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Prenatal and postnatal cocaine exposure predict teen cocaine use

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Abstract

Preclinical studies have identified alterations in cocaine and alcohol self-administration and behavioral responses to pharmacological challenges in adolescent offspring following prenatal exposure. To date, no published human studies have evaluated the relation between prenatal cocaine exposure and postnatal adolescent cocaine use. Human studies of prenatal cocaine-exposed children have also noted an increase in behaviors previously associated with substance use/abuse in teens and young adults, specifically childhood and teen externalizing behaviors, impulsivity, and attention problems. Despite these findings, human research has not addressed prior prenatal exposure as a potential predictor of teen drug use behavior. The purpose of this study was to evaluate the relations between prenatal cocaine exposure and teen cocaine use in a

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Conflict of interest statement

Nothing declared.

prospective longitudinal cohort (n = 316) that permitted extensive control for child, parent and community risk factors. Logistic regression analyses and Structural Equation Modeling revealed that both prenatal exposure and postnatal parent/caregiver cocaine use were uniquely related to teen use of cocaine at age 14 years. Teen cocaine use was also directly predicted by teen community violence exposure and caregiver negativity, and was indirectly related to teen community drug exposure. These data provide further evidence of the importance of prenatal exposure, family and community factors in the intergenerational transmission of teen/young adult substance abuse/use.

Keywords

Cocaine; Opiates; Marijuana; Self-report; Biologic sample

1. Introduction

As early initiation of drug use has been associated with an increased risk of later drug problems [4,59–61] it is critical to identify risk factors for early teen drug use. Substantial research over the past two decades has suggested that early drug use may be related to a host of teen [59], family [28,60,61], and community problems [40,68,100]. Teen behavioral problems associated with early initiation of drug use [34,77,92] have included aggressive behavior [59], increased risk seeking [101], poor school achievement [40,48], conduct disorder [60,70], and attention deficit disorder [33]. Additionally some researchers have suggested that exposure to violence [99], a current PTSD diagnosis [42], or the presence of stress factors [11,44], especially during periods of vulnerability [3], may also play a role in the initiation of substance use. While child characteristics are important, other studies have suggested that parental substance [46,94] or alcohol use [18,59], harsh parenting style [28], family disruption [46], or failure to adequately monitor children's behavior [46] may also account for some of the risk of teen drug use.

While no published human studies have linked prenatal cocaine exposure with postnatal adolescent cocaine use, animal studies and prenatal cocaine-associated child behavioral problems suggest that cocaine exposure during fetal development may be a risk factor for later cocaine use. Preclinical studies have linked prenatal cocaine exposure with postnatal alterations in cocaine and alcohol self-administration and behavior following drug administration. Prenatal cocaine-exposed adult rats self-administered cocaine (but not water) at more than three times the rate of un-exposed controls [57]. Similar findings have been reported by Hecht et al. and Rocha et al. [47,87]. Furthermore, low-dose prenatal cocaine (10 mg/kg/day) increased postnatal self-administered alcohol in mice, more so in females [58]. Crozatier et al. [17] showed unique profiles of locomotor sensitization and stereotypy to a challenge dose of cocaine in adult mice exposed prenatally to 20 or 40 mg/kg/day of cocaine on embryonic days 8 to 17, even after controlling for nutritional effects [17]. The results from these animal studies suggest that prenatal cocaine has long-term effects on drug-related postnatal behavior.

Human studies of prenatal cocaine exposure have also identified an increased risk of externalizing behavior [5,8,10,26,75,82] and impulsivity/attention problems [9,62,73,79] following prenatal cocaine exposure, both known risk factors for substance use/abuse in teens and young adults [34,37]. Furthermore, caregiver and environmental factors that have been associated with drug use in the home may also be predictors of teen drug use. Despite these preclinical and human findings, studies evaluating risk factors for early teen drug use do not typically address prior prenatal exposure as a potential predictor, nor do they assess “postnatal” exposure (as current caregiver use of cocaine) using biologic measures. Based upon previous preclinical studies and our findings of child behavior problems at 7 years of age related to prenatal cocaine exposure [24,74,75,93], our specific research hypothesis was that, even following extensive control for other child, caregiver and community risk factors, prenatal cocaine exposure would be associated significantly with an increase in teen cocaine use in our large, prospective, high-risk longitudinal cohort.

2. Methods

The Wayne State University Institutional Review Board approved this study prior to participant enrollment.

2.1. Procedures

African American teens were initially identified through a prospective pregnancy study conducted at our inner city university maternity center with a predominantly minority clientele. To reduce collinearity between alcohol and drug use, the pregnancy study utilized a block-sampling design with over sampling of heavy and moderately exposed pregnancies. This technique helped to identify sufficient numbers of women with varying levels of cocaine and alcohol use. Exclusions in the pregnancy study were known maternal HIV or, because of the prospective screening for alcohol and drugs exposure, no prenatal care. Additional inclusion criteria for the longitudinal child study were singleton birth between September 1989 and August 1991 and continued residence within the Detroit area during the age 7 year assessments. Exclusion criteria for the longitudinal child study included children with multiple malformation syndromes and offspring from repeat pregnancies to the same participating mother. Further details of subject recruitment and age 7 assessments were published previously [24]. For this teen study, female research assistants blind to participant drug history evaluated teens and caregivers/legal guardians independently in private testing rooms.

Parents or legal guardians provided informed consent and parental permission. Assent was obtained from teens prior to study participation. A *Certificate of Confidentiality* described in the consent documents provided assurance to all participants that no drug-related information would be released without the primary caregiver’s signed release. Interviewers also assured the teens and their parents that all teen data collected, including any self-reported drug use, would not be shared with anyone, including other family members or authorities.

2.2. Independent predictor variable: prenatal cocaine exposure

All mothers of study teens had undergone a prospective assessment of drug and alcohol use during the index pregnancy as previously detailed [23]. Evidence of prenatal cocaine exposure was obtained prospectively from laboratory results and self-report, including prospective structured research interviews conducted throughout pregnancy, medical records from the prenatal clinic and hospital admission (including delivery, postpartum and nursery records), and retrospective report by the mothers at the age 7- and/or 14-year child assessments. Laboratory evidence of cocaine use during pregnancy consisted of positive maternal urine collected at prenatal visits or at delivery, or positive neonatal urine or meconium. Fewer than 10% of infants had meconium testing because meconium testing was initiated only near the end of subject recruitment. Both a dichotomous ('yes/no') and an ordinal prenatal cocaine exposure variable (None, Some, Heavy and/or Persistent) were utilized. Admission to use of cocaine two or more times per week anytime during pregnancy was considered "Heavy", an assessment similar to that employed by other investigators [54]. We defined "Persistent" prenatal exposure as continued cocaine use throughout pregnancy, evidenced by a positive maternal urine specimen within a week of delivery, and/or positive neonatal urine. Among women in the "Persistent" group who denied cocaine use, biologic measures confirming earlier pregnancy exposure were available for all but two women who did not initiate prenatal care until the third trimester. Sensitivity of assays for cocaine and benzoylecgonine analytes in urine was <35 ng/mL (the lowest reliable detected concentration by immunoassay>0). Urine specimens were collected by clinical staff and sent directly to the toxicology lab for analysis. All positive specimens were re-tested with a second EMIT assay.

2.3. Outcome: identification of teen cocaine use

Information regarding teen drug use (cocaine, opiates, marijuana and alcohol) was collected with a multi-method strategy that included: teen self-report, obtained by both paper-and-pencil survey and interview; parent report, via written questionnaire and interview about their teen; and analysis of teen biologic specimens (hair, sweat, or urine) for drug metabolites. A similar strategy was employed for parent drug use with the exception that teens were not queried about their parent's drug use. In an attempt to reduce inaccurate denial of drug use, during the consenting process and prior to data collection, teens and parents were assured by the interviewers that only suspicion of child abuse or plans for self-injury or injury to others would be reported. As previously noted, teens were specifically told that no information about drug use would be shared with anyone, including their parent.

Teen biologic specimens for drug testing were obtained on the second study day, as detailed in Delaney-Black et al. [19,20]. The original study design was to assess illicit drug use information from hair specimens as well as from self- and parent-report measures. However, while only 6 (1.4%) teens and 9 (2.1%) parents refused to provide teen drug-report information, hair specimens could not be consistently obtained, primarily from male teen participants. Therefore, urine and sweat specimens were added to the study design when a hair specimen was either refused or could not be obtained. Furthermore, because we recently identified under-reporting of both teen and parent cocaine and opiate use in this cohort [19,20], evidence of cocaine and opiate use in the current analyses was based solely on

biological specimens — from hair, sweat or urine. Thus, analyses including cocaine or opiate data were necessarily limited to those teens that provided a biologic specimen. In contrast to cocaine and opiate use, previous studies have identified less denial of marijuana use [67]. For this reason, and because of the known poor detection of marijuana biomarkers in hair [36,51,71,80,95] teen and parent assessment of marijuana included self- and/or parent report. While the reduction in sample size was unfortunate, at least one adequate biological specimen was obtained from more than 70% of both teens and caregivers. Further, analyses comparing teens who gave a biologic specimen for cocaine with those from whom no specimen was available revealed no differences in teen or parent IQ, SES, parental education, or number of subjects' residing with their biological mother. Only two differences were noted. Not surprisingly, because of the difficulty in getting an adequate quantity of hair from some boys and the late addition of sweat patches and urine testing, fewer boys than girls provided a biologic specimen ($\chi^2 = 9.96$, $p < 0.002$). Teens for whom a specimen was not available were also more likely to be living in a single parent home ($\chi^2 = 4.96$, $p = 0.026$). Additional information for the biological samples is provided below in the Section 3.

2.4. Biologic specimens: hair

Hair specimen analyses were performed by Omega Laboratories, Inc., Mogadore, OH. Each specimen was weighed and washed with an organic solvent to remove possible external contamination. Hair specimens were pulverized, subjected to solid phase extraction, and analyzed by gas chromatography–mass spectroscopy (GSMS), tandem GCMSMS or GCGCMS depending upon the drug class evaluated. There was no initial screening of specimens by immunoassay. All specimens were analyzed at the limit of quantification. For cocaine, a test was positive if cocaine was present at 100 pg/mg, and benzoylecgonine (BE), norcocaine or cocaethylene was present at the limit of detection (LOD) of 20 pg/mg hair. For opiates, a positive result was reported if morphine or 6-acetylmorphine was 100 pg/mg. A hair specimen was reported as marijuana positive if the primary metabolite 11-nor-9-carboxy-9-tetrahydrocannabinol was present at a concentration of 0.1 pg/mg.

2.5. Biologic specimens: sweat and urine

Teens and parents unwilling or unable to provide a hair specimen were asked to wear a PharmChek® sweat patch or provide a urine specimen. Sweat patches were placed on the participant's bicep by a research assistant. One week later, the assistant removed the patch during a home visit. Drug elution was performed with a buffer solution of 75% methanol/25% 0.2 M sodium acetate at pH = 5.0. The specimen was then screened by ELISA. Specimens testing positive were analyzed using liquid chromatography–dual mass spectrometry (LCMSMS) for confirmation analysis. Patch screen and confirmation cut-off for cocaine and opiates was 25 ng/patch. For marijuana, screen cut-off was 1.5 ng/patch and 0.5 ng/patch for confirmation. For urine specimens, participants were brought to a private lavatory adjacent to the study site and asked to provide a specimen. Urine drug assays were performed with a qualitative and semi-quantitative homogenous enzyme immunoassay (Olympus AU640), with EMIT II Plus reagents. Cut-off values were cocaine: 300 ng/mL, opiates: 300 ng/mL and marijuana: 50 ng/mL.

2.6. Variables used for the model predicting teen cocaine use

Based upon information from the literature, a variety of prenatal, teen, parent and community characteristics, detailed below, were utilized to predict teen cocaine use.

2.7. Other prenatal exposures

As previously described in this cohort [24], prenatal alcohol exposure was measured prospectively by structured antenatal interviews for the peri-conceptional period and across pregnancy. Women were interviewed at each prenatal visit. A 14-day recall by beverage source estimated average ounces of absolute alcohol consumption per day (AAD), ounces of absolute alcohol per drinking day (AADD), proportion of drinking days, and volume and pattern indices. In addition to alcohol and cocaine use, women were similarly queried about their marijuana, opiate, heroin and tobacco use.

2.8. Teen behavior, psychological problems and exposures

To assess teen behavior, both teens and parents completed the Conduct Disorder Checklist (CDC) and Oppositional Defiant Disorder Checklist (ODDC). The CDC and ODDC constructed by our laboratory are modeled after the DuPaul ADHD checklist [31]. All 12 of the items for the CDC and 8 items for the ODDC were obtained from the DSM-IV symptoms necessary for the respective diagnosis. Conduct Disorder symptoms relevant to preteen years were not included. Teens rated the frequency of each symptom over the past six months on a 4-point Likert scale (0 = never/rarely, 1 = sometimes, 2 = often, and 3 = very often). Total score for both scales was used in the analyses. In addition, a trained research assistant conducted the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS-PL) [56]. The K-SADS-PL uses the DSM-IV, the gold standard for making psychiatric diagnoses [56]. To assess symptoms, the K-SADS-PL includes a flexible, systematic question format in separate semi-structured interviews for both teens and caregivers. Trained masters- and doctoral-level researchers conducted these interviews. Conduct Disorder and Oppositional Defiant symptoms within the K-SADS-PL were summed and total scores were used in analyses. In the model analysis, teen behavior problems were represented by a single latent factor using the CD and ODD checklists and the K-SADS-PL.

Teen Post-Traumatic Stress Disorder (PTSD) symptoms were also assessed with a multi-method approach (teen and parent report and clinical interview). Teens and parent completed the 20-item Post-Traumatic Stress Disorder Reaction Index (PTSD-RI) that assesses stress and anxiety symptoms [41]. DSM-IV criteria for PTSD were assessed with the K-SADS-PL [56]. Both the K-SADS-PL and the UCLA PTSD-RI provide a PTSD diagnosis and indicate whether the subject met all criteria for the diagnosis or if the subject met most of the criteria for a PTSD diagnosis. If the subject met criteria on either the K-SADS-PL or the UCLA PTSD-RI, they were considered positive for PTSD. If they were probable on either measure, they were given a probable PTSD diagnosis. To further assess evidence of teen PTSD symptoms, teens and parents completed the 28-item Checklist of Children's Distress Symptoms (CCDS) [83]. Although a PTSD diagnosis based on DSM criteria can be computed from this measure, individual validated scales were utilized to quantify PTSD components: Intrusive, Vigilance, Distractibility, Despondent, Emotional

Numbing, and Lack of Belonging. In the analyses to assess predictors of teen drug use, a single latent factor represented PTSD. Teen and Parent CCDS report, and a probable PTSD diagnosis (met all or most PTSD DSM-IV criteria) from both the K-SADS-PL and/or the PTSD-RI were considered indicators for this factor.

Community violence exposure (CVE) was evaluated at age 7 years with the “Things I Have Seen and Heard” (TISH) [84]. The TISH is a 20-item child self-report instrument that includes 17 exposure items that range from hearing gunshots to witnessing beatings, stabbings, or seeing dead bodies. At age 14 years, CVE was assessed with the Children’s Report of Exposure to Violence (CREV) [16] and the Survey of Exposure to Community Violence (SECV) [85]. The CREV is a brief but broad assessment of witnessed and experienced community violence exposure including sexual abuse and family violence [16]. Exposure to violence is assessed with four CREV modes: media, reports of others, witnessed, and victimization. Twenty-nine items were rated for frequency of lifetime exposure on a 5-point Likert scale. In addition, for situations where the child/teen was not the victim, the responder is asked to identify if and how s/he knew the victim. The SECV adds contextual information regarding the exposure [85]. Frequency of exposure (on a 9-point scale), types of exposure (direct victimization, witnessing, or hearing about the violence), and location of each exposure (home, school or other community sites) were queried. In addition to assessing trauma exposure via community violence, the PTSD-RI asked teens if they had been exposed to a trauma that they considered personally life-threatening. This trauma variable was operationalized as a dichotomous yes/no response.

In this study, we also included a specific measure of exposure to community drug use. At the age 7 assessment, the TISH contains two items that ask the child to report on drug exposure both within their home and within their community (i.e., “I have seen drug deals”; “I have seen drugs in my home”). At the age 14 visit, drug exposure at home and in the community was obtained using the SECV. There are 5 items on the SECV which query about drug exposure: 1) How many times you have been asked to get involved in drugs; 2) How many times you have been asked to take drug; 3) How many times you have seen someone asked to get involved with drugs; 4) How many times have you heard about someone being asked to get involved with drugs; and 5) How many times you have seen others using or selling drugs. Teens rated each of these questions on a 9-point scale (1 = never to 9 = almost every day). Responses from these 5 items are summed for a total community drug use score. In analyses predicting teen drug use, teen exposure to community drug use was represented by a latent factor which included both teen and caregiver report.

As IQ [38] and gender [28,96] have also been identified as predictors of teen drug use, we included both in the prediction model. IQ was assessed at age 14 with the Wechsler Intelligence Scales for Children-III [98].

2.9. Parent measures

2.9.1. Current parent drug use—As detailed above and in Delaney-Black et al. [19–21] biologic specimens requested from all participating caregivers defined current caregiver drug use with the exception of caregiver marijuana use that also included self-report.

2.9.2. Caregiver psychiatric problems and parenting style—The Personality Diagnostic Questionnaire-4th ed. (PDQ-4) assessed current caregiver psychopathology [53]. The PDQ-4 assists in personality disorder diagnoses consistent with DSM-IV criteria using a “true/false” format for 100 descriptions of abnormal behaviors. Follow-up questions regarding the duration of behaviors and functional impairment determine clinical diagnosis. Continuous caregiver psychopathology scores, not diagnoses, were included in the SEM model. Substance Abuse Disorder was not included as one of the PDQ summary scores in the Caregiver Psychopathology latent variable. The PDQ latent variable included the following PDQ scales: Paranoid, Antisocial, Avoidant, Negativistic, Schizotypal, and Borderline. Parenting style was assessed with the Parenting Styles and Dimensions Questionnaire (PSDQ) [86]. Using the PSDQ, caregivers reported their and their spouse’s/partner’s parenting style. When the caregiver had a partner in the home, the two sets of parenting style scores were averaged to obtain summary parenting style scores. If only one parent was in the home, only a single set of values was used. Scores on the following parenting scales were obtained: Authoritative, Authoritarian, Permissive, Autonomy, Coercive, Punitive, and Connectedness.

2.9.3. Maternal IQ—Parent IQ assessed with the performance subscale of the Wechsler Adult Intelligence Scale-Revised [97] at child age 7 years was utilized in the model unless a new caregiver was identified at age 14. For those cases, the later assessment was included.

2.9.4. Demographic questionnaire—This study-specific instrument collected various demographic information including family structure/changes, child health, and education history at child ages 7 and 14 years. Caregiver stability was defined as stable if the teen always lived with and was cared for by the biological mother. Conversely, the caregiver was considered unstable if there had been any change in caregiver through the child’s lifetime. Maternal/caregiver education was defined as the number of years of education. A GED was coded as 12 years of education. The SES score included in the SEM model was based on the Hollingshead Scoring System [49]. The Hollingshead scores consider both years of education and job/career status (see Table 1).

2.9.5. Statistical analyses—Prior to analyses addressing the hypotheses, checks were performed for missing and out-of-range data, and for normality. Covariates to be included in the model as predictors of teen cocaine use were initially identified via correlation analyses (Table 1). All control variables even modestly related to each outcome (at $p < 0.10$) were included in a logistic regression analysis. All variables were entered in the equation by a forward stepwise procedure ($p_{\text{entry}} = 0.05$, $p_{\text{removal}} = 0.10$). Once predictors were identified, Structural Equation Modeling (SEM) was performed using Mplus [72] to assess relations among current teen cocaine use, prenatal cocaine exposure, CVE, teen behavior and IQ. The SEM performed included 1) all variables empirically identified in the regression analysis as significant predictors of teen cocaine use; 2) standard covariates: SES, caregiver IQ, caregiver education, caregiver status, and teen gender; and 3) all prenatal exposures. Postnatal exposures were included only if they were significant predictors in the regression analysis. Finally, previous analyses provided a rationale for including IQ, PTSD, violence exposure, and negative teen behavior, as addressed below. As fit indices are not available

when the outcome is dichotomous and Maximum Likelihood Robust estimates are used, to estimate fit indices, a second model was estimated using a Weighted Least Squares Mean and Variance Adjusted Estimator (WLSMV) [89]. Using the WLSMV estimator fit was assessed by the comparative fit index (CFI), root mean square error of approximation (RMSEA) and 90% confidence interval for RMSEA. CFI >0.95 and RMSEA <0.06 indicate a good fitting model [50]. Due to non-normality in the data, the Satorra–Bentler scaled chi square was used [90]. Paths that were not significant at $p = 0.10$ were removed from the model. For the final dichotomous model, results are reported as unstandardized path coefficients.

3. Results

3.1. Sample and attrition

Of 656 eligible children at 7 years of age, 94% agreed to participate, and 85% completed lab testing ($N = 556$; 49.1% female). No differences in newborn characteristics were identified between participating and non-participating children at age 7 years. While non-participating mothers did not differ from those taking part on any prenatal drug or alcohol variable, mothers of participants were older and had more children. At age 7, study families within the Detroit area were not geographically stable with 86% reporting at least one move since the child was born (mean = 3.1). Further description of the 556 study participants at age 7 was previously published [24].

Table 2 provides sample characteristics for the 432 teens and 431 caregivers who participated in the age 14 assessment. No parent information was obtained for one teen who resided in a group home. SES from the age 7-visit was used for that subject. Compared to the age 7 assessment, the potential teen study sample was reduced by 4.9% to 530 subjects by interim out-of-state moves ($N = 15$), closed adoptions ($N = 2$), teen incarcerations ($N = 6$), and three youth deaths (one from leukemia, two homicide victims). Twenty-six families (4.7% of the 7-year sample) could not be located, 39 refused participation (7.0%) and 31 (5.6%) were “passive refusers,” who despite multiple scheduled visits, failed to attend a testing session. Youth assessments were obtained from 81.5% of the available age seven sample. Those who participated in the teen follow-up did not differ from those not tested on most demographic measures (e.g., maternal IQ or age, parent education or SES, and child gender), or on prenatal alcohol or drug exposure. At age 14 years participants were more likely to have parents who were married ($\chi^2 = 5.5$, $p = 0.019$) and to be living with their biological mother ($\chi^2 = 16.2$, $p = 0.001$) than those not tested.

3.2. Teen drug use assessment

Hair specimens were reported in detail in Delaney-Black et al. [19]. Biologic specimens were predominantly hair; however, as previously noted, sweat and urine specimens were added to the study protocol as hair was not always available. The primary aim of this study was to determine factors that predicted teen cocaine use, thus, the laboratory was instructed to test first for cocaine, then opiates if sufficient hair specimen remained. An adequate biologic specimen was obtained to test for at least one drug from 316 of 432 teens (hair: 266, sweat: 23, urine: 27) and 325 of the 431 caregivers (hair: 292, sweat 17, urine: 16).

Table 3 provides drug specimen results: 29.4% of teens tested positive for cocaine; 5.2% for opiates; and 4.2% for marijuana. For the reasons previously noted, self-report (21.2%) was combined with the biologic specimen data to identify teen use of marijuana (23.2%).

3.3. Caregiver drug use at the age 14 assessment

At the age 14 assessment, 25.5% of caregivers tested positive for cocaine; 16.3% for opiates; and 29.7% either tested positive or admitted to marijuana use. Concordance was high for caregiver cocaine use measured during pregnancy and at the child's age 14 assessment. Fifty-two percent ($N = 39$) of the 75 biological mothers who used cocaine during pregnancy again tested positive for cocaine at the age 14 assessment ($Kappa = .39$, $p < 0.001$). In contrast, 15.7% of the 185 biological mothers who had not used cocaine prenatally tested positive for cocaine at age 14 ($Kappa = -.05$, $p = ns$; McNemar $\chi^2 = 1.02$, $p = ns$). The incidence of cocaine use among caregivers who were not the biological mother at the 14 year visit was intermediate between the other two groups of caregivers at 26%. Teens prenatally exposed to cocaine were three times more likely to have a caregiver that was not the biological mother ($\chi^2 = 37.1$, $p < 0.001$). As a result, consistency of prenatal and postnatal cocaine exposure was reduced (McNemar $\chi^2 = 11.45$, $p < 0.001$). Overall, current cocaine use was the same for biologic mothers as it was for the caregivers who were not the biological mother, perhaps related to the extent of kinship-care present in this sample. Only 3.5% of all teens were being cared for by a non-kin caregiver. Among teens not being cared for by the biologic mother 83% were still in the custody of a relative.

3.4. Analyses assessing quantity of prenatal cocaine exposure

Our previous studies have demonstrated that heavy and/or persistent but not more modest prenatal cocaine exposure predicted negative child behavior [23,24]. However, as other research groups have identified cocaine effects with any prenatal exposure, chi square analyses were used to evaluate if any prenatal cocaine exposure, not just heavy and/or persistent exposure, was predictive of teen cocaine use. A chi square was performed comparing the trichotomous prenatal cocaine exposure variable (none, some, and heavy/persistent) with teen cocaine use. Among those teens *not* exposed prenatally to cocaine, 22% used cocaine. Similar rates of teen cocaine use were found in both the some and heavy/persistent prenatal cocaine exposure groups: 43% of teens with some exposure; and 40% of teens with heavy/persistent exposure ($\chi^2 = 13.01$, $p < 0.001$). Teens in both the some and heavy/persistent prenatal exposure groups used cocaine twice as often as those teens not exposed to prenatal cocaine. As a result, all analyses that followed used the dichotomous prenatal cocaine variable: "none" vs. "any" exposure.

3.5. Preliminary analyses

Based on existing literature and earlier findings from this cohort, a wide array of potential covariates of the association between prenatal cocaine exposure and adolescent cocaine use has been identified as theoretically meaningful. To establish a more parsimonious model for the present structural equation model (SEM) analysis, a series of preliminary analyses were conducted to determine a set of covariates that was empirically justified from the larger set of theoretically relevant covariates.

3.6. Gender effect

Analyses were performed on the influential effect of gender as our previous studies have suggested a greater influence of prenatal cocaine exposure on behavior in boys [24] and on IQ in girls (unpublished data). However, in these current analyses gender did not have a significant impact on teen cocaine use. The incidence of teen cocaine use was 33% among the girls and 25% for boys ($\chi^2 = 2.14$, $p = 0.144$). In addition, a gender $\times$ prenatal cocaine $\times$ teen cocaine use analysis identified no gender by teen cocaine use difference for teens prenatally exposure to cocaine ($\chi^2 = 0.69$, $p = 0.408$), or for teens not prenatally exposed to cocaine ($\chi^2 = 0.80$, $p = 0.370$). Thus, although gender was included as a covariate in the analyses, including in the final model, further gender effects were not examined.

3.7. Other variables related to teen cocaine use

As previously noted in Section 2, to identify other important covariates that predict teen cocaine use, we assessed the univariate Pearson's Correlation Coefficients (r) between teen cocaine use and teen behavior, cognition, academic achievement, psychopathology, and violence exposure. In addition, other prenatal exposures and numerous caregiver measures (current drug use, demographic data, negativity and psychopathology) were also examined. Table 1 provides all constructs and measures that significantly ($p < 0.05$) predicted teen cocaine use. Our study hypothesis that prenatal cocaine exposure would be associated with teen cocaine use was also confirmed by the univariate analysis. Additionally, teen cocaine use was predicted by prenatal nicotine exposure (i.e., number of cigarettes) as well as by current caregiver cocaine use (Table 4).

3.8. Regression analysis predicting teen cocaine use

To identify important predictors of teen cocaine use, all potential predictors (presented in Table 1), and all pre- and postnatal exposures were entered into a logistic regression analysis using a forward stepwise procedure (p entry = 0.05, p removal = 0.10). As shown in Table 5, after control for important covariates, both current caregiver cocaine use (i.e., at 14 years) and the dichotomous ('yes/no') prenatal cocaine exposure measure uniquely predicted teen cocaine use. In addition, teen cocaine use was predicted by exposure to community violence exposure, community drug use, and parent negativity measured by the PDQ.

3.9. Structural Equation Modeling (SEM) to predict teen cocaine use

Following the regression analysis, a SEM was performed. In addition to prenatal cocaine exposure, we included in the model age 14 caregiver cocaine use as well as the three other predictors significant in the regression analysis: community violence exposure, caregiver psychopathology from the PDQ, and community drug exposure. Finally, standard covariates (SES, caregiver IQ, caregiver education, lifetime change in child custody status, and teen gender) and all other prenatal exposures (opiates, marijuana, cigarettes, and alcohol) were included. No postnatal exposures other than caregiver current cocaine use were included in the model, as they were not significant predictors in the regression analysis. Community violence exposure (CVE) and PTSD were also included in the model because previous analyses of our age 7 data identified PTSD as a predictor of negative teen behavior [21]. CVE and drug exposure measures at age 7 were also included to allow for identification of

developmental paths. Finally, although not significant, teen IQ and negative teen behavior (CD/ODD) were also included in the model as previous analyses of these data have identified relations between teen CVE and IQ and behavior changes [20,21]. Results of the model are presented in Fig. 1. Paths that were not significant at $p \leq 0.10$ were removed from the model. For the final logistic model, results were reported as unstandardized path coefficients. As previously mentioned, as fit indices are not available when the outcome is dichotomous and Maximum Likelihood Robust (MLR) estimates are used, a second model was estimated using a Weighted Least Squares Mean and Variance Adjusted (WLSMV) estimation procedure. While this procedure does not provide as efficient estimates as the MLR procedure for dichotomous outcomes, it does allow for the estimation of standard fit indices [89]. Using this alternative estimation procedure, the final model yielded an adequate fit to the data: $\chi^2(77) = 109.42$, $p < 0.01$, RMSEA = .042, CFI = .943. To simplify presentation of these results, only the standardized total effect of the predictor on the outcome is given for the logistic model.

Caregiver IQ (measured primarily at child age 7) and caregiver psychiatric symptoms were both related to a caregiver covariate factor that included SES and caregiver education ($B = .42$, $p < 0.001$ and $B = -.25$, $p < 0.001$, respectively). Caregiver psychiatric problems also increased teen PTSD symptoms ($B = .09$, $p < 0.001$) whereas caregiver IQ was positively related to teen IQ ($B = .29$, $p < 0.001$). Higher scores on the caregiver covariate factor were also positively related to teen IQ ($B = .31$, $p < 0.001$) and negatively related to caregiver current cocaine use ($B = -.09$, $p < 0.001$). Maternal prenatal cocaine use was negatively related to consistent maternal custody (Always Mom's custody) ($B = -.09$, $p < 0.001$). Mothers who used cocaine during pregnancy were more likely to use cocaine at the 14 year assessment ($B = .23$, $p < 0.001$). Maternal loss of custody e.g., not always residing with the biological mother, increased 7 year child violence exposure ($B = -.15$, $p = 0.003$). Teen PTSD symptoms were positively influenced by 7 year violence exposure ($B = .11$, $p = 0.029$) as well as 14 year violence exposure ($B = .19$, $p < 0.001$). Violence exposure at both ages increased teen PTSD symptoms, and both age 7 and teen violence predicted lower teen IQ scores ($B = -.45$, $p < 0.001$ and $B = -.34$, $p = 0.005$, respectively). Important to these relations was the influence of gender and community drug use on teen violence exposure. Boys (coded as 1) were exposed to higher levels of violence ($B = -.24$, $p < 0.001$); and teens with more community drug exposure were also exposed to more violence exposure ($B = .41$, $p < 0.001$). Although an increase in teen conduct problems was related to higher levels of PTSD symptoms ($B = 1.06$, $p = 0.013$), negative teen behavior did not directly or indirectly influence teen cocaine use in this sample. The only significant predictors of teen cocaine use were prenatal cocaine exposure ($B = .90$, $p = 0.008$) and current caregiver cocaine use ($B = 1.79$, $p < 0.001$). Teens whose caregivers currently used cocaine were almost 6 times more likely to use cocaine; teens exposed to cocaine prenatally were more than twice as likely to use cocaine at the 14 year assessment.

4. Discussion

The present study evaluated relations between teen cocaine use and a variety of teen, caregiver and community risk factors in a longitudinal cohort of high-risk urban young adolescents. In this cohort, 5.2% of teens tested positive for opiates and over five times as

many, 29.4%, had a positive biological test for cocaine. Teen exposure to cocaine and other drugs (opiates, marijuana and alcohol) during their own fetal development, as well as biologic measures of current illicit drug use by the caregiver, and community characteristics (drug-related activity and community violence), not previously available in other studies, were all assessed. This prospective cohort and these diverse measures, including biologic assessments provide a unique opportunity to assess predictors of cocaine use among high-risk urban teens. In this sample, only two direct predictors of teen cocaine use remained in the final model: caregiver's current cocaine use (i.e., "postnatal" cocaine exposure), and the dichotomous prenatal cocaine exposure.

Unfortunately, but perhaps not surprisingly, many biological mothers who used cocaine during the index pregnancy were still using cocaine at the 14 year assessment. Caregiver substance use [76,94] and maternal cocaine use during pregnancy [14,24,27,32,55,75,81,82,93] have been identified as risk factors for adverse child outcomes[45], and both risks are associated with certain environmental conditions known to alter child outcome, including poverty [35] and harsh parenting style [78]. These associations may confound the observed relations between prenatal cocaine exposure and teen cocaine use. Our analyses controlled for SES and caregiver psychiatric conditions. Although some investigators have suggested that the reported behavioral effects of prenatal cocaine exposure may be solely related to postnatal environmental or experiential factors rather than the prenatal cocaine exposure itself [52], the current analyses do support the hypothesis that *both* prenatal exposure and experience with maternal cocaine are powerful influences.

While we found no other peer-reviewed published studies addressing the relation between prenatal cocaine exposure and teen cocaine use, animal research provided substantial evidence of such a relation. Preclinical studies of prenatal cocaine exposure demonstrate altered central neurochemical function in postnatal rats, including reduced cholinergic transmission to amphetamine challenges [43], increased sensitivity to both D1 and D2 dopamine receptor-selective agonists [69], decreased D2 receptor binding in nucleus accumbens and markedly increased D3 receptor binding in nucleus accumbens and striatum in males but not females [91], increased serotonin 5HT_{2A} receptor sensitivity but decreased 5HT levels [7,13,15], and increased opiate receptor binding potential [14]. In preclinical studies, prenatal cocaine exposure altered cocaine reinforcement in both male and female adult rats.

It is tempting to speculate on the roles that possible teratogenic effects of prenatal cocaine exposure on brain function may play in the risk for early substance use in these teens. Indeed, as evidenced by recent fMRI work, the strong direct relation we found between the mothers' cocaine use during her pregnancy 14 years previously and her teen's current cocaine use may be mediated by neurochemical changes [65].

Despite prior findings of gender-specificity, our study hypothesis that prenatal cocaine exposure would be associated with greater teen cocaine use among males, but not females, was not substantiated by our study results. Both preclinical [6,30,39,91] and human studies [10], including our own prior publications [24,27], have identified gender-specific effects of

behaving badly or of psychopathology. Rather, the CVE, caused in part by community drug use, is another factor – like current caregiver cocaine use – that defines the community and home environments where cocaine use is common and may be socially acceptable.

Although this study has many positive design elements – including prospective pregnancy assessment of maternal drug use, large sample size, control for many child, family and community factors as well as biologic testing for both teen and caregiver drug use at the age 14 assessment – it is not without limitations. Hair specimens for cocaine metabolites were limited to 72% of the teens and 74% of the caregivers. Conversely no drug use data are available for 27% of the teens and 25% of the caregivers. Although the incidence of cocaine use was high in this sample, because 10% of the teens and 17% of the caregivers refused a biologic specimen, these data may still under-estimate cocaine use in this high-risk urban sample. As with all new findings, confirmation of the relation between prenatal cocaine exposure and teen cocaine use should be addressed by other research groups with large, prospective studies and biologic measures of postnatal drug use. In the interim, however, pregnant women and their caregivers should be cautioned that prenatal cocaine exposure may have important, long-term effects on drug use by their unborn children.

In conclusion, this study found that both postnatal (i.e., parent/caregiver) cocaine use and prenatal cocaine exposure were each independently related to teen use of cocaine at 14 years of age. Data from this study provide further evidence of the importance of both prenatal cocaine exposure and maternal/caregiver cocaine use in the trans-generational perpetuation of illicit substance use/abuse.

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Fig. 1.

Model predicting teen cocaine use. Caregiver IQ and psychiatric symptoms were related to a caregiver covariate factor that included SES and caregiver education. Caregiver psychiatric problems also increased teen PTSD symptoms. Higher scores on the caregiver covariate factor were negatively related to caregiver current cocaine use. Maternal prenatal cocaine use was negatively related to consistent maternal custody (Always Mom's custody). Maternal custody loss increased 7 year child community violence exposure (CVE). Further, both 7 and 14 year CVE were associated with increased teen PTSD symptoms. Teens with more community drug exposure were also exposed to more violence exposure. The only significant predictors of teen cocaine use were prenatal cocaine exposure and current caregiver cocaine use. Teens whose caregivers currently used cocaine were almost 6 times more likely to use cocaine; teens exposed to cocaine prenatally were more than twice as likely to use cocaine at the 14 year assessment.

Table 1

Domains and variables related to teen drug use.

Teen predictors	Measures
Point subtraction aggression paradigm	Total # of responses, total money; total aggressive responses
Memory	Digit span reaction time
Achievement	WIAT Numerical Operations Scales Score; WIAT Math Standard Score; APS Academic Problems
Behavior — CD/ODD/externalizing behaviors	CBCL: aggressive behavior problems; Conduct Disorder Total Score; Externalizing Behaviors Total Score; K-SADS-PL CD Sum Score; K-SADS-PL ODD Sums Score; number of suspensions
Behavior — anxiety/PTSD	Anxiety Total Score; APS anxiety, APS PTSD, UCLA Exposed to Trauma Scale
Behavior — other	ADHD Checklist Parent Report; CBCL ADHD Total Score
Parent Child Conflict Tactics Scale	Total severe corporal punishment; total corporal punishment; overall physical violence
Perception of discrimination	Total racial discrimination
Community predictors	Measures
Violence exposure	CREV and SECV Factor Scores: witness major/victimization; witness minor; told about violence
Community drug use	Teen and Caregiver SECV Report
Caregiver predictors	Measures
Demographics	Caregiver education; SES; primary caregiver changes; number of children in household
Psychopathology	SCL-90-R anxiety; PDQ negativity

Table 2

Sample characteristics.

	N	Mean or %	SD	Range
<i>Caregiver</i>				
Education (years)	431	12.2	2.0	2–21
Marital status (% married)	431	24.1	–	–
SES ^a	432	28.5	11.4	8–66
Age at 14-year visit (years)	430	43.4	9.8	27.0–79.6
Primary caregiver				
% Mother	432	80.8	–	–
% Father	432	2.5	–	–
% Foster/adoptive care	432	3.5	–	–
<i>Teen</i>				
Age at the teen visit (years)	432	14.5	0.9	12.9–17.8
Gender (% male)	432	49.5	–	–
IQ ^b	424	78.8	13.7	40–143

^aBased on Hollingshead four factor index of social status, 1975.^bWISC-III.

Table 3

Teen and parent drug use specimens.

	Teens			Parents		
	Cocaine	Marijuana	Opiate	Cocaine	Marijuana	Opiate
Bioassay results available	309 (71.5%)	299 (69.2%)	279 (64.6%)	319 (74.0%)	303 (70.3%)	275 (63.8%)
Reasons for no hair specimen						
Refused hair specimen ***	44 (10.2%)	44 (10.2%)	44 (10.2%)	73 (16.9%)	73 (16.9%)	73 (16.9%)
Hair too short for sampling	52 (12%)	52 (12%)	52 (12%)	9 (2.1%)	9 (2.1%)	9 (2.1%)
Insufficient hair specimen	8 (1.9%)	18(4.2%)	38 (8.8%)	9 (2.1%)	25 (5.8%)	52 (12.1%)
Hairstyle (braids, weave etc)	10 (2.3%)	10 (2.3%)	10 (2.3%)	9 (2.1%)	9 (2.1%)	9 (2.1%)
Teen did not complete testing	9 (2.1%)	9 (2.1%)	9 (2.1%)	9 (2.1%)	9 (2.1%)	9 (2.1%)
Laboratory error	–	–	–	3 (0.7%)	3 (0.7%)	4 (0.9%)
No caregiver	–	–	–	1 (0.2%)	1 (0.2%)	1 (0.2%)

* 316 (73.1%) of teens and

** 325 parents (75.4%) provided an adequate biologic specimen for testing of at least one drug (cocaine, opiates or marijuana).

*** 6 of the caregiver participants listed as “Refusers” initially agreed to the sweat patch but removed and discarded the patch.

Table 4

Univariate relations between prenatal and “postnatal” alcohol/drug exposure and teen cocaine use.

	<u>Teen cocaine use</u>
	<u>r</u>
<i>Prenatal exposures</i>	
Alcohol	.13*
Nicotine	.15**
Illicit drugs	
Cocaine	.20***
Opiates	.09
Marijuana	.16**
<i>Current caregiver use</i>	
Alcohol	.10 [†]
Nicotine	.14**
Illicit drugs	
Cocaine	.37***
Opiates	.09
Marijuana	.08

[†]
p<0.10.*
p<0.05.**
p<0.01.***
p<0.001.

Table 5

Multiple regression results predicting teen cocaine use.

Predictor	Teen cocaine use
	β
Prenatal cocaine exposure	.18*
Current caregiver cocaine use	.34**
PTSD-RI trauma exposure	.13 [†]
Caregiver PDQ negativity	.17*
Community drug exposure	.16*

[†]
p<0.10.*
p<0.05.**
p<0.001.