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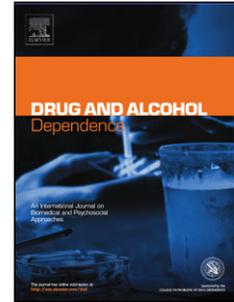
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The association of prenatal cocaine exposure, externalizing behavior and adolescent substance use

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Highlights

- Prenatal cocaine exposure (PCE) may increase adolescent substance use

- Externalizing behavior mediated PCE effects on tobacco and substance abuse disorder

- Effects of PCE on marijuana use was more pronounced for boys than girls

- Exposure to violence was also related to increased teen substance use

Abstract

Prenatal cocaine exposure (PCE) may increase adolescent substance use through alterations of neurotransmitter systems affecting fetal brain development. The relationship between PCE and substance use at 15 and 17 years was examined. Subjects (365: 186 PCE; 179 non-cocaine exposed (NCE)) supplied biologic and self-report data using the Youth Risk Behavior Surveillance System (YRBSS) and Computerized Diagnostic Interview Schedule for Children (C-DISC 4) at ages 15 and 17. The relationship between PCE and substance use was assessed using General Estimating Equation (GEE) analyses controlling for confounding factors including violence exposure and preschool lead level. Teens with PCE vs. NCE teens were 2 times more likely to use tobacco (OR=2.1; 95% CI 1.21-3.63; p<.001) and marijuana (OR=1.85; CI 1.18-2.91; p<.001) and have a substance use disorder at age 17 (OR=2.51; CI 1.00-6.28; p<.05). Evaluation of PCE status by gender revealed an association between PCE and marijuana use that was more pronounced for boys than girls at 17 years. Violence exposure was also a significant predictor of alcohol (p<.001), tobacco (p<.05), and marijuana (p<.0006) use and substance abuse/dependence (p< .01). Externalizing behavior at age 12 fully mediated the effects of PCE on substance use disorder at age 17 and partially mediated effects of PCE on tobacco use, but did not mediate effects on marijuana use. The percentage of substance use reported increased between 15 and 17

years, with no differences between the PCE and NCE groups. Data suggest specialized drug use prevention measures for children with PCE may benefit this high risk group.

Keywords:

Prenatal Cocaine, Adolescent, Substance Use, Externalizing

1. I**ntroduction**

Adolescent substance use is a significant concern in the United States, with 6.5% of 12th graders reporting daily marijuana use (Johnston et al., 2014), 1.0% of 12-17 year-olds reporting five or more drinks at one time at least five days during the past 30 days (Center for Behavioral Health Statistics and Quality, 2015) and 20.8% of high school students reporting binge drinking five or more drinks in a row on at least one day in the past 30 days (Kann et al., 2014). In 2014, the national rate of past year substance use disorder for adolescents aged 12-17 was estimated to be 5%, with 2.7% of youth aged 12-17 having an alcohol use disorder and 3.5% having an illicit drug use disorder (Center for Behavioral Health Statistics and Quality, 2015). Earlier initiation of substance use for children and adolescents is associated with a number of problems including academic failure (Yule AM and Prince JB, 2012), not attending or completing college (King et al., 2006), and risk for development of a substance use disorder later in life (Substance Abuse Mental Health Services Administration (SAMHSA), 2013).

Problematic substance use is regarded as multi-causal and children born with prenatal cocaine-exposure (PCE) often have more risk factors than those with no PCE. Risks specific to children with PCE include direct teratological effects of cocaine on the developing brain and self-regulatory systems (King et al., 2006; Nigg et al., 2006; Thompson et al., 2009; Zucker et

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al., 2011; Yule and Prince, 2012; Substance Abuse Mental Health Services Administration (SAMHSA), 2013; Kann et al., 2014; Johnston et al., 2014), genetic transmission of substance use traits (Agrawal and Lynskey, 2008), and/or accumulation of negative environmental experiences such as exposure to violence (Lynskey et al., 2010).

1.1 Prenatal Cocaine Exposure and Adolescent Substance Use

Prenatal cocaine exposure is hypothesized to have direct teratologic effects on fetal brain development via cocaine induced hypoxia resulting from vasoconstriction in uterine and placental blood vessels (Malanga and Kosofsky, 1999) and negative effects on monoamine neurotransmitter functions of the developing fetal brain (Kosofsky et al., 1994; McCarthy et al., 2014). Evidence suggests that PCE alters prenatal responses to stress in reaction to environmental insults (Lester and Padbury, 2009). The combination of these early alterations in brain development can result in pervasive, subtle developmental problems of self-regulation, including executive functioning deficits, behavioral problems and poor impulse control (Singer et al., 2008; Thompson et al., 2009; Minnes et al., 2010; Minnes et al., 2014).

Existing research on adolescents who have experienced PCE has found that they are about 2-3 times more likely to use substances or develop substance use problems than their non-cocaine exposed peers. At age 14, adolescents with PCE were twice as likely to use cocaine as non-exposed teens (Delaney-Black et al., 2011). Fifteen-year olds with PCE were found to be 1.8 times more likely to have early initiation of alcohol or marijuana use (Richardson et al., 2013), about twice as likely to have used alcohol, marijuana, or tobacco at age 15 (Minnes et al., 2014), and 2.8 times more likely to have problems related to substance use than their non-exposed peers (Min et al., 2014b). The risk of developing problematic substance use appears to increase with the amount of prenatal exposure the adolescent experienced (Frank et al., 2011). To our

knowledge no studies have looked beyond adolescent substance use among youth with PCE to examine the percentage of those who meet diagnostic criteria for substance use disorders.

1.2 Externalizing Behavior as a Mediator of Cocaine's Association with Adolescent Substance Use

There is converging evidence that an indirect pathway to adolescent substance use among children with PCE may occur through increased externalizing behavior. Externalizing typically refers to overt behavior problems that involve impulsivity and insufficient self-regulation of behavior or emotion, but can also be considered broadly as a neurodevelopmental style of self-regulation and learning that is more responsive to environmental than internal influences (Tucker et al., 2015). PCE has been associated with increased behavioral dysregulation throughout infancy and early childhood, and increased externalizing, disruptive, and risk-taking behaviors through middle childhood and into adolescence (Richardson et al., 2011; Lambert and Bauer, 2012). Problems with poor inhibitory control can manifest in behaviors that show impulsivity and poor judgment for adolescents with PCE. Examples of such behavior include earlier initiation of sexual activity (De Genna et al., 2014; Min et al., 2015), more engagement in risky sexual behavior (Min et al., 2016), and more damage, theft, and status offenses by age 15 (Richardson et al., 2015) than non-exposed adolescents.

Relatively few studies have examined the mediating effect of externalizing behavior in the relationship between prenatal cocaine exposure and teen substance use. Only the Maternal Life Style (MLS) study reported that childhood externalizing problems mediated the effects of PCE on the risk of initiating use of any substance by age 16 (Lester et al., 2012). Other studies have found direct relationships between PCE and increased risk of problematic substance use. However, they have either not directly examined the mediating effects of externalizing behaviors

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(Frank et al., 2011; Warner et al., 2011; Richardson et al., 2013) or have not found a significant mediating effect (Frank et al., 2011; Warner et al., 2011; Richardson et al., 2013). Additional investigation is warranted to clarify a potential pathway to substance use among prenatally drug exposed teens.

Differential relationships based on gender may exist between PCE and externalizing behaviors, as some studies have found boys with PCE to have higher levels of externalizing behaviors than girls (Greenwald et al., 2011; Bennett et al., 2013), while others have found only girls with PCE report more externalizing (Minnes et al., 2010; McLaughlin et al., 2011) and risk taking behaviors (Min et al., 2015). Increased levels of PCE are also linked to lower caregiver ratings of executive functioning at age 12 in girls but not boys, indicating dysfunction in the areas of the brain related to judgment and behavioral regulation (Minnes et al., 2014). To date, it is not clear how gender may interact with PCE to predict adolescent substance use.

1.3 Other Prenatal Drug Exposure and Environmental Covariates

Children with PCE also have higher levels of prenatal exposure to other drugs of abuse, including alcohol, opiates, and tobacco (Singer et al., 2000). These additional prenatal drug exposures have been associated with both neurobehavioral regulatory problems and increased risk of substance use in adolescence (Glantz and Chambers, 2006).

Environmental influences can constitute up to 70% of the variation in initiation and problematic substance use (Lynskey et al., 2010) and are important to consider when evaluating the association of PCE and substance use. A potent negative environmental influence, violence exposure, has been associated with early initiation of alcohol use (Taylor and Kliewer, 2006; Bossarte and Swahn, 2008), marijuana use (Mason, 2010; Richardson et al., 2013), cocaine use (Delaney-Black et al., 2011), and general substance use (Pinchevsky et al., 2014) for adolescents.

Repeated exposure to violence is reported to set the stage for greater rates of substance abuse and other mental and physical health problems later in development (Moffitt, 2013). There is also existing evidence that violence exposure is a contributing factor to substance abuse after accounting for PCE (Frank et al., 2014; Minnes et al., 2014).

Additionally, *post*-natal exposure to ongoing substance use by household members for children with PCE has been associated with a nearly six-fold increase in risk of problematic adolescent substance use (Frank et al., 2014). Furthermore, PCE and caregiver current substance use were both found to independently predict adolescent cocaine use by 14 years (Delaney-Black et al., 2011). Elevated blood lead levels, which often co-occur within low socioeconomic status households and, therefore, at high rates in our sample (Min et al., 2009), are also associated with increased risk of behavioral problems in childhood through early adulthood in the general population (Wasserman et al., 1998; Burns et al., 1999; Lane et al., 2008; Wright et al., 2008), and were found to be related to alcohol use in adolescents with PCE (Minnes et al., 2014). Other caregiver characteristics known to independently influence behavioral outcomes include caregiver psychological distress, receptive vocabulary skills, non-verbal reasoning ability and quality of the home environment (Bennett et al., 2008; Singer et al., 2008; Singer et al., 2015). Generally, poor environmental and socioeconomic conditions are often prevalent among parents with substance use disorders and are important factors to consider in evaluating the relationship between PCE and teen substance use. These multiple factors have rarely been evaluated simultaneously in a large well-defined prospective sample.

1.4 Purpose and Hypotheses

The purpose of the current study advances previous research by aiming to better understand the relationship between PCE and substance use patterns in the teen years, controlling

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for important confounders including early elevated lead levels and exposure to violence that often co-occur in low socioeconomic households and influence behavioral outcomes. We hypothesize that PCE will be associated with substance use, defined as use in the past 30 days, at ages 15 and 17 years, and with diagnoses of substance use disorders at age 17 based on self-report. Gender by PCE interactions will be explored based on previous behavior differences found in this cohort (Minnes et al., 2010) as well as general findings of differences in patterns of drug use by gender (Becker et al., 2016). In addition, externalizing behaviors are expected to mediate PCE's relationship with current adolescent substance use.

2. Method

2.1. Sample

The study sample consisted of 365 adolescents (186 PCE, 179 NCE) who were followed prospectively from birth and assessed for substance use at ages 15 and 17 years. The participants and their birth mother were recruited between September 1994 and June 1996 from a large urban teaching hospital in the Midwest for a longitudinal investigation of the developmental effects of prenatal cocaine exposure.

Drug toxicology screens were administered to 647 mothers and infants at delivery who were identified to be high risk. Hospital policy specified operational criteria for detecting pregnant women suspected of substance use: lack of prenatal care, maternal behavior suggesting intoxication, self-admitted drug use, or a history of involvement with the Department of Children and Family Services. Maternal and infant urine specimens were collected immediately before or after delivery to screen for metabolites of cocaine and other illicit drugs, including opiates, cannabinoids, phencyclidine, amphetamines, and benzodiazepines. Urine specimens were

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analyzed using the Syva Emit method (Syva Company, Palo Alto, California), followed by gas chromatography for the confirmation of presumptive positive test results (Singer et al., 2002). Infant meconium collected by the research staff was further analyzed for cocaine and metabolites of other drugs, including cocaethylene, benzoylecgonine, and meta-hydroxybenzoylecgonine. Identification of prenatal cocaine exposure (PCE) was based on either positive results of biologic indicators (i.e., maternal and infant urine or infant meconium) or maternal self-report of cocaine use during pregnancy to medical or research staff. Non-cocaine-exposed status (NCE) was assigned if all screening measures on cocaine were negative. The NCE group, however, may have been exposed to alcohol, tobacco, and/or marijuana.

During the screening procedure for eligibility, 54 mother-infant dyads were excluded due to confounding conditions that might obscure the effects of PCE: maternal age less than 19 years (2); primary heroin use (2); maternal psychiatric history of severe depression, bipolar disorder or schizophrenia (16); maternal low intellectual functioning (1); maternal chronic illness (4); HIV positive status (5); lack of meconium (15); fetal alcohol syndrome (1); infant Down syndrome (2); infant illness (3); and other (3). Of the 593 eligible mothers, 415 (218 PCE, 197 NCE) consented for participation in the study, whereas 155 mothers (49 PCE, 106 NCE) refused to participate and 23 mothers (9 PCE, 14 NCE) were not present for the enrollment interviews. Since enrollment, 12 children (9 PCE vs. 3 NCE, $X^2 = 2.50$, $p = .11$) died from sudden infant death syndrome (4 PCE, 2 NCE), respiratory distress syndrome (1 PCE, 1 NCE), cardiopulmonary arrest (1 PCE), pneumonia (1 PCE), accidental asphyxia (1 PCE), and unknown illness (1 PCE). The present study used data from 365 adolescents who completed drug use assessments at ages 15 ($n=358$) and/or 17 ($n = 350$), representing 91% retention of the 403 active, living participants in the original study.

No difference was found by PCE status between the 365 participants and the 38 nonparticipants (20 drop-out, 17 lost contact, 1 low intellectual functioning (IQ < 50)), except that the participants were more likely to be African American ($p < .008$). Of the 365 adolescents who had substance use data, the 186 participating adolescents with PCE had caregivers with higher nonverbal reasoning ability than the 23 adolescents with PCE who did not participate ($p < .0002$). The 179 participating non-exposed adolescents were more likely to be African American ($p < .02$), have birth mothers who were younger ($p < .02$), less likely to have been married ($p < .02$), and had less years of education ($p < .04$) compared with the 15 non-exposed adolescents not included in the study.

2.2. Procedure

The Institutional Review Board of the participating hospital reviewed and approved all research procedures. The initial screenings and enrollment were performed in the hospital. The longitudinal follow-up assessments were conducted at the university-based developmental research lab at subject ages 6, 12, and 18 months and 2, 4, 6, 9, 10, 11, 12, 15, and 17 years. Parents or caregivers provided signed informed consent at each visit. Written assent was obtained from youth beginning at age 9. The consent document included a Certificate of Confidentiality number (DA-98-91) issued by U.S. Department of Health and Human Services, protecting the release of drug-related information. At each follow up visit, a trained research assistant blind to cocaine exposure status administered the cognitive and behavioral assessment protocol to the youth. A different research assistant administered caregiver interviews privately. As part of the 15- and 17-year assessments, adolescents were referred to the affiliated hospital's National Institute of Health (NIH) supported Clinical Research Unit for collection of biologic specimens (i.e., urine, hair, and/or bloodspots) by trained research nurses. All participants were

compensated with a monetary stipend and given lunch; transportation costs were provided if needed. For the 15 and 17 year assessments each subject received $100 compensation, with an additional $10 if they provided a biological specimen for drug use screening.

2.3. Measures

2.3.1. Prenatal exposure to cocaine and other substances.

All biologic mothers of subjects had a retrospective (during pregnancy and 1 month prior) assessment of prenatal substance use patterns immediately post-partum. For cocaine, the number of approximately $20 "rocks" used and/or the amount of money spent per day were collected, which was converted to a standard "unit" of cocaine equivalent to 1 rock and/or $20 worth of cocaine. For alcohol, the number of drinks of beer, wine, or hard liquor consumed was recorded, with each drink equivalent to 0.5 oz. of absolute alcohol. The number of tobacco cigarettes smoked per day and the number of marijuana joints smoked per week were also acquired. Frequency of substance use was rated on a Likert-type scale with a range from 0 (not at all) to 7 (daily use), with data summarized to indicate the average number of days of substance use per week. Frequency was multiplied by the amount of use per day to yield summary measures of average cocaine units (per week), alcohol drinks (per week), cigarettes (per day), and marijuana joints (per week) used during each trimester of pregnancy and the month prior to conception and then averaged over the pregnancy. The substance use assessment was updated with the adolescent's current caregiver at each follow-up visit to assess caregiver substance use during the last 30 days.

2.3.2. Adolescent Substance Use Outcomes.

Adolescent's substance use was assessed at ages 15 and 17 using self-report data and biologic samples. Self-reported alcohol, tobacco, and marijuana use in the past 30 days were

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measured using the Youth Risk Behavior Surveillance System (YRBSS) (Centers for Disease Control and Prevention, 2009). Biologic specimens of urine, hair, and/or bloodspots were collected with the assistance of research nurses from the university's NIH-funded Clinic Research Unit. Analysis of adolescent biologic assays for drug metabolites of amphetamines, benzodiazepines, cocaine, opiates, cannabinoids, cotinine, and ethyl glucuronide was performed by the United States Drug Testing Laboratory (USDTL) (Minnes et al., 2014). Adolescents who were positive on any one self-report data or biologic sample for a particular substance were assigned a positive code (1 = yes) for that substance. Adolescents who were positive on any one substance were also coded positive (1 = yes) for a measure of "any substance use."

Adolescent's substance abuse and dependence symptoms were self-reported at age 17 via the Computerized Diagnostic Interview Schedule for Children IV (C-DISC 4) (Shaffer et al., 2000). C-DISC 4 is a reliable and valid structured interview that measures DSM-IV diagnoses for children and adolescents ages 9 to 17. This investigation used alcohol abuse and dependence, nicotine dependence, and marijuana abuse and dependence data from the C-DISC 4 sections on substance use disorders.

A summary variable of the number of symptoms scored positive was used as the C-DISC 4 measure of each substance use disorder. A cut-off of one or more out of the four symptoms without presence of dependence was used for a diagnosis of a substance abuse (Shaffer et al., 2000; First and Ross, 2000). A cut-off of three or more out of the seven symptoms for each substance was employed for a diagnosis of dependence for that particular substance (Shaffer et al., 2000). Adolescents who were diagnosed with either abuse or dependence on a substance were coded 1 (yes) for a composite abuse/dependence variable for that substance. Adolescents who were diagnosed with any one substance abuse/dependence were coded 1 (yes) for an "any

substance abuse/dependence" variable.

2.3.3. Externalizing Behavior.

Externalizing behavior was assessed at age 12 using the Youth Self-Report (YSR) (Achenbach and Rescorla, 2001). The YSR is a commonly used adolescent self-report measure consisting of 105-items designed to assess emotional, behavioral and social problems in the last 6 months. *T*-scores of externalizing summary score (i.e., aggression and rule-breaking behavior) that were standardized for gender and age were used for this investigation. Higher scores indicated more problem behaviors with internal consistency (Cronbach's α) of .87.

2.3.4. Adolescent, Maternal, and Caregiver Variables.

Infant and maternal demographic and medical characteristics were obtained from hospital birth records. Included were infants' gender and race, gestational age, birth weight, height, and head circumference as well as maternal age at delivery, parity, and number of prenatal care visits. Maternal education and work history, family composition, and socioeconomic status based on Hollingshead score of IV or V (Hollingshead, 1957) were added via post-partum research interviews. At each follow-up interview, time dependent information was updated, including the child's placement (with either biological mother/relative or adoptive/foster caregiver) and shifts, if any, in placement, determined by a change in both primary caregiver and physical setting lasting greater than one month. Concurrent assessment of current caregivers' receptive vocabulary, non-verbal reasoning ability, psychological distress, and recent drug use were also obtained.

At infant birth, maternal and/or current caregiver receptive vocabulary and nonverbal reasoning ability were assessed using the Peabody Picture Vocabulary Test-Revised (PPVT-R)

(Dunn et al., 1997) and two subscales—Picture Completion and Block Design—of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981). Maternal and/or current caregiver self-reported psychological distress was assessed using the Global Severity Index (GSI), a summary measure on the Brief Symptom Inventory (BSI) (Derogatis, 1992), at birth. At the 15 year follow-up visit, the quality of the caregiving environment was assessed using an interview format of the Home Observation for Measurement of the Environment Inventory-Early Adolescent version (EA-HOME; $\alpha = .83$) (Caldwell and Bradley, 2003).

At 2 and/or 4 years, blood lead level was assessed for a subset of children ($n = 294$). At age 12, violence exposure was assessed using the Assessment of Liability and Exposure to Substance Use and Antisocial Behavior (ALEXSA) (Ridenour et al., 2009). The ALEXSA is an illustration-based, computerized, audio self-report measure of substance use, antisocial behavior and associated risk factors for children ages 9 to 12. The ALEXSA violence exposure subscale is composed of 8 items representing ever experiencing or witnessing violence, including a beating, a robbing or mugging, and a stabbing or shooting ($\alpha = .75$). Items were rated on a 5-point Likert scale ($0 = 0$ times to $5 = 5$ times or more) and averaged to form a composite violence exposure variable, with higher scores indicating more exposure to violence. At age 15, adolescents' intelligence was assessed by an examiner unaware of the youth's prenatal cocaine exposure status and trained by a licensed child clinical psychologist using the full Wechsler Intelligence Scales for Children-Fourth Edition (Wechsler, 2003).

2.4. Data Analyses

Study variables that followed a positively skewed distribution were normalized using log transformation prior to analyses. Univariate distributional characteristics were reported based on the original data, with transformations used in bivariate and multivariate analyses. Adolescent

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demographics and maternal and current caregiver characteristics were compared by PCE status using *t*-tests or the Wilcoxon-Mann-Whitney test for continuous variables. The Chi-square tests or Fisher's Exact test were employed for categorical variables. Zero-order Pearson correlations were estimated to examine relationships between observed variables. The associations of PCE with alcohol, tobacco, and marijuana use were assessed at 15 and 17 years using Generalized Estimating Equation (GEE) modeling procedures for correlated binary outcomes with logit link (Liang and Zeger, 1986). Since the number of adolescents who had confirmed substance abuse or dependence for alcohol, nicotine, and marijuana by 17 years was small (Table 3), logistic regression was only completed on use of any one substance.

Covariates correlated ($p \leq .2$) with each substance outcome for at least onetime point and different by PCE status ($p \leq .2$) were assessed one-by-one for possible inclusion in the multivariate models for each outcome variable. Covariates that were significant at an alpha of .10 or that changed the estimate for PCE by 10% were retained in the model. A gender by PCE interaction term was created and entered into the model last to examine interaction effects. Mediation was evaluated based on the logic of Baron and Kenny (Baron and Kenny, 1986). Since our previous study established PCE effects on self-reported externalizing behavior at age 12 (Min et al., 2014a), multivariate models were specified independent of and then with earlier externalizing behavior. If the PCE effects on adolescent substance outcomes were markedly reduced with statistical control for externalizing behavior at age 12, significance of the mediated effect was evaluated using the PRODCLIN program (MacKinnon et al., 2007). Adolescent gender was tested for interaction with PCE status. All analyses were conducted using SAS software, Version 9.4. Results were noted as statistically significant with a two-tailed alpha level of .05.

3. Results

3.1. Sample Characteristics

Table 1 provides birth outcome and demographic characteristics of study participants by cocaine exposure status. Those with PCE had lower average gestational age, birth lengths, and head circumferences and were small for gestational age compared with non-exposed infants. Adolescents with PCE reported more externalizing behavior problems at age 12 and had lower IQ scores at age 15 than their non-exposed counterparts. Adolescents with PCE were more likely to be placed in non-kinship foster or adoptive care at both 15 and 17 years of age. Compared with the NCE group, they also had a trend for lower blood lead levels at 2 and/or 4 years old (p = .06). No group differences were found for gender, race or exposure to violence at age 12.

Table 2 presents the demographic and drug use characteristics of biologic mothers and current caregivers by cocaine exposure status. Birth mothers of adolescents with PCE were older, less educated, less likely to be married, and had higher parity compared with birth mothers of non-exposed adolescents. They also had fewer prenatal care visits, lower receptive vocabulary scores, and more psychological distress compared to those in the NCE group. Women who used cocaine during pregnancy reported greater use of other substances, including tobacco, alcohol, and marijuana, than women who did not use cocaine. Cocaine using women averaged 25.5 (SD 38) units of cocaine per week over the course of their pregnancy. Characteristics of current caregivers did not differ, except that caregivers of adolescents with PCE were less likely to complete high school and smoked more cigarettes per day than caregivers of non-exposed adolescents.

3.2. Effects of PCE on Substance Use at Ages 15 and 17

Table 3 describes unadjusted percentages of last 30 day use of alcohol, tobacco, and marijuana and any drug use by PCE group status at ages 15 and 17. Adolescents with PCE had higher percentages of alcohol, tobacco, marijuana, and any drug use than their NCE counterparts at both 15 and 17 years, with significant group difference in marijuana use ($p \le .01$) and any drug use ($p \le .05$) at age 15 years only.

A greater number of adolescents used substances by age 17 than at 15 years, regardless of PCE status (Table 4). There was a significant increase in reported past 30 day substance use from ages 15 to 17 as reflected in the significant odds ratio of alcohol (OR = 1.62, 95% CI = 1.06-2.46, $p \le .05$), tobacco (OR = 1.98, 95% CI = 1.50-2.62, $p \le .001$), and marijuana use (OR = 1.61, 95% CI = 1.18-2.18, $p \le .01$) from 15 to 17 years, with no differences in the rate of change between PCE and NCE groups.

Table 4 summarizes the effects of PCE on current substance use at ages 15 and 17 after controlling for covariates. Model 1 is a base model without assessing for mediating effects of externalizing behavior at 12 years. Adolescents with PCE were approximately 2 times more likely to use tobacco (OR = 2.1, 95% CI = 1.21-3.63, $p \le .01$) and marijuana (OR = 1.85, 95% CI = 1.18-2.91, $p \le .01$) in the past 30 days than their NCE counterparts after controlling for covariates. There was a non-significant trend for PCE status to be associated with increased odds of current alcohol consumption (OR = 1.66, 95% CI = 0.96-2.85, $p < .07$).

Model 2 evaluated earlier externalizing behavior as a mediator of PCE. Externalizing behavior at age 12 was associated with increased odds of current tobacco use at ages 15 and 17 (OR = 1.03, 95% CI = 1.00-1.07, $p = .03$ and mediated PCE effects on current tobacco use at 15 and 17 years of age (mediated OR=1.19, CI=1.00-1.27, p<.05); PCE status remained significant

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even when accounting for the variance in tobacco use associated with earlier externalizing behavior. Externalizing behavior at age 12 was not significantly related to the odds of current marijuana use (OR = 1.01, 95% CI = 0.99-1.04, p = .25), and thus did not mediate the effects of PCE status. Since no significant association was established between PCE status and alcohol use, further mediation examination was not conducted.

Interaction effects (PCE by gender) were evaluated. Figure 1 reflects estimated probability (%) of marijuana use by PCE status and gender adjusted for covariates at ages 15 and 17 years. Evaluation of PCE status by gender interaction ($p \leq .05$) revealed that the negative effects of PCE on marijuana use were more pronounced for boys compared to girls at age 17. Boys with PCE were approximately three times more likely than NCE boys to use marijuana both at 15 (OR = 3.62; 95% CI= 1.49-8.76; p = .004) and 17 years of age (OR = 3.12; 95% CI= 1.42-6.84; p = .004). A significant gender effect was also noted among the adolescents with PCE at age 17. Boys with PCE were 2.09 times more likely than girls with PCE to use marijuana in the past 30 days at age 17 (41% for PCE boys vs. 25% for PCE girls) (OR = 2.09; 95% CI=1.01-4.29; p = .045). Change in percentage of marijuana use between 15 and 17 years of age was significantly different for girls with PCE only (OR=2.32; 95% CI=1.18-4.58, (p=.015). There were no gender or cocaine by gender interaction effects for tobacco or alcohol use.

3.3. Effects of PCE on Substance Use Disorders at 17 years

Adolescents with and without PCE were compared on self-reported diagnostic criteria (C-DISC 4) for substance use disorders at age 17 years (Table 3). Adolescents with PCE had higher unadjusted frequencies than the NCE controls for nicotine dependence. There were no differences by PCE group status in terms of alcohol and marijuana abuse or dependence. A greater number of adolescents with PCE reported abuse or dependence of any substance,

including alcohol, nicotine, marijuana, and other illicit drugs, than NCE adolescents, although the difference was marginally significant ($p \leq .06$).

As presented in Table 5 (Model 1), adolescents with PCE were 2.51 times more likely than NCE adolescents to abuse or depend on any substance (OR = 2.51, 95%CI = 1.00-6.28, $p \leq .05$), after controlling for covariates. When externalizing behavior at age 12 was assessed in the model (Model 2) results indicated that it was a significant mediator of PCE's association with any one substance abuse or dependence disorder (mediated OR=1.43, CI=1.14-1.79, p< .05).

3.4. Association of Other Environmental Factors and Substance Use at Ages 15 and 17

As presented in Table 4 (Model 1), other significant factors were found to be correlated with the current (past 30 days) use of alcohol, tobacco, and marijuana at ages 15 and 17 years. Older age of biologic mothers (OR = 0.95, 95% CI = 0.90-1.00, $p < .04$) and having more children (OR = 0.83, 95% CI = 0.72-0.96, $p < .01$) at the time of infant birth decreased the odds of current alcohol use. The birth mother's being married at the time of child delivery was related to an increased odds of current alcohol consumption (OR = 2.49, 95% CI = 1.24-4.98, $p < .01$) and marijuana use (OR = 2.23, 95% CI = 1.14-4.36, $p < .02$). African American adolescents were 63% less likely to use tobacco than non-African American adolescents (OR = 0.37, 95% CI = 0.20-0.68, $p \leq .001$). Higher quality of home environment was related to lower odds of tobacco use (OR = 0.96, 95% CI = 0.93-1.00, $p < .02$) and marijuana use (OR = 0.96, 95% CI = 0.93-0.99, $p < .02$) at 15 and 17 years of age. Violence exposure assessed at age 12 increased the odds of current alcohol (OR = 1.37, 95% CI = 1.10-1.69, $p < .004$), tobacco (OR = 1.30, 95% CI = 1.04-1.62, $p < .02$), and marijuana (OR = 1.41, 95% CI = 1.16-1.72, $p < .0006$) use at 15 and 17 years of age. Further adjustment of externalizing behavior by age 12 did not change the

association of these environmental factors with substance use at ages 15 and 17, except for the associations of home environment and violence exposure with current tobacco use (Model 2 in Table 4). Quality of the home environment ($p = .06$) and exposure to violence ($p = .32$) were no longer related to tobacco use at 15 and 17 years of age when externalizing behavior was accounted for.

As reported in Table 5 (Model 1), other prenatal exposures and environmental factors were associated with abuse or dependence of any substance by age 17. Higher prenatal exposure to cigarettes (OR = 1.52, 95% CI = 1.06-2.17, $p = .02$), the biologic mother's being married at the time of child birth (OR = 4.46, 95% CI = 1.62-2.17, $p = .003$), and exposure to violence assessed at age 12 (OR = 1.66, 95% CI = 1.18-2.33, $p = .004$) increased the odds of substance use disorders in terms of any substance, including alcohol, tobacco, marijuana, and other illicit drugs. Older age of birth mothers decreased the odds of any substance abuse or dependence at age 17 (OR = 0.89, 95% CI = 0.82-0.96, $p = .005$). Maternal psychological distress at infant delivery, ongoing caregiver substance use and quality of the home environment assessed at 12 years were not related to any substance abuse or dependence. The associations that these significant prenatal exposures and environmental factors had with any substance abuse or dependence did not change with statistical adjustment for externalizing behavior at age 12 (Model 2 in Table 5).

4. Discussion

4.1 Overall Findings and Relationship to Existing Research

Data from this study indicate that both prenatal cocaine exposure and environmental factors are associated independently with increased incidence of teen substance use in the past 30 days and self-reported diagnosis of abuse or dependence of any substance by 17 years of age

after control for covariates. Specifically, at ages 15 and 17, youth with PCE reported greater tobacco and marijuana use over the past 30 days. Past 30 day use likely indicates more regular use patterns. Interestingly, the difference in marijuana use by teens with PCE was largely driven by a greater number of males compared to girls with PCE. Given findings indicating that marijuana use among teens increases risk for psychosis (Green et al., 2016), poorer visual selective attention (Nicholls C et al., 2015), lower academic achievement (Arria et al., 2015; Bechtold et al., 2016), and reduction in cortical thickness (Mashhoon et al., 2015), males with PCE could be at increased risk for negative effects of marijuana use. However, additional studies considering use quantity, frequency and/or marijuana use disorder symptoms would provide important clarifying information.

Similarly, concerning results were found for self-reported diagnosis of substance abuse or dependence for any one substance among youth with PCE, supporting the hypothesis that PCE not only increases the risk for teen substance use in the past 30 days but also the percentage of adolescents that may succumb to problematic use by age 17. This data is important because intransigent substance use, primarily tobacco and marijuana use in this sample, can have persistent mental and physical health consequences (Caspers et al., 2009; Minnes et al., 2014). While not directly comparable, a summary of trends for daily substance use (indicating problem use) for 10th and 12 graders in 2015 indicated usage rates at 3-5% for tobacco, 0.5-1.9% for alcohol and 3-6% for marijuana. Results from this study indicate that the sample has elevated nicotine and marijuana abuse/dependence compared to the US population and that prenatal cocaine exposure exerts additional risk (Johnston et al., 2015). Rates of binge drinking, five or more drinks at one or more times in the past two weeks, appear higher only for the teens with PCE. These results support and extend earlier research indicating that teens with PCE are at

increased risk of drug use (Glantz and Chambers, 2006; Delaney-Black et al., 2011; Frank et al., 2011; Minnes S. et al., 2014) compared to non-exposed teens of similar race and SES. Previous studies indicating that teens with PCE are almost three times more likely to have problems related to substance use than their NCE peers (Minnes et al., 2012; Min et al., 2014b) and earlier initiation of substance use (Richardson et al., 2013), raise additional concerns for potential abuse and dependence, as well as for social problems related to substance use, for this high risk group. There was an increase in the rate of past 30-day substance use from ages 15 to 17 years, indicating that prevention and/or early intervention is important to stop potential progression to abuse and dependence.

Mounting behavioral data (Aguirre, 2003; Minnes et al., 2010; Richardson et al., 2011; Lambert and Bauer, 2012) indicate that children with PCE are, as a group, at increased risk for problems of inhibitory control (Thompson et al., 2009). Given that these weaknesses in self-regulation usually present earlier in development, they may foreshadow risk for substance use experimentation and problematic use, and indicate a common liability (Nigg et al., 2006; Lester et al., 2012) particularly among children with PCE. In this study, more self-reported externalizing behavior problems at age 12 was found to be a significant mediator of cocaine's effect on previous 30 day tobacco use and on the presence/risk of substance abuse or dependence. These results lend support to those of Lester et al., (2012) who found that neurobehavioral disinhibition predicted initiation of substance use in prenatally cocaine exposed children. While these results differ somewhat from that reported by other researchers (Frank et al., 2011; Warner et al., 2011; Richardson et al., 2013), methodological differences between the studies, including the use of a potentially more sensitive self-report assessment of externalizing behaviors at the later age of 12 rather than at ages 9-10, may account for differences in findings. Further

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exploration of the pathway to substance use among adolescents with PCE is warranted to better understand the early predictors of substance use as well as the protective factors that might lead to prevention of substance use in groups at risk for problematic use in emerging adulthood and beyond.

As hypothesized, exposure to violence was associated with current teen alcohol, tobacco and marijuana use, as well as with higher rates of self-reported substance use diagnoses, supporting findings which indicate long term developmental harm related to exposure to violence (Moffitt, 2013; Howell et al., 2016). Exposure to violence has been specifically associated with various types of early substance use in the general population (Pinchevsky et al., 2014) and also for adolescents with PCE (Frank et al., 2014; Minnes et al., 2014). Further studies are required to test the potentially mediating or moderating aspects of exposure to violence in adolescents with PCE. In a related finding, poorer quality of the home environment during the teen years was also found to be related to greater rates of past 30 day tobacco and marijuana use. In addition, early environmental factors such as the biologic mother being married, number of siblings, and maternal psychological distress were associated with alcohol use. Marital status, possibly related to greater access to drugs, was also related to any one substance use disorder and to both tobacco and marijuana use. These findings indicate that early childhood factors, in addition to prenatal cocaine exposure and violence exposure, also have an influence on teen substance use. Surprisingly, maternal psychological distress at birth, blood lead level, adoptive or foster care placement and most other prenatal drug exposures did not predict rates of last 30 day substance use or any one substance abuse or dependence diagnosis. The only exception was that higher prenatal tobacco exposure predicted higher rates of any substance use disorder diagnosis at age 17, consistent with a previous finding (Goldschmidt et al., 2012).

4.2 Strengths and Limitations

There are some limitations to consider in this study. These data do not tell us much about the patterns of drug use in the past 30 days, for example whether or not the alcohol or marijuana use was regular. In addition, it does not indicate how teen polydrug use or problems associated with drug use relate to later rates of drug and alcohol abuse or dependence. Because the rates of self-reported diagnoses of each substance at age 17 were generally too small to complete logistic regression, the information gleaned from that finding is not specific. In addition, the strength and inclusiveness of the violence exposure finding is very compelling but it too is a very general measure of violence exposure collected retrospectively at 12 years of age. Given the consistency of this predictor variable in different risk populations, additional research investigating the interaction of PCE and violence exposure could lead to a more specific understanding of how violence exposure leads to substance use and abuse/dependence, and to development of potentially targeted prevention strategies. The findings of this study apply to a group of high risk, low SES, minority individuals that were prenatally exposed to crack cocaine, limiting the ability to generalize these findings beyond this high risk population.

This study extends our knowledge of risk for substance use and abuse among prenatally cocaine-exposed teens through the age of 17, beyond the age that most studies have assessed. The study was one of the few that directly explored self-reported externalizing behavior at age 12 as a mediator. Support for this indirect pathway toward substance use among prenatally cocaine exposed children could be helpful in designing targeted drug use prevention programs. An added strength of this study is that the data come from a prospectively designed longitudinal study and very well characterized sample with a very low attrition rate, therefore increasing the validity of the findings. In addition, early blood lead levels, time varying caregiver and

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environmental conditions, and assessment of violence exposure have not been controlled for simultaneously in other studies and strengthen the current findings that support a specific association of prenatal cocaine exposure and teen substance use. In addition, this study utilized infant meconium to examine cocaine metabolites, ensuring that group status was correct and reducing error that may have come from sole reliance on maternal retrospective self-report. Multiple assessment methods, including biologic samples (teen hair, blood spot and urine drug screening and infant meconium to ensure maternal substance use during pregnancy) in addition to standardized and privately administered substance use questionnaires, were utilized. This ensured the most accurate account of teen drug use as well as assessment of biologic mothers' drug use during pregnancy. Lastly, this study is the only one to our knowledge that examined both use of drugs in the last 30 days and standard diagnostic criteria indicating problematic use.

4.3 Implications

Study findings indicate that adolescents with PCE are at increased risk for drug use and self-reported diagnoses of substance abuse/dependence. Given the serious disabling aspects of chronic substance use and potential exposure to the next generation if use continues during pregnancy, every effort should be made to develop prevention and early intervention programs for at risk youth. Findings also suggest that a path toward substance use in those with PCE may be indicated by early externalizing behavior problems and therefore those children manifesting problems with inhibitory control should be considered at special risk. This may be especially true for those children known to have been exposed to violence. Continued studies into adulthood will elucidate whether the childhood behavioral problems and early indications of substance use in adolescence persist through early adulthood and affect social and vocational adjustment.

AUTHOR DISCLOSURES

Contributors

Dr. Meeyoung Min performed the statistical analyses, and drafted the manuscript. Dr. Sonia Minnes conceptualized the paper, designed the study and interpreted the data. Dr. Adelaide Lang coordinated the study, performed the measurements, and proofread the manuscript. Ms. Miaoping Wu participated in the interpretation of data. Ms. June-Yung Kim assisted in the literature review, drafting, and proofing the manuscript. Ms. Meredith Francis assisted in the literature review, drafting, and proofing the manuscript. Dr. Lynn Singer participated in the study's conception and design, interpretation of data, and reviewed the manuscript. All authors read and approved the final manuscript.

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Conflict of Interest

"No conflict declared"

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Figure Legends

Figure 1. Adjusted estimated percentages of current marijuana use by PCE status and gender at 15 and 17 years. Estimated values calculated after adjusting for PCE status*gender, race, gender, marital status, HOME score, and average prenatal marijuana exposure, violence exposure and externalizing behavior. Significant differences found between PCE boys and NCE boys at both 15 (OR = 3.62; 95% CI= 1.49-8.76; p = .004) and 17 years (OR = 3.12; 95% CI= 1.42-6.84; p = .004) and PCE boys and PCE girls at 17 years (OR = 2.09; 95% CI= 1.01-4.29; p = .045). There is a significant increase in percentage of marijuana use between age 15 and 17 for NCE girls (OR=2.32;95% CI=1.18-4.58, p=.015) only.
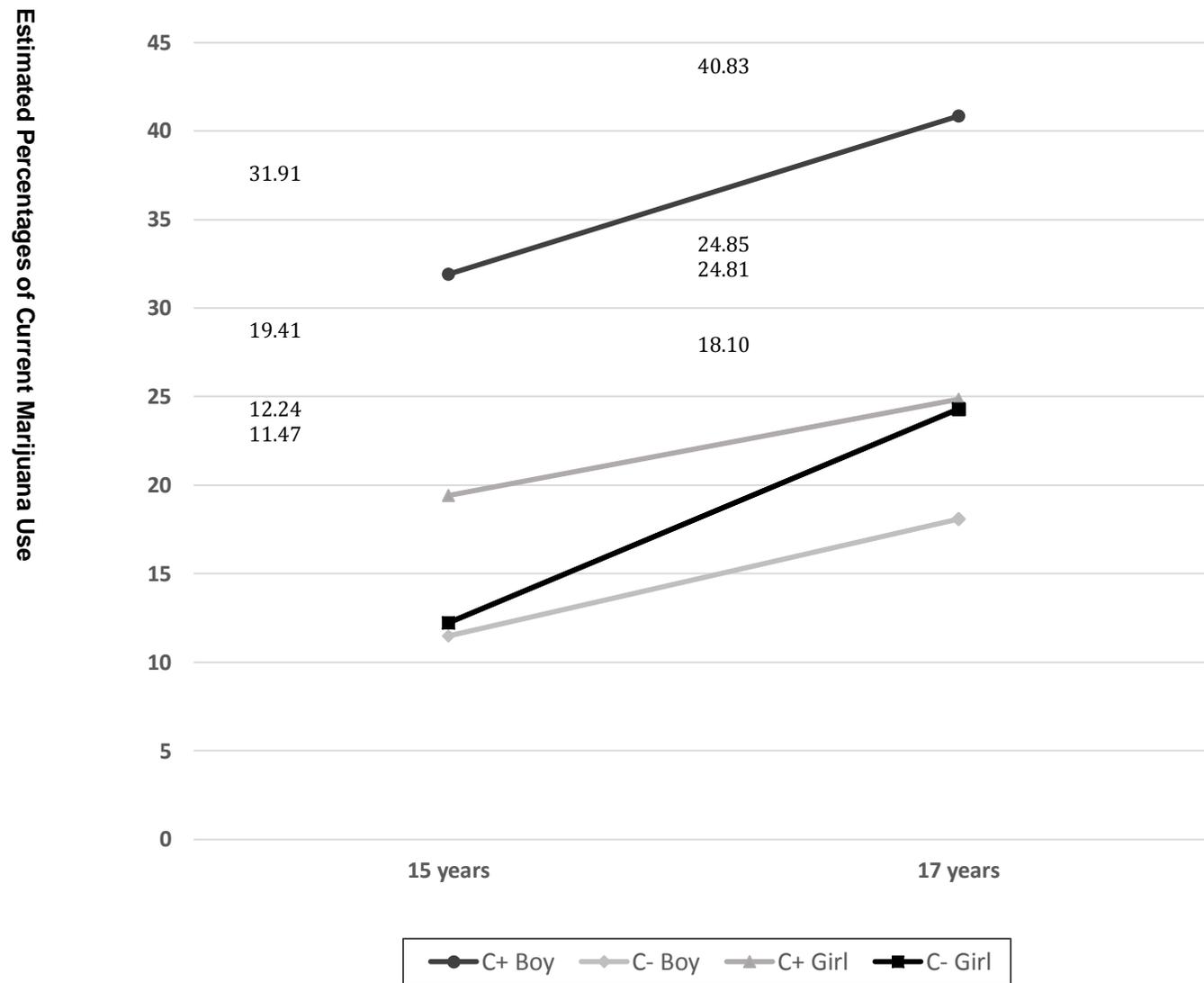
Figure 2.

Table 1. Adolescent demographics

	PCE (*n*=186)		NCE (*n*=179)		*p*
	n (%)	*M (SD)*	*n (%)*	*M (SD)*	
Male	83 (44.62)		87 (48.60)		.45
African-American	152 (81.72)		145 (81.01)		.86
Gestational Age		37.76 (2.86)		38.47 (2.88)	.02
Birth weight (grams) [a]		2705 (654)		3104 (702)	<.0001
Birth length (cm) [a]		47.27 (3.97)		49.15 (3.76)	<.0001
Head circumference (cm) [a]		32.27 (2.17)		33.47 (2.40)	<.0001
Head circumference <10th %	27 (14.75)		8 (4.52)		.001
Small for gestational age	25 (13.37)		4 (2.20)		<.0001
2yrs and/or 4yrs Lead Level [b]		7.07 (4.14)		8.04 (4.66)	.06
Violence exposure at 12yrs		0.63 (0.77)		0.59 (0.81)	.50
YSR externalizing behavior at 12 years		51.07 (10.07)		47.79 (9.75)	.002
WISC-IV Full Scale IQ at 15 years		81.05 (11.57)		83.78 (14.09)	.05
Age at assessment					
15 years		15.69 (0.27)		15.67 (0.27)	.48
17 years		17.81 (0.26)		17.79 (0.26)	.40
Adopted/Foster care					
15 years	44 (24.04)		6 (3.43)		<.0001
17 years	39 (22.41)		5 (2.89)		<.0001

[a] P-value is adjusted for prematurity.
[b] Sub-sample size of lead is 284, included 145 PCE and 139 NCE.

Table 2. Maternal and Current Caregiver Characteristics

	PCE (*n*=186)		NCE (*n*=179)		*p*
	n (%)	*M (SD)*	*n (%)*	*M (SD)*	
Biologic mother					
Mother's age at birth		29.75 (5.01)		25.45 (4.72)	<.0001
African-American	153 (82.26)		146 (81.56)		.86
Maternal years of education		11.55 (1.67)		11.92 (1.38)	.02
Completion of high school	96 (51.61)		120 (67.04)		.003
Married	15 (8.06)		28 (15.64)		.02
Low SES	181 (97.84)		175 (97.77)		.96
Parity		3.55 (1.89)		2.76 (1.86)	<.0001
Number of prenatal visits		5.19 (4.59)		8.71 (4.83)	<.0001
PPVT Standard Score		73.53 (14.36)		77.70 (14.79)	.008
WAIS-R Block Design Scale		6.88 (2.11)		7.18 (2.10)	.18
WAIS-R Picture Completion		6.74 (2.16)		6.95 (2.34)	.38
BSI Global Severity Index		0.83 (0.75)		0.51 (0.54)	<.0001
Substance use during pregnancy [a]					
Drinks per week [b]		9.80 (17.64)		1.38 (4.64)	<.0001
Cigarettes per day [c]		11.55 (11.08)		3.85 (7.13)	<.0001
Marijuana per week [d]		1.35 (3.48)		0.61 (3.55)	<.0001
Cocaine per week [e]		22.52 (37.96)	-	-	-
Current caregiver					
Years of education		12.53 (2.29)		12.86 (1.96)	.15
Completion of high school	125 (69.06)		134 (79.29)		.03
PPVT Standard Score		80.05 (14.90)		78.93 (15.18)	.50
WAIS-R Block Design Scale		7.11 (2.11)		7.27 (1.95)	.49
WAIS-R Picture Completion		7.54 (2.49)		7.11 (2.30)	.10
BSI Global Severity Index		0.34 (0.42)		0.34 (0.46)	.43
Substance use in the past 30 days [a]					
Drinks per week [b]		1.81 (4.52)		2.01 (4.64)	.47
Cigarettes per day [c]		4.78 (7.14)		3.46 (6.54)	.01
Marijuana per week [d]		0.53 (5.43)		0.45 (3.08)	.60
Cocaine per week		0		0	NA
HOME environment					
15years		47.81 (6.73)		48.94 (6.05)	.10
17years		50.60 (4.62)		52.80 (1.79)	.35

BSI = Brief Symptom Inventory; NCE = non cocaine exposed; PCE = prenatal cocaine exposure; PPVT = Peabody Picture Vocabulary Test; SD = standard deviation; WAIS-R = Wechsler Adult Intelligence Scale-Revised; M = mean.

[a] P-value based on *n* (%).

[b] Average drinks of beer, wine, or hard liquor per week, each equivalent to 0.5 oz. absolute alcohol.

[c] Average number of cigarettes smoked per day.

[d] Average joints of marijuana per week.

[e] Average unit of cocaine equivalent to 1 rock and/or $20 worth of cocaine rocks

Table 3. Unadjusted frequencies of substance use outcomes by cocaine group status and age

	15 years ($n = 358$)				17 years ($n = 350$)			
	PCE ($n = 183$)	NCE ($n = 175$)	X^2	p	PCE ($n = 175$)	NCE ($n = 175$)	X^2	p
	n (%)	n (%)			n (%)	n (%)		
Any drug use [a]	66 (36.07)	46 (26.29)	3.98	.05	76 (43.43)	63 (36.00)	2.02	.16
Alcohol use [a]	24 (13.11)	21 (12.00)	0.10	.75	38 (21.71)	34 (19.43)	0.28	.60
Nicotine use [a]	34 (18.58)	20 (11.43)	3.57	.06	51 (29.14)	38 (21.71)	2.55	.11
Marijuana use [a]	45 (24.59)	25 (14.29)	6.04	.01	52 (29.71)	43 (24.57)	1.17	.28
Any substance abuse/dependence [b]	-	-	-	-	31 (19.14)	19 (11.59)	3.58	.06
Alcohol abuse/dependence [b]	-	-	-	-	6 (3.70)	2 (1.22)	2.10	.15
Nicotine dependence [b]	-	-	-	-	15 (9.26)	5 (3.05)	5.46	.02
Marijuana abuse/dependence [b]	-	-	-	-	18 (11.11)	15 (9.15)	0.35	.56

[a] Assessed using self-report YRBSS (past 30 days) and biologic samples (urine specimens, hair, and/or bloodspots) and 15 and 17 years.
[b] Assessed DSM-IV diagnosis of substance use disorders using self-report CDISC at 17 years.

Table 4. Effects of prenatal cocaine exposure on adolescent past 30-day substance use at 15 and 17 years mediated by earlier externalizing behavior

	Alcohol use[a]		Tobacco use				Marijuana use			
			Model 1		Model 2		Model 1		Model 2	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
PCE	1.66†	0.96-2.85	2.1**	1.21-3.63	1.89*	1.08-3.30	1.85**	1.18- 2.91	1.79**	1.13- 2.83
Time, 17 years	1.62*	1.06-2.46	1.98***	1.50-2.62	2.01***	1.51-2.67	1.61**	1.18-2.18	1.61**	1.19-2.19
Adolescent sex, male [b]	-	-	-	-	-	-	1.32	0.85- 2.07	1.33	0.85- 2.08
Race, African-American	0.59†	0.33-1.06	0.37***	0.20-0.68	0.4**	0.22- 0.73	0.61†	0.34-1.07	0.63	0.35- 1.12
Mother's age at birth [b]	0.95*	0.90- 1.00	0.97	0.92-1.02	0.97	0.92, 1.02	-	-	-	-
Marital status	2.49**	1.24- 4.98	1.92†	0.91-4.06	1.82	0.87- 3.83	2.23*	1.14-4.36	2.17*	1.11- 4.23
Parity [b]	0.83**	0.72- 0.96	-	-	-	-	-	-	-	-
Maternal BSI GSI at birth [b]	1.69†	0.94- 4.07	-	-	-	-	-	-	-	-
HOME environment [bc]	-	-	0.96*	0.93-1.00	0.97†	0.93-1.00	0.96*	0.93-0.99	0.96*	0.93- 0.99
Violence exposure [d]	1.37**	1.10-1.69	1.3*	1.04-1.62	1.14	0.88-1.47	1.41***	1.16-1.72	1.34**	1.07-1.66
Externalizing behavior [d]	-	-	-	-	1.03*	1.00-1.07	-	-	1.01	0.99-1.04

BSI = Brief Symptom Inventory; GSI = Global Severity Index; PCE = prenatal cocaine exposure; CI = confidence interval; OR = odds ratio.

Model 1 = base model without assessing mediating effects of 12 year externalizing behavior

Model 2= evaluates 12 year externalizing behavior as a mediator of PCE

[a] Model 1, mediation was not tested for, since no statistically significant association was established between PCE and alcohol use.

[b] Blank spaces indicate that the variable did not meet the criteria (e.g., not significant at the bivariate level) and therefore was not included in the model.

[c] Assessed quality of home environment at 15 years.

[d] Assessed at 12 years.

† p ≤ .10; * p ≤ .05; ** p ≤ .01; *** p ≤ .001.

Table 5. Adjusted association of any substance abuse/dependence at 17 years with PCE status

| | Any Substance Abuse/Dependence[a] | | | |
| | Model 1 | | Model 2 | |
	OR	95% CI	OR	95% CI
PCE	2.51[*]	1.00-6.28	1.83	0.71-4.70
Prenatal nicotine exposure [b]	1.52[*]	1.06-2.17	1.67[**]	1.14-2.46
Mother's age at birth	0.89[**]	0.82-0.96	0.89[**]	0.82-0.97
Marital status	4.46[**]	1.64-12.10	3.24[*]	1.14-9.24
Maternal BSI GSI at birth	1.35	0.46-3.93	0.68	0.21-2.23
HOME environment [c]	1.00	0.94-1.05	1.02	0.96-1.08
Violence exposure [d]	1.66[**]	1.18-2.33	1.49[*]	1.04-2.13
Externalizing behavior [d]			1.10[***]	1.05-1.16

BSI = Brief Symptom Inventory; GSI = Global Severity Index; NCE = non cocaine exposed; PCE = prenatal cocaine exposure; CI = confidence interval; OR = odds ratio.

Model 1 = base model without assessing mediating effects of 12 year externalizing behavior

Model 2= evaluates 12 year externalizing behavior as a mediator of PCE

[a] Measured via self-report CDISC. Any substance includes alcohol, tobacco, marijuana, or any other illicit drug.

[b] Average number of cigarettes smoked per day.

[c] Assessed at 15 years.

[c] Assessed at 12 years.

* $p \le .05$; ** $p \le .01$; *** $p \le .001$.