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Estimated Risk of Developing Selected DSM-IV Disorders Among 5-Year-Old Children with Prenatal Cocaine Exposure

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Abstract

This study estimated childhood risk of developing selected DSM-IV Disorders, including Attention-Deficit Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD), and Separation Anxiety Disorder (SAD), in children with prenatal cocaine exposure (PCE). Children were enrolled prospectively at birth (n=476) with prenatal drug exposures documented by maternal interview, urine and meconium assays. Study participants included 400 African-American children from the birth cohort, 208 cocaine-exposed (CE) and 192 non-cocaine-exposed (NCE) who attended a 5-year follow-up assessment and whose caregiver completed the Computerized Diagnostic Interview Schedule for Children. Under a generalized linear model (logistic link), Fisher's exact methods were used to estimate the CE-associated relative risk (RR) of these disorders. Results indicated a modest but statistically robust elevation of ADHD risk associated with increasing levels of PCE ($p<0.05$). Binary comparison of CE versus NCE children indicated no CE-associated RR. Estimated cumulative incidence proportions among CE children were 2.9% for ADHD (vs 3.1% NCE); 1.4% for SAD (vs 1.6% NCE); and 4.3% for ODD (vs 6.8% NCE). Findings offer suggestive evidence of increased risk of ADHD (but not ODD or SAD) in relation to an increasing gradient of PCE during gestation.

Keywords

prenatal cocaine exposure; DSM-IV Disorders; ADHD

Despite a decade of research, the emotional and behavioral adaptation of children with prenatal cocaine exposure (PCE) remains a public health concern. Pregnant women, lacking a clear public media messages regarding the impact of illicit drugs such as cocaine, continue to use illicit drugs such as cocaine during pregnancy. Recent estimates indicate 4% of

pregnant women acknowledge illicit drug use during pregnancy (SAMHSA, 2006). Cocaine's teratogenic influence has been hypothesized through multiple direct and indirect pathways including maternal hypertension, decreased uterine blood flow, fetal vasoconstriction and hypoxemia, and nutritional deficiencies (Frank et al., 1990; Moore, Sorg, Miller, Key, & Resnik, 1986; Volpe, 1992) with implications for structural and functional aspects of fetal brain development (Mayes, 1999; 2002). Due to a concentration of cocaine's effects on monoaminergic pathways, arousal and attention regulatory systems in the developing fetus are believed to be particularly vulnerable (Mayes 1999; 2002). Many contemporary behavioral teratology models conceptualize the effects of a toxin as being expressed as a function of genetics and the environment. The effects of PCE on behavioral regulation, for example, may become more apparent under stressful environmental conditions such as increased academic and social demands or disruptive home environments (Mayes, 2002; Mayes, Grillon, Granger, & Schottenfeld, 1998). Prenatal drug exposure is often associated with parenting environments that may include parental neglect and abuse, caregiver drug use and mental health issues, family instability and homelessness, exposure to violence, and environmental disparities associated with poverty (Mayes, 2002; Mayes & Ward, 2003).

Although PCE-associated deficits in arousal and attention regulation are believed to place children at increased risk for the development of behavior problems in early childhood, results reported from clinical studies have been mixed. Delaney-Black and colleagues (1998) found cocaine-exposed children at age 6 exhibited more problems on the Problem Behavior Scale, an investigator-developed teacher report measure, but not on the Conners' Teacher Rating Scale (CTRS). In a series of studies examining the moderating influence of gender and alcohol exposure, PCE in girls was linked to an increase in caregiver-reported aggressive behavior (Sood et al., 2005) and teacher-reported externalizing and aggressive behavior (Bailey et al., 2005), but only when alcohol exposure was factored out through stratified analyses. Conversely, relationships between externalizing behaviors, particularly delinquent behavior, were noted only in cocaine-exposed boys who were also prenatally exposed to alcohol (Bailey et al., 2005).

Other studies have failed to support an association between PCE and increased childhood behavior problems on parent-rated questionnaires such as the Achenbach Child Behavior Checklist (CBCL) (Accornero, Anthony, Morrow, Xue, & Bandstra, 2006; Accornero, Morrow, Bandstra, Johnson, & Anthony, 2002; Bennett, Bendersky, & Lewis, 2002; Richardson, Conroy, & Day, 1996). Bendersky, Bennett, and Lewis (2006) reported PCE to be predictive of aggression at age 5, with boys living in more stressful environments being the group at greatest risk. Only one study has specifically evaluated DSM-IV diagnostic criteria in young children with PCE. Linares and colleagues (2006) found that cocaine-exposed children at age six were more likely to self-report symptoms in the probable clinical range for oppositional defiant disorder and attention deficit hyperactivity. Parent report using the CBCL, by itself, did not differentiate cocaine-exposed from non-cocaine-exposed children in any domain.

Women who use cocaine during pregnancy often use other drugs that may have independent effects on child behavioral regulation. For example, prenatal nicotine exposure has been

related in some studies to children's conduct problems in boys (Maughan, Taylor, Caspi, & Moffitt, 2004) and has been linked to symptoms of hyperactivity and ADHD (Kotimaa et al., 2003; Linnet et al., 2003; Mick, Biederman, Faraone, Sayer, & Kleinman, 2002; Rodriguez & Bohlin, 2005). Prenatal alcohol exposure has also been linked to ADHD (Burd, Klug, Martsof, & Kerbeshian, 2003; Mick, Biederman, Faraone, Sayer, & Kleinman, 2002), aggressive and externalizing behavior (Sood et al., 2001), and depressive symptoms in young children (O'Connor & Paley, 2006). Similar findings have been observed for prenatal marijuana exposure in children (Goldschmidt, Day, & Richardson, 2000; Gray, Richardson, & Day, 1997).

This empirical research report investigates a hypothesized relationship between PCE and the risk of developing several DSM-IV Disorders of Childhood, including Attention-Deficit Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD), and Separation Anxiety Disorder (SAD). Risk hypotheses were evaluated for both the gradient of potential cocaine exposure based upon maternal self-report, and between-group differences in estimated risk. These three disorders were selected due to their typical emergence during early childhood, and due to hypotheses that these disorders may be exacerbated by the arousal modulation difficulties and environmental stressors associated with PCE. Drawing upon computerized diagnostic assessments, children aged five to six years with PCE were hypothesized to be at increased risk for developing one or more of these DSM-IV Disorders, independent of potentially confounding prenatal drug exposures or environmental influences. Boys with PCE histories were expected to be at greatest risk when compared to all other subgroups. The number of study participants with DSM-IV disorders at age five years was too small to probe the multiple behavioral teratology models that posit toxin effects on these outcomes or to investigate additional DSM-IV conditions. Nonetheless, by age five, most children already have faced stressful environmental conditions that might provoke disruptions in behavioral regulation, and have entered the effective period of risk for developing ADHD, ODD, and SAD (Egger & Angold, 1996).

Methods

Participant Information

Participants were drawn from a prospective longitudinal study of the effects of prenatal cocaine exposure on child development known as the Miami Prenatal Cocaine Study (MPCS). The study was approved by the Institutional Review Board and conducted under a federal Department of Health and Human Services Certificate of Confidentiality with informed consent. The originating birth cohort of 476 infants [253 cocaine-exposed (CE) and 223 non-cocaine-exposed (NCE)] was recruited from the obstetrical service of a large urban hospital between November 1990 and July 1993. Recruitment procedures have been extensively detailed in earlier reports (Bandstra, Morrow, Anthony, Churchill, Chitwood, Steele, Ofir, & Xue, 2001a; Morrow, Bandstra, Anthony, Ofir, Xue, & Reyes, 2001). CE infants were also exposed to varying combinations of alcohol, tobacco and cannabis. Of the 223 NCE infants, 76 were exposed to varying combinations of alcohol, tobacco and cannabis and 147 were drug-free at birth. The birth cohort was similar with regard to full-term gestational age (37 completed weeks), socioeconomic status, and African American race/

ethnicity. Exclusion criteria included maternal HIV/AIDS; prenatal exposure to opiates, methadone, amphetamines, barbiturates, benzodiazepines or phencyclidine; major congenital malformation; chromosomal aberration; or disseminated congenital infection. From the original birth cohort of 476 infants, 400 children had caregiver interviews completed on the Computerized Diagnostic Interview Schedule for Children (C-DISC) at the 5-year assessment and were included in the analyses for the present report.

Classification of Prenatal Drug Exposure

Prenatal cocaine exposure was determined by maternal self-report and/or at least one cocaine-positive biomarker, including maternal urine, infant urine, and meconium. Alcohol and tobacco exposures were determined by self-report, and cannabis exposure was indicated by self-report and/or a positive toxicology screen. Drug-free mothers had negative self-report drug histories during and for 3 months preceding pregnancy, negative life-time histories for cocaine use, and negative results on all available toxicology assays.

Maternal interview—Detailed postpartum maternal interviews were obtained regarding pattern and severity of drug and alcohol use before and during pregnancy by trimester, and included number of weeks used, usual days per week, and usual dose per day. Dosage was measured in number of cigarettes smoked, number of cannabis joints smoked, number of drinks of beer, wine or hard liquor, and number of cocaine lines/rocks, recorded in increments of usual daily dose, usual days per week, and number of weeks used. Standard definitions were used for determining 1-drink units for each type of alcohol (beer 12 oz., wine 5 oz., and liquor 1.5 oz.). Self-reported pregnancy exposure composites of amount of use were calculated for each drug by multiplying the number of weeks used by the usual days per week and the usual dose per day.

Biological markers—Screening of maternal and infant urine and infant meconium for cocaine metabolite (benzoylecgonine) was performed by EMIT® (Syva D.A.U.), at a cut-off of 150 ng/ml urine and 150 ng/gm meconium, respectively. Cocaine-positive specimens were confirmed by gas chromatography/mass spectrometry (GC/MS) (Mulé & Casella, 1988). Urine specimens were assayed by EMIT® for cannabis, opiates, amphetamines, barbiturates, benzodiazepines, and phencyclidine. Meconium specimens were assayed by EMIT® for cannabis and opiates. In the original cohort, 100% had at least one biological marker, 96% had at least two biologic markers, and 68% had all three biological markers available for analysis.

Procedures and Follow-up Measures

Maternal and child characteristics—At birth enrollment, detailed maternal interviews and hospital record reviews documented important medical and demographic characteristics. During the immediate postpartum period, research staff performed a standardized research interview and collected the biological specimens. Trained research personnel, blinded to drug exposure status, performed the Ballard gestational age assessment (Ballard, Novak, & Driver, 1979) within 36 hours of delivery and obtained occipital-frontal head circumference and recumbent crown-heel birth length. At each follow-up research assessment visit, the mother or primary caregiver was interviewed to obtain demographic information,

psychosocial history, and current maternal/caregiver drug use patterns. The caregiver demographic and drug use covariates included in the analyses were drawn from this structured interview.

DSM-IV diagnostic classification—Select modules from the Computerized Diagnostic Interview Schedule for Children (C-DISC, v2.3) (Shaffer et al., 1996) were administered to the caregiver by trained research associates blind to drug exposure status. The caregiver assessment at age five was extensive, therefore a subset of C-DISC modules was administered to limit response burden. Modules were selected for administration that represented emerging externalizing and internalizing disorders in early childhood that might be impacted by prenatal cocaine exposure. Attention-Deficit Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD), Separation Anxiety Disorder (SAD) are disorders that are usually first diagnosed in childhood or adolescence, and may be diagnosed during the preschool and early school years (American Psychiatric Association, 2000). Evidence supports the C-DISC as a reliable, valid, and inexpensive means of identifying psychiatric disorders and psychological symptoms in children and adolescents (Schwab-Stone et al., 1996; Shaffer et al., 1996).

Blood lead levels—At the 3- and 5-year follow-up visits, screening lead levels were performed by capillary sample and processed at the State of Florida Department of Health Laboratory. Abnormal capillary lead levels, i.e., $10 \mu\text{g/dL}$, were confirmed by repeat specimen obtained by venipuncture. The higher blood level at either visit was categorized dichotomously as <10 and $10 \mu\text{g/dL}$ and used as a single composite covariate in the analyses.

Statistical Analyses

Cumulative incidence proportions were estimated using STATA software (Statacorp, 2003). Under LogXact 8 with Cytel Studio software (Cytel, Incorporated, 2008) Cytel, Inc. LogXact 8 with Cytel Studio (http://www.cytel.com/Products/LogXact/LogXact_brochure.pdf web document last accessed 10 April 2008). A generalized linear regression model (GLM) allowed estimation of disorder risk, expressed as a function of a gradient of PCE, followed by statistical adjustment for each covariate, introduced as covariate terms one by one. The form of the GLM was that of binary logistic regression with a logistic link function to yield regression slope estimates that are interpretable as relative risk (RR) estimates. Initial data review procedures included visual inspection of frequency distributions for all variables under study. The regression models were restricted to a set of covariates specified in advance (child sex, age at exam, and prenatal exposures to alcohol, tobacco, and cannabis). This approach reveals individual covariates that might the effect estimate for prenatal cocaine exposure. The limited sample size (and collinearity of certain covariates) precluded concurrent statistical adjustment for all covariates in a single model. Variation in the CE-associated excess risk estimates across the several multiple logistic regression models is examined using the ‘change in estimate’ approach, with a forest plot used to convey the degree to which confounding might have occurred, as described by Wang (2007).

Results

Sample Characteristics

Attrition Information—A total of 415 children representing 87% of the original cohort (221 CE and 194 NCE) returned for the 5-year follow-up assessment. For all but 15 children, the caregiver completed a C-DISC assessment when interviewed, yielding 400 C-DISC assessments for this analysis. Estimation of bivariate associations as part of attrition analyses showed no differences in missing C-DISC data between CE and NCE children. Children with complete C-DISC data were also not different from children with incomplete data on key demographic variables including maternal age, employment and marital status at birth, number of prenatal care visits, birth weight, length, or head circumference, gestational age, or sex of the child. Caregivers who attended and completed the C-DISC did differ in years of education (C-DISC completers: 11.2, ± 1.4 ; C-DISC non-completers: 11.5 ± 1.6 ; $p = .036$).

Sample Descriptive Information—Tables 1 and 2 present a description of selected maternal and infant characteristics at birth for the 400 children included in the present report. Cocaine-using mothers were older, were less often employed, and utilized less prenatal care than non-cocaine-using mothers. CE infants had slightly shorter mean length of gestation and were smaller in birth weight, length and head circumference than NCE infants. A higher percentage of cocaine-using mothers reported prenatal use of alcohol, tobacco, and cannabis. Among cigarette smokers, cocaine-using mothers also smoked a higher mean number of cigarettes. Table 3 depicts selected social and demographic characteristics of the primary caregiver measured at the 5-year assessment and child characteristics measured during the preschool assessment visits. CE children were less likely to be in the primary care of the biological mother and were more likely to have a caregiver reporting ongoing drug use. CE children also had higher blood lead levels and were less likely to have attended a preschool or Head Start program.

Risk for Developing a DSM-IV Disorder

Analyses of amount of maternal self-reported PCE and other drug exposures in relation to DSM-IV Disorders—Analyses for each disorder began with a base model that included the prenatal cocaine exposure composite (calculated by multiplying the number of weeks used by the usual days per week and the usual dose per day based on maternal report at birth). Initial analyses of the ODD ($n=21$) and SAD ($n=6$) diagnoses were null, indicating no cocaine-associated increase in risk for developing either disorder. Accordingly, no further covariate modeling was conducted for these diagnostic outcomes.

A total of 12 children had developed ADHD by the time of the age five study visit. Figure 1 presents a ‘forest plot’ that conveys the RR estimate based upon the initial GLM binary logistic regression model in which the odds of ADHD are expressed in relation to the number of cocaine lines/rocks consumed by the mother during pregnancy, as well as the covariate-adjusted RR estimate derived by introducing covariate terms, one at a time. The 95% confidence intervals and p-values are based upon exact methods, due to the small numbers of ADHD cases in this sample. The forest plot approach permits visual inspection of the degree to which each covariate might be confounding the RR estimate. These results

can be summarized as follows: (1) There is a cocaine-associated increased risk of ADHD in relation to the gradient of PCE such that each additional unit increase in the level of PCE is associated with a modest but statistically robust 1.0002-fold increase in ADHD risk (i.e., unadjusted RR estimate = 1.0002; 95% confidence interval, CI = 1.00001, 1.0004; exact $p = 0.038$). (2) Covariate adjustment yields either modest or no attenuation of this initial RR estimate. For example, with covariate adjustment for both child's sex and prenatal tobacco exposure, the original unadjusted RR estimate shifts modestly leftward toward the null (RR = 1.0001), but the covariate-adjusted RR has a 95% lower confidence bound that remains larger than the null value. (3) There was no attenuation of the cocaine-associated relative risk of ADHD when prenatal exposures to other drugs were controlled under this model.

Categorical analyses of cocaine and other drug exposures—We also estimated cumulative incidence proportions for each disorder, stratified by a binary cocaine exposure variable (exposed versus non-exposed). Cumulative incidence proportions and estimated risk ratios for CE and NCE children are reported in Table 4. As noted, when considering only presence versus absence of PCE we found no CE-associated increase in risk for any of the DSM-IV disorders (Table 4). Results did not change with covariate adjustment for age, sex, or prenatal exposures to alcohol, marijuana, and tobacco. Maternal-reported alcohol, tobacco, and cannabis use during pregnancy were also not independently related to increased risk for any of the three diagnostic conditions under study, although prenatal cannabis exposure approached conventional significance (RR = 1.27, 95% CI = 0.98, 1.56; $p = 0.06$).

Multiple diagnoses were rare; only 3 children qualified for more than one diagnosable disorder. Accordingly, further group difference analyses and covariate modeling were not conducted, although male-female subgroup variations were explored. Boys were more likely to have developed ADHD as compared to girls, but for both boys and girls, separately, there was no evidence of male-female subgroup variation in the size of the slope estimate linking PCE to DSM-IV disorders. Quantified via estimated cumulative incidence proportions and relative risk values, the male-female variation in ADHD risk was as follows: (a) risk of developing ADHD for boys: 4.98%, and for girls 1.01%; estimated relative risk = 5.1; Fisher's exact $p = 0.04$; 95% CI = 1.07, 48.8).

Discussion

This study found a modest but statistically robust increase in risk for being diagnosed with ADHD in relation to gradient levels of maternal-reported cocaine use during pregnancy, a finding that was not evident in the analyses of group differences between children with and without prenatal cocaine exposure histories. Given the overall small number of cases of ADHD identified in this sample at age five, however, these results should be considered preliminary until replicated by other studies. These findings underscore the importance of studying prenatal drug exposures in relation to levels or degree of exposure, and not just in relation to exposed versus non-exposed subgroups. One might posit a conceptual model in which there is a threshold level of exposure to cocaine prenatally, below which there is no excess ADHD risk and above which there is an increased risk. The number of ADHD cases in this sample was too small to permit conclusions about this type of threshold model. Risk for ODD and SAD was not related to PCE in any of the analytic models, and the estimated

occurrence of DSM-IV disorders in all categories was infrequent, as might be expected given the young age of the children being assessed. Observed rates of occurrence in the current study sample were generally consistent with prior research on samples of preschool-aged children, but tended to be at the lower end of the range of previously published rates. For example, Egger and Angold (2006) reviewed several pediatric and community preschool samples and reported rates for ADHD ranging from 2-5.7%, ODD 4-8%, and 0.3-5% for SAD. Consistent with much of the available research, boys in the study cohort, irrespective of drug exposure status, were substantially more likely than girls to have developed ADHD.

While not the focus of the current study, analyses of alcohol, tobacco, and marijuana exposure indicated no statistically robust independent contribution to risk for developing the disorders studied, although marijuana approached conventional significance. Prenatal exposure to alcohol, tobacco, and marijuana have been independently linked in some studies to ADHD and conduct symptoms in children (Burd et al., 2003; Goldschmidt, Day, & Richardson, 2000; Kotimaa et al., 2003; Linnet et al., 2003; Mick et al., 2002; and Rodriguez & Bohlin, 2005). Between-study discrepancies might be traced back to differences in diagnostic assessments, or possibly to between-sample differences in the gradient of prenatal substance exposures and other sample-specific variation.

Parent-report measures, used frequently in both research and clinical assessments, can yield valuable information regarding child behavioral functioning but are not without limitations. Parent questionnaires offer only one perspective of the child's behavior, and ratings may be influenced by other factors such as parental psychological functioning and social desirability (Chilcoat & Breslau, 1997; Merydith, Prout, & Blaha, 2003). In this study cohort at ages five and seven, children with PCE were rated by examiners as having more behavioral regulation difficulties during structured testing (Accornero et al., 2006b; Accornero et al., 2005), while parent report on the Achenbach Child Behavior Check List at the same age points found no cocaine-related differences in internalizing or externalizing symptoms (Accornero et al., 2006a; Accornero et al., 2002). Other researchers have also noted cocaine-associated attention deficits, impulsivity, and behavior problems based on examiner ratings (Richardson, 1998), child self-report (Linares et al., 2006), and a teacher-report questionnaire (Delaney-Black et al., 2004).

Performance decrements in attention processing in children with PCE, assessed by computerized measures and laboratory tasks, have also been noted in other studies, including findings from our own study cohort (Accornero, Amado, Morrow, Xue, Anthony, & Bandstra, 2007; Bandstra, Morrow, Anthony, Accornero, & Fried, 2001b; Bendersky & Lewis, 1998). Published results from this study cohort have documented 5 to 6 point increases in omission errors and slower reaction times in CE children when compared to NCE children at ages 5 and 7 (Accornero et al., 2007; Bandstra et al., 2001b). These findings suggesting a cocaine-related impact on sustained attention processing abilities that may manifest as a diagnosable disorder only at higher exposure levels. Findings such as these also relate the importance of conducting multi-modal assessments when assessing child emotional and behavioral functioning in at risk populations.

The current study cohort included African-American children born full-term and residing in socially disadvantaged inner-city neighborhoods. The homogeneity of the study sample resulted in decreased variability on many of the demographic, health, and social conditions that might influence child development, increasing the study's capacity to draw conclusions when evaluating multi-determined, complex child outcomes. Generalization of the current reports findings to other age ranges, samples or more diverse populations is uncertain; confirmations and replication studies by others are needed. The mechanisms by which cocaine influences child development may differ in samples of children with more varied risk levels, different racial/ethnic backgrounds, or who were born prematurely or with other health conditions. Finally, the present study design benefited from extremely thorough methods for assessing prenatal drug exposure status, including the collection of both urine and meconium samples, and the use of both self-report and bioassay methodologies to validate exposure status. Despite these state-of-art methodologies, it is possible that misclassification errors in exposure status may have occurred, possibly affecting the study's capacity to yield unbiased cocaine effect estimates.

Notwithstanding limitations such as these, the current study findings suggest some guidelines for future research. For example, it is interesting to see no real difference in occurrence rates of ADHD when PCE is expressed in binary form (exposed versus non-exposed), but to find a modest but statistically robust cocaine-associated deficit when the gradient of PCE is considered. Furthermore, there will be clear advantages when multiple informants (e.g., blinded independent examiner-raters; knowledgeable caregivers) are used in the assessment of neurobehavioral and psychiatric outcomes.

The psychopharmacological mechanisms of PCE suggest several routes of viable teratogenic influence on fetal neurodevelopment that might impact behavioral regulatory systems. Nonetheless, studies relying on parent report measures have not been consistent in documenting an increased risk for behavioral or emotional difficulties related to PCE. Data from studies relying on examiner ratings, laboratory tasks, and teacher or child-self reports are more suggestive of an impact on emotional and behavioral regulation, but clearly further studies are needed to determine the clinical implications of such findings. As the line of research on PCE moves in the direction of studies on diagnosable conditions of clinical importance (e.g., ADHD), there is an increment in complexity because these conditions are best understood in relation to component cause models where no individual causal influence is apt to be 100% sufficient and necessary. The causal influences on behavioral and emotional disorders in early childhood clearly are complex and multi-faceted. Current evidence supports an ecological perspective: children appear to be at greater risk for developing these disorders when the component cause models are extended to include community contextual determinants and environmental conditions in the home environment that might be cumulative in their effects (Atzaba-Poria, Pike, & Deater-Deckard, 2004; Garnezy & Rutter, 1983)

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Figure 1.

Forest plot of statistically robust estimates for a gradient of prenatal cocaine exposure, with statistical control for child's sex, alcohol, tobacco and marijuana exposure, and an interaction term for child's sex and tobacco exposure ($n = 400$).

Table 1Maternal and infant characteristics at birth ($n = 400$)

Maternal characteristics	Non-exposed (n=192)	Exposed (n=208)
Maternal age (years)	23.8 (5.4)	28.9 (4.8)
Education (years)	11.2 (1.36)	11.1 (1.40)
Unemployed **	83.3% (160)	94.7% (197)
Never married	88.0% (169)	91.4% (190)
Prenatal care C4 visits **	83.3% (160)	69.7% (145)
<i>Infant characteristics</i>		
Birth weight (gm) **	3309 (494)	2961 (491)
Birth length (cm) **	50.8 (2.3)	48.8 (2.5)
Birth head circumference (cm) **	33.8 (1.5)	33.0 (1.6)
Gestational age (wks) **	39.7 (1.4)	39.4 (1.4)
Male (%)	51.6% (99)	49.0% (102)

Note: Maternal and infant characteristics are expressed as mean (standard deviation) or percentage (numerator n) where (%) is indicated

* $p < 0.05$

**
 $p < 0.01$

Table 2Maternal self-reported drug use during pregnancy ($n = 400$)

	Non-cocaine-exposed ($n = 192$)		Cocaine-exposed ($n = 208$)	
	Median dosage (Min, Max)	Reporting use % (n)	Median dosage (Min, Max)	Reporting use % (n)
Alcohol (# drinks) ^b	57 (2, 1680)	31.3% (60)	97 (1, 5226)	66.8% (139)
Tobacco (# cigarettes) ^{a, b}	854 (3, 5880)	16.7% (32)	2282 (1, 8820)	76.0% (158)
Marijuana (# joints) ^b	32 (1, 807)	12.0% (23)	24 (1, 1229)	43.3% (90)
Cocaine/crack(# lines/rocks)			127 (1, 19320)	70.2% (146)

Note: Maternal substance use is expressed as median (min/max) due to skewed distributions. Median values were based only on mothers who reported/acknowledged drug use at birth within the sub-sample of 400 children; drug use composites were calculated as follows: (number of weeks used) 9 (usual number of days per week) 9 (usual dose per day)

^a $p < 0.05$, between group comparison of median maternal drug use (columns 1 and 3)

^b $p < 0.01$, between group comparison of percentage reporting drug use (columns 2 and 4; all p -values were < 0.01 for these comparisons)

Table 3Child and caregiver characteristics ($n = 400$)

	NCE (n=192)		PCE (n=208)	
	<i>n^a</i>	<i>Result</i>	<i>n^a</i>	<i>Result</i>
<i>Assessed at 5-year research visit</i>				
Child's examination age (months)	192	66.1 (2.4)	208	65.9 (2.4)
Biological mother as caregiver **	191	95.8% (183)	205	67.8% (139)
Caregiver education (years)	189	11.5 (1.5)	201	11.2 (1.8)
Caregiver unemployment	189	60.9% (115)	201	65.7% (132)
Caregiver past year cocaine use **	188	2.1% (4)	200	21.5% (43)
Caregiver past year marijuana use **	188	16.0% (30)	200	27.0% (54)
Caregiver past year alcohol use	189	64.6% (122)	198	60.6% (120)
Caregiver past year tobacco use **	188	22.3% (42)	199	55.8% (111)
Head Start/Prekindergarten *	188	68.6% (129)	201	58.7% (118)
Child blood lead C10 lg/dl * (@ 3 or 5 years)	192	7.8% (15)	208	14.9% (31)

Notes: Child and caregiver characteristics are expressed as means (standard deviations) or percentages (n)

* $p < 0.05$ for between group comparisons

** $p < 0.01$ for between group comparisons

^a Group n 's for covariates are drawn from children who attended the 5-year follow-up with available DSM-IV scores ($n = 400$) and had the associated covariate data available

Table 4

Estimated cumulative incidence proportions and cocaine-associated risk for developing a DSM-IV disorder (binary contrast of CE versus NCE children; $n = 400$)

	ADHD % (<i>n</i>)		ODD % (<i>n</i>)		SAD % (<i>n</i>)	
Estimated cumulative incidence for CE children	2.9% (6)		4.3% (9)		1.4% (3)	
Estimated cumulative incidence for NCE children	3.1% (6)		6.8% (13)		1.6% (6)	
	Est. risk ratio	95% CI	Est. risk ratio	95% CI	Est. risk ratio	95% CI
Unadjusted model for cocaine-associated risk	0.9	0.2, 3.5	0.6	0.2, 1.6	D.9	0.1, 7.D

Note: 95% CI are based upon exact methods. All models yielded modest relative risk estimates that were not statistically robust. See Figure 1 for statistically robust estimates based upon an alternative specification for the gradient of prenatal cocaine exposure.