd, Rose, & Sherman, 1998; Wakschlag, Pickett, Middlecamp, Walton, Tenzer, & Leventhal, 2001). As shown in Table 1, the majority of studies have controlled for parenting and/or the quality of the home environment in some fashion. However, statistical control alone does not rule out the impact of even measured confounders on an outcome due to measurement error (Marshall, Hastrup, & Ross, 1999). To date, studies of prenatal exposure and offspring antisocial behavior have generally measured parenting via maternal report or proxy measures (e.g., having considered an abortion, Brennan et al., 1999). Utilizing observational methods in studies of smoking during pregnancy is important for more rigorously establishing that the effects of exposure are not spurious to the caregiving environment provided by maternal smokers, particularly in samples at high risk for caregiving dysfunction.

The present investigation examines the association of maternal smoking during pregnancy and conduct symptoms at middle childhood in a sample of urban, African-American youth at high risk for developmental psychopathology. Data are derived from the 10-year follow-up of a prospective study. The longitudinal nature of the present study, following a cohort from pregnancy through school age, provides a unique opportunity to examine pathways from prenatal exposure to cigarettes to conduct problems within a developmental framework. The following specific questions are addressed:

1. Is maternal smoking during pregnancy associated with child CD symptoms in an urban, African-American sample, and is this association moderated by sex of the child?
2. Does the sex of the child also moderate exposure effects on infant outcomes?
3. Do exposure-related vulnerabilities during infancy mediate the association between maternal smoking and later CD symptoms?
4. Does early maternal responsiveness moderate the association of smoking during pregnancy and CD symptoms in youth?

Methods

Sample

The sample consists of 77 African-American children (mean age = 10.0 years, range = 8.9–11.8 years) who participated in the 10-year follow-up of a longitudinal study begun in 1978 to examine the effects of prenatal exposure to opioids on child development (see details of sampling methods in Grattan & Hans, 1996). Thirty-six of the children (including four sibling pairs) had a documented history of prenatal exposure to opioid drugs; 41 (including three sibling pairs) were not exposed to opioids prenatally. Forty were boys; 37 were girls. At the time of recruitment into the study, all families were of low to very low socioeconomic status. All families were recruited at the same urban hospital from obstetrical clinics for low-income women, including a specialized clinic for drug-dependent women. At the time of recruitment, mothers were excluded from the study who had major medical conditions other than substance abuse, who were under the age of 18 or over the age of 35, or who showed evidence of mental retardation or thought disorder during a screening interview. The attrition rate from the neonatal assessments through age 10 years was 23% and was unrelated to maternal opioid use or smoking. Loss to follow-up was primarily caused by child death

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or handicapping condition, reluctance of foster parents to participate in the study, and inability to locate families who had moved out of the area.

Following procedures approved by the Institutional Review Board, mothers gave their written informed consent at the time of recruitment and before the 10-year follow-up; children provided their verbal assent at the 10-year follow-up.

Procedure

Assessments were conducted twice during the pregnancies and eight different times between the child's birth and age 10 years. Data for the present paper are derived from the pregnancy assessments, infant assessments at 4, 12, and 24 months, and the 10-year follow-up. At each assessment, examiners of the child were blind to information about maternal substance abuse.

Pregnancy research sessions were conducted with all mothers and 31 fathers. These sessions included questions about family demographics, parental mental disorder, and parental use of substances including cigarettes, alcohol, and illicit drugs. After birth, all children remained in the custody of their biological mothers. At the infant assessment visits, mothers were interviewed and developmental assessments were conducted. At middle childhood, the assessment was conducted over three sessions scheduled as near as possible to the children's 10th birthdays. Respondents included all 77 of the children, 56 biological mothers, and 21 other primary caregivers for children whose mothers were unavailable to be interviewed (15 from the opioid group and 6 from the comparison group; these children participated with their primary caregivers; see Hans, Bernstein, & Henson, 2002, for information about foster care arrangements).

Measures

Child conduct symptoms during middle childhood. Child CD symptoms were assessed using The Diagnostic Interview for Children and Adolescents (DICA; Herjanic & Reich, 1982; Reich, Herjanic, Welner, & Gandhy, 1982). The DICA, a fully structured child psychiatric interview, was administered during the second session by masters-level psychologists through separate simultaneous interviews with the child and caregiver. A psychiatric social worker and a psychologist each reviewed the written interview protocols (and if necessary watched videotapes of the interviews) and independently assigned DSM-III-R (APA, 1987) best estimate diagnoses. For cases where the two diagnosticians disagreed, an additional psychologist independently reviewed the protocols to resolve the discrepancies. Agreement between the two diagnosticians was high for CD (Cohen's $\kappa = .88$). Five of the children met criteria for CD. None of these children were sibling pairs.

Because of sample size constraints and the small number of children meeting diagnostic criteria for CD, we decided to generate a CD symptom score (Cronbach's $\alpha = .60$; for details, see Wakschlag & Hans, 1999). Responses to the eight CD symptoms on the DICA CD screen were summed: each item was scored on a four-point scale (no, rarely, sometimes, yes). Only parent DICA items were used in constructing the CD symptom score, because children typically underreport symptoms of conduct problems (Bird, Gould, & Staghezza, 1992). Boys had higher CD symptom scores than girls, a difference that was significant at the trend level. Mean scores were 3.5 ($SD = 4.15$, range = 0–15) for boys and 2.22 ($SD = 2.14$, range = 0–7) for girls, $t\ (75) = 1.69$, $p < .10$.

Prenatal exposure to cigarettes. Women's use of cigarettes during pregnancy in each trimester was assessed through an interview adapted from the University of Washington Pregnancy and Health Questionnaire (1974) administered during the last trimester of pregnancy. Because reports across trimesters were highly correlated ($r = .92$) and were actually being made during the third trimester of pregnancy, smoking status was determined based on third trimester smoking. For purposes of the present paper, prenatal exposure to cigarettes was coded into three levels. Twenty-nine percent

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of the mothers were classified as nonsmokers (n = 22), 57% as light to moderate smokers who smoked up to a pack a day (n = 44), and 14% as heavy smokers who smoked more than a pack a day (n = 11). Mothers smoked between 2 and 45 cigarettes a day, with a median of 15.

To rule out the possibility that any associations between prenatal cigarette exposure and child psychopathology might be due to confounding of maternal smoking with other perinatal and family risk factors for child conduct problems, a set of theoretically derived variables was identified a priori based on previous research showing them to be related to maternal smoking and/or child conduct problems. These included exposure to other substances prenatally, socioeconomic status, single parent status, parent antisocial behavior, and maternal responsiveness.

Prenatal exposure to other substances. In addition to self-report of maternal smoking, repeated urine toxicology screening was conducted during pregnancy to verify the self-reports for a large panel of illegal substances. Opioid use was the focus of the original sample selection, and mothers were coded dichotomously as users (n = 36) or nonusers (n = 41). All but three of the opioid-using women were involved in low-dose methadone-maintenance programs for the treatment of chronic heroin addiction; their dosages during pregnancy ranged from 3 to 40 mg per 24-hr period with a mean of less than 20 mg. Most had been involved in methadone maintenance throughout pregnancy; some had sought treatment during pregnancy. Because their methadone dosage levels were all relatively low and because some mothers occasionally supplemented with illegal opioids, no effort was made to quantify opioid exposure.

Based on the mothers' self-reports, third trimester alcohol use was coded into four categories: abstinence (n = 52), light drinking of less than one drink per day on average (n = 21), moderate drinking of less than two drinks per day (n = 0), and heavy drinking of greater than or equal to two drinks a day (n = 3). Third trimester marijuana use was coded into four categories: abstinence (n = 50), irregular use of once a week or less (n = 9), regular light use of two to five joints per week (n = 7), and regular heavy use of five joints or more per week (n = 10). A small number of mothers used other nonopioid drugs, including cocaine, diazepam, and Phenobarbital, but use of these drugs was so infrequent that they were not used for statistical analyses.

Although women who used one substance during pregnancy were also more likely to use other substances, smoking and other substance use variables were far from confounded. Of the smokers, 28% also drank alcohol, 58% were opioid users, and 42% were marijuana users. Of the nonsmokers, 14% also drank alcohol, 18% were opioid users, and 14% were marijuana users.

Mother and father antisocial behavior. Lifetime mental disorder was assessed for all mothers before the birth of the child using the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (Endicott & Spitzer, 1978; Spitzer & Endicott, 1975) and supplemental interview questions assessing personality disorders drawn primarily from the Current and Past Psychopathology Scale (Endicott, Spitzer, Fleiss, & Cohen, 1976). Based on these interviews, DSM-III (APA, 1980) best estimate diagnoses were made (Leckman, Sholomskas, Thompson, Belanger, & Weissman, 1982). The best estimate procedure involved the interviewer making a case presentation to a team that included a psychiatrist, two psychologists, and a psychiatric social worker. All diagnoses were made consensually. This consensual approach to diagnosis was used to insure uniform application of diagnostic standards throughout the sample. For 31 of the fathers, the same procedures were used to arrive at a psychiatric diagnosis. For the remaining fathers, the mothers were interviewed about the fathers' history of antisocial behavior, including history of arrests, incarcerations, and violent behavior. Based on the diagnostic interview and maternal report, dichotomous variables were coded to indicate whether each parent had a history of antisocial behavior.

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Sociodemographic factors. Family socioeconomic status was measured at the time of pregnancy (Hollingshead & Redlich, 1958; 39 Class V, 29 Class IV, 9 Class III). Family structure was also coded as 0 (*married*, n = 24) or 1 (*single*, n = 53).

Maternal responsiveness. The Parent–Child Observations Guides for Program Planning (PCOG; Bernstein, Percansky, & Hans, 1987) were used to assess maternal responsiveness during infancy based on observation of a series of videotaped interactional tasks. All ratings were based on observations of the entire videotaped sequence. At 4, 12, and 24 months, mothers and children were videotaped for approximately 40 min in a laboratory "living room" in a series of age-appropriate structured and unstructured activities.

Responsiveness ratings assessed maternal behavior in terms of timing, pacing, flexibility, and emotional engagement. Ratings emphasized gentle handling of the child, prompt response to child upset or need, interest in the child's activities, and behavior that was paced so as not to be intrusive and was sensitive to the developmental level of the child.

Two PCOG raters blind to exposure status evaluated videotapes. A different pair of raters was used at each age. Interrater reliability coefficients ranged from .75 to .85 for the mothers' scores on Responsiveness at 4, 12, and 24 months. Disagreements between raters on individual items were resolved consensually. Alpha coefficients for maternal responsiveness items at 4, 12, and 24 months ranged from .71 to .82 with an average of .79. For the purposes of the present paper, 4-, 12-, and 24-months ratings on the PCOG were first standardized and then averaged to create an early maternal responsiveness index.

Infant birth weight and neurobehavioral vulnerability. Data on infant birth weight were gathered from hospital records (mean birth weight = 3050 g, SD = 99 g). At each of the follow-up ages where videotaping was done, infants were also assessed with the Bayley Scales of Infant Development (Bayley, 1969). Carefully trained and supervised female examiners who were blind to any information about the mothers' drug use or infants' medical history administered the examination. Indices of infant neurobehavior, in terms of cognitive, motor, and attentional and socioemotional functioning, were derived from this assessment.

The Bayley Scales of Infant Development consist of three parts. The Psychomotor Developmental Index (PDI) and the Mental Development Index (MDI) assess acquisition of milestones in motor and mental functioning. The Infant Behavior Record (IBR) is a series of 9- and 5-point items rating qualitative aspects of the infant's behavior. They are completed by the examiner at the end of the testing session and are based on clinical impressions made throughout the session. Matheny (1980) has identified factors for consolidating the 27 IBR items; the item composition of these factors was slightly different at different ages. Following Matheny's analyses, we summed a subset of IBR items to create an attention index: orientation/interest in objects (#8), persistence in goal directed effort (#11), and persistence in attention (#12). We also summed a subset of reverse-scored IBR items to create a low sociability/negative emotionality index: responsiveness to persons (#1), responsiveness to examiner (#2), cooperativeness (#4), general emotional tone (#7), and endurance (#13). Average vulnerability scores were computed across 4, 12, and 24 months for the MDI, PDI, and IBR indices.

Data analysis. Analyses were computed using ordinary least squares regression. Because the dependent variable, the CD symptom score, was skewed, it was subjected to a square root transformation in order to approximate a normal distribution for the regression analyses. We first tested the association of smoking during pregnancy and the transformed CD symptom score and examined whether this association was moderated by the sex of the child. We then examined whether exposure-related vulnerabilities during infancy mediated this association. Finally, analyses were conducted to examine moderational effects of maternal responsiveness. However, these analyses were considered exploratory because of the small cell sizes for this set of analyses

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(crossed by gender and by maternal responsiveness). All analyses were computed with and without adjustment for covariates. One-tailed tests of significance were conducted because of a priori predictions about direction of effect.

Results

Is maternal smoking during pregnancy associated with child CD symptoms in an urban, African-American sample, and is this association moderated by sex of the child?

For the sample as a whole, mean CD symptom scores increased with heaviness of exposure. On average, children born to nonsmoking mothers had mean CD symptom scores of 2.0 ($SD = 2.10$), those born to light to moderate smoking mothers had mean scores of 3.0 ($SD = 3.13$), and those born to heavy smoking mothers had mean scores of 4.27 ($SD = 5.57$). Smoking during pregnancy and CD symptoms were significantly correlated for the sample as a whole ($r = .22$, $p < .05$) and for the boys ($r = .52$, $p < .001$) but not for the girls ($r = -.07$, *ns*).

Regression analyses were then computed on the transformed CD symptom scores with maternal smoking during pregnancy (three levels), sex of child (higher = female), and their interaction. The overall model was significant $F\ (3, 73) = 4.71$, $p < .01$, adjusted $R^2 = 0.13$. Because there was a statistically significant interaction between maternal smoking during pregnancy and sex of child ($t = -3.12$, $p < .01$), regressions were computed separately for boys and girls. For girls, maternal smoking during pregnancy did not predict CD symptom scores, $F\ (1, 35) = 0.55$, adjusted $R^2 = 0.0$. In contrast, maternal smoking during pregnancy was significantly associated with boys' CD symptom scores, $F\ (1, 38) = 10.67$, $p < .01$, adjusted $R^2 = 0.20$, standard coefficient = .47, $t = 3.27$, $p < .01$. Because smoking during pregnancy was unrelated to CD symptom scores in girls, subsequent analyses predicting CD symptom scores were conducted for boys only.

Table 2. *Summary regression analysis for variables predicting CD symptom score (square root transformation) for boys (n = 40)*

Variable	Standard Coefficient	*t*
Maternal smoking	.36	2.14*
Maternal opioid use	–.32	–1.64
Maternal marijuana use	–.06	–0.30
Maternal alcohol use	–.01	–0.09
Single mother	.25	1.60
Socioeconomic status	–.04	–0.27
Mother antisocial	.32	1.55
Father antisocial	.07	0.40
Early maternal responsiveness	–.18	1.14

*$p < .05$, one-tailed test.

To explore the possibility that the association between maternal smoking during pregnancy and boys' CD symptom scores might be due to other potentially confounding factors, a multivariate regression analysis was next conducted, controlling for family socioeconomic status, single parent status, maternal antisocial history, paternal antisocial history, early maternal responsiveness and prenatal exposures to opioid drugs, marijuana, and alcohol. This model was significant, $F\ (9, 30) = 2.28$, $p < .05$, adjusted $R^2 = 0.23$, and the unique effect of maternal smoking on CD symptoms remained significant (see Table 2).

Are there sex differences in the effects of smoking during pregnancy on infant neurobehavioral outcomes?

Table 3 reports correlations between maternal smoking and birth weight and Bayley MDI, PDI, and IBR attention and low sociability/negative emotionality scores for the entire sample and for boys and girls separately. For both boys and girls, prenatal exposure to cigarettes was associated with lower birth weight, MDI, and attention scores (and these associations remained significant after adjusting for covariates). Sex differences were apparent, however, in relation to infant socioemotional vulnerability. Prenatal exposure to cigarettes

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Table 3. *Correlations between infant perinatal and neurobehavioral vulnerability and maternal smoking during pregnancy by sex of child (adjusted coefficients)*

	Boys ($N = 40$)	Girls ($N = 37$)	All ($N = 77$)
Birth weight	−.30*	−.43**	−.40***
	(−.26)	(−.13)	(−.28*)
MDI	−.31*	−.20	−.23*
	(−.33*)	(−.24)	(−.23*)
PDI	.07	−.17	−.06
	(.15)	(.05)	(.14)
Attention (IBR)	−.31*	−.35*	−.35**
	(−.36*)	(−.29)	(−.31*)
Low sociability/negative emotionality (IBR)	.30*	−.03	.08
	(.13)	(−.15)	(.10)

*$p < .05$, one-tailed test. **$p < .01$. ***$p < .001$.

was negatively associated with low sociability/negative emotionality for boys but was unrelated for girls. However, this association did not remain significant after adjusting for covariates.

Do exposure-related vulnerabilities during infancy mediate the association between maternal smoking and later CD symptoms?

The only potential mediator among the infant neurobehavioral vulnerabilities was birth weight because this was the only vulnerability that was associated with both prenatal smoking and CD symptoms ($r = -.29$, $p < .05$). A regression analysis was computed on the transformed CD symptom score, with birth weight added to the model illustrated in Table 2, to examine possible mediation. There was no evidence of mediational effects. In this model, smoking during pregnancy remained a significant predictor of CD symptom scores, and its effects were not greatly reduced by the inclusion of the infancy measures in the model ($\beta = .42$, $t = 2.76$, $p < .01$). In addition, after controlling for maternal smoking during pregnancy, birth weight was no longer significantly related to boys' CD symptoms ($\beta = -.16$, $t = -1.06$, *ns*). Thus, there was no evidence that early vulnerabilities mediated effects of prenatal cigarette exposure on boys' CD symptoms.

Does early maternal responsiveness moderate the association of smoking during pregnancy and CD symptoms in youth?

Exploratory analyses were then conducted to examine whether effects of prenatal exposure were moderated by maternal responsiveness during infancy.[5] Table 4 shows the mean CD symptoms scores for boys whose mothers smoked and were responsive and unresponsive to them (median split of the responsiveness variable). As these data indicate, exposed boys had elevated CD symptoms only if they also had unresponsive mothers during infancy. Separate regression analyses were then computed to examine the effects of prenatal exposure to cigarettes for boys who had responsive mothers during infancy and those who did not, controlling for the factors shown in Table 2. For boys with responsive mothers during infancy, there was no relation between maternal smoking during pregnancy and child CD symptom scores at age 10 years, F (1, 16) = 0.20, adjusted $R^2 = 0.00$, *ns*). In contrast,

5. We also examined whether maternal responsiveness *mediated* the association of prenatal exposure and CD symptoms in boys, utilizing a stepwise regression approach. The inclusion of maternal responsiveness in the model did not substantially reduce variance explained by prenatal exposure, and exposure remained a highly significant predictor of CD symptoms ($p < .009$).

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Table 4. *Boys' mean CD symptom scores by maternal smoking status and early maternal responsiveness* (*means, standard deviations, and cell sizes*)

	No Smoking	Smoking	All
Nonresponsive	2.00	5.88	4.82
	(3.52)	(5.01)	(4.90)
	$n = 6$	$n = 16$	$n = 22$
Responsive	1.43	2.18	1.89
	(1.27)	(2.64)	(2.19)
	$n = 7$	$n = 11$	$n = 18$
All	1.69	4.37	
	(2.46)	(4.53)	
	$n = 13$	$n = 27$	

Note: For ease of interpretation, the means of the nontransformed CD symptom score are presented here.

maternal smoking during pregnancy and boys' CD symptom scores were strongly related for boys whose mothers were unresponsive during infancy, $F\ (1, 20) = 10.85$, $p < .01$, adjusted $R^2 = .32$; $\beta = 0.59$, $t = 3.29$, $p < .01$.

Discussion

Maternal smoking during pregnancy was associated with symptoms of childhood-onset conduct disorder in this sample of high-risk youth. Previous studies have focused predominantly on European-American populations. The present study adds to an emerging body of evidence demonstrating that this association is also evident in African-American youth at high psychosocial risk (e.g., Gibson et al., 2000; Wakschlag & Keenan, 2001). The replication of this specific risk:disorder relationship in a prospective study of inner-city minority youth is particularly striking given the high-risk nature of this sample and the rigorous, prospective measurement of those risk domains that covary with maternal smoking status. In particular, control for the quality of *early* parenting, as assessed with a robust observational measure of parent–infant interaction, adds further weight to the supposition that the relationship of maternal smoking and behavioral outcomes is not spurious to the quality of the caregiving environment provided by maternal smokers.

We have shown that smoking during pregnancy is associated with early-onset CD symptoms in a prospective cohort of preadolescents. (However, we could not test whether this was unique to early-onset compared to adolescent-onset symptoms because of the age of the cohort.) This is consistent with the early-onset pathway hypothesized from a behavioral teratologic perspective.

All children were not at equal risk for experiencing the behavioral sequelae of in utero exposure to cigarette smoke. Boys were at increased risk of conduct problems if their mothers smoked during pregnancy, but girls were not. This is generally consistent with previous research on smoking during pregnancy and antisocial behavior (e.g., Fergusson et al., 1998; Weissman, Warner, Wickramaratne, & Kandel, 1999, but see Gibson et al., 2000), as well as with evidence that boys are more vulnerable than girls to teratologic effects in general (Hans, 1994). There is also supportive evidence for sex differences in effects of prenatal exposure to nicotine from animal studies. Male rodents are more likely to show adverse effects of prenatal exposure to nicotine and are more likely to show behavioral impairment due to hypoxic insult (Faraday, Scheufele, Rahman, & Grunberg, 1999; Koylu, Demirgoren, London, & Pogun, 1997; Lichtensteiger & Schlumpf, 1993; Tashima, Nakata, Anno, Sugino, & Kato, 2001; Tizabi et al., 1997; Zaren, Lindmark, & Bakketeig, 2000).

To our knowledge, the present findings are the first to indicate that sex differences in the effects of smoking during pregnancy on behavioral regulation may be present as early as infancy. Smoking during pregnancy was associated with increased neurobehavioral vulnerability in both girls and boys, including lower birth weight and developmental and attentional functioning. However, exposure was associated with low sociability/negative emotionality in boys only, although this association did not remain significant after adjusting for covariates. Given sample size constraints when examining sex differences in this cohort, as well as limitations of measurement of this key construct, we believe that the *pattern of difference* that emerged suggests prelimi-

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narily that sex differences in behavioral trajectories of prenatally exposed offspring may begin in the first years of life. Further longitudinal research with samples large enough to systematically examine sex differences is needed to establish whether this represents a true, early emerging difference.

Although these early problems in behavioral regulation did not mediate the association to CD symptoms in boys, this may be attributable to limitations of measurement in the present data set. First, we did not have a measure of temperament per se; it is possible that more robust measures of infant temperament specifically designed to capture stable manifestions of early behavioral dysregulation would be more strongly related to later conduct problems. In addition, we lacked measures of behavioral regulation across time. Given complex pathways from early vulnerability to later disorder (Cicchetti & Rogosch, 1996), it is not surprising that measures of behavioral regulation in the first 2 years of life do not mediate the association of conduct problems nearly a decade later.

Although the present study adds to a consistent body of evidence that prenatal smoking does not increase the risk of CD in girls, it also suggests that girls are not "immune" to the effects of smoking during pregnancy because neurobehavioral vulnerabilities were present for both girls and boys during infancy. Just as the pattern of neurobehavioral effects differs for girls and boys during infancy, a similar differential pattern may be present at later ages. For example, prenatal smoking has been associated with other types of problem behavior in girls, including smoking and substance abuse (Griesler, Kandel, & Davies, 1998; Niaura et al., 2001; Weissman et al., 1999). Systematic testing of the association of smoking during pregnancy to broader manifestations of problem behavior in girls (e.g., Crick, 1997; Wakschlag, Gordon, Lahey, Loeber, Green, & Leventhal, 2001) will be important for elucidating this issue.

We have also provided preliminary evidence that parenting moderates the effects of prenatal exposure to cigarettes. Exposure was associated with increased risk of CD symptoms in boys, only in combination with unresponsive care during infancy. These findings are consistent with previous research that has shown that youth whose mothers smoked during pregnancy are at especially increased risk of antisocial behavior when exposure is combined with other early risk factors for antisocial behavior (Brennan et al., 1999; Gibson & Tibbets, 1998, 2000; Rasanan et al., 1999). They move beyond previous research by demonstrating the role that more qualitative aspects of the postnatal environment may play in moderating this risk.

There has been a great deal of theoretical importance placed on the quality of the caregiving environment in determining outcomes of children with in utero drug exposure (e.g., Mayes & Bornstein, 1997). Moderational effects of parenting on the outcomes of prenatally exposed children have rarely been demonstrated empirically, however. Although our findings do not demonstrate a specific mechanism of effect, we hypothesize that this interactive effect may occur via the interaction of temperamental vulnerabilities associated with prenatal exposure and the parenting environment. Outside of the teratologic domain, there is ample evidence that child temperamental vulnerability and early parenting interact in pathways to child conduct problems (Bates, Petit, Dodge, & Ridge, 1998; Kochanska, 1997; Shaw, Winslow, Owens, Vondra, Cohn, & Bell, 1998). There is also evidence from animal studies that the quality of early maternal behavior has long-lasting effects on offspring neuroregulatory functioning (Caldju, Diorio, & Meaney, 2000; Gunnar, 2000). Future studies that measure the transaction of maternal behavior (including stage-salient domains of parenting across time) and exposure-related vulnerabilities can more specifically elucidate these processes.

Taken together, these findings suggest that pathways from prenatal exposure to cigarettes to conduct problems in offspring are not linear but are instead complex and multidetermined. Limitations of the present study must be acknowledged, however. First, the sample is relatively small and not representative in nature. Sample size may have attenuated our ability to detect interaction effects. The selection of the sample based on the presence or

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absence of maternal opioid use may also limit generalizability to other populations of maternal smokers and to other low-income African-American populations. Second, the prevalence of opioid exposure in this sample and its correlation with smoking is a shortcoming of this data set for pinpointing nicotine-specific effects. On the other hand, we note that (a) prenatal exposure to opioids was unrelated to CD symptoms, (b) poly-drug exposure is a difficulty endemic to behavioral teratologic research in general (Jacobson & Jacobson, 1996), and (c) the present findings are consistent with data from multiple, unselected samples (Table 1) and are interpreted within that broader context.

The absence of biologic measurement of prenatal exposure to cigarettes is also a limitation of the present study. Although self-reported usage data were gathered prospectively and data were gathered at a time when social pressures not to smoke were substantially lower than they are presently, this limitation of measurement may have contributed to an underestimation of exposure and, as a result, an attenuation of true effects. Error in measurement may also have attenuated relationships between exposure to other substances and CD symptoms. Exposure to other substances (e.g., alcohol) may have been somewhat underestimated because smoking is a more habitual behavior and more reliably recalled than use of alcohol and other substances (Jacobson & Jacobson, 1996). However, in general, drinking was not very prevalent in this sample. Methadone exposure was biochemically verified. The absence of long-term effects of methadone exposure is consistent with earlier findings from this study (Wakschlag & Hans, 1999) and the work of others (Hutchings & Zmitrovich, 1995).

These limitations notwithstanding, this study represents a first step in applying a developmental framework to understanding the well-established association of prenatal exposure to cigarettes and antisocial behavior in offspring. To our knowledge, it is the first prospective study of the association of smoking during pregnancy and offspring CD to examine effects at multiple developmental periods over time and to systematically examine how infant characteristics and family processes interact with exposure in pathways to CD. It has been suggested that trajectories to antisocial behavior reflect a complex set of interactions in which biologic susceptibility is actualized by interaction with environmental risk processes (Lahey et al., 1999; Rutter, Dunn, Plomin, Simonoff, Pizkles, Maughan, Ormel, Myer, & Eaves, 1997). Consistent with this notion, the present findings suggest that prenatal exposure to cigarettes does not inexorably lead to the onset of developmental psychopathology. Rather, exposure appears to contribute to heightened vulnerability, which, in interaction with other risk factors, increases the likelihood of a trajectory to CD in exposed youth.

The use of a developmental framework for delineating long-term behavioral effects of smoking during pregnancy is important not only in terms of establishing teratologic effects per se, but also because it provides a more general paradigm for understanding how insults to the developing brain affect early behavior and how such behavior interacts with contextual factors over the course of the life cycle to contribute to trajectories to developmental psychopathology. The present findings lend further weight to the burgeoning evidence that smoking during pregnancy and CD in boys are linked. Whether prenatal exposure to cigarettes plays a direct etiologic role or serves as a marker for other risk factors for CD is not yet clear (Fergusson, 1999; Koren, 1999; Wakschlag, Pickett, & Leventhal, 2000). What is clear, however, is that factors during pregnancy and the first few years of life may significantly influence the likelihood that youth will develop serious antisocial behavior (e.g., Moffitt, 1993; Neugebauer et al., 1999; Raine, Brennan, & Mednick, 1994; Wakschlag, Gordon, et al., 2001; Wakschlag & Hans, 1999). Trajectories to CD appear to involve the interaction of multiple risks *and* a number of these early risk factors are potentially modifiable. This underscores the potential of prevention efforts in the first few years of life to substantially alter pathways to this very serious mental disorder of youth.

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