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Problematic Substance Use in Urban Adolescents: Role of Intrauterine Exposures to Cocaine and Marijuana and Post-Natal Environment

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Abstract

Background—Linkages between intrauterine exposures to cocaine and marijuana and adolescents' problematic substance use have not been fully delineated.

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Contributors

Deborah A. Frank designed the study and oversaw development of the manuscript. Seth Kuranz managed literature searches and wrote portions of the paper. Danielle Appugliese, Howard Cabral, Timothy Heeren and Clara Chen conducted and presented statistical analysis. Denise Crooks, Jane Liebschutz, Mark Richardson, and Ruth Rose-Jacobs read and commented on multiple drafts of the manuscript.

Conflict of Interest

All authors declare they have no conflicts of interest

Methods—Prospective longitudinal study with assessors unaware of intrauterine exposure history followed 157 urban participants from birth until late adolescence. Level of intrauterine exposures was identified by mother's report and infant's meconium. Problematic substance use, identified by the Voice Diagnostic Interview Schedule for Children (V-DISC) or the Audio Computer Assisted Self-Interview (ACASI) and urine assay, was a composite encompassing DSM-IV indication of tolerance, abuse, and dependence on alcohol, marijuana, and tobacco and any use of cocaine, glue, or opiates.

Results—Twenty percent (32/157) of the sample experienced problematic substance use by age 18 years, of whom the majority (22/157) acknowledged abuse, tolerance or dependence on marijuana with or without other substances. Structural equation models examining direct and indirect pathways linking a Cox survival model for early substance initiation to a logistic regression models found effects of post-natal factors including childhood exposure to violence and household substance use, early youth substance initiation, and ongoing youth violence exposure contributing to adolescent problematic substance use.

Conclusion—We did not identify direct relationships between intrauterine cocaine or marijuana exposure and problematic substance use, but did find potentially modifiable post-natal risk factors also noted to be associated with problematic substance use in the general population including earlier substance initiation, exposure to violence and to household substance use.

Keywords

Adolescence; Intrauterine Cocaine Exposure; Marijuana; Problematic Substance Use; Household Substance Use

1. INTRODUCTION

Substance misuse is widespread among America's youths and young adults (Shih et al., 2010; Wu et al., 2011). Among 12 to 17 year olds in the United States, 7.3% reported dependence or abuse of illicit drugs or alcohol during the past year. The national prevalence of past year dependence or abuse of illicit drugs or alcohol was 16.6% among 18 year olds and 20.0% among 19 and 20 year olds (Substance Abuse and Mental Health Services Administration (SAMHSA), 2011).

Studies have delineated racial/ethnic, male/female, and regional variability in substance use, dependence, and abuse (Shih et al., 2010). Among high school students in Boston, 2.3% of males and 1.2% of females reported using any form of cocaine, while 21.2% of females and 32.7% of males in reported using marijuana in the past 30 days. These data, derived from high school students, may underestimate actual prevalence of use in the age cohort, since they cannot account for use by adolescents who have dropped out of school, a population with higher rates of use (SAMHSA, 2011).

The predictors of adolescent substance use and abuse are complex, encompassing exogenous social factors, the adolescent's cognitive and behavioral characteristics, and endogenous factors (intrauterine exposures, genetic predisposition, sex, race/ethnicity; Galea et al., 2004). Exogenous factors are diverse and numerous. For example, in a retrospective study of Adverse Childhood Experiences (ACEs) exposure to household substance use, household

dysfunction such as criminal behavior or observing a mother treated violently, and physical, sexual, and psychological abuse as a child were found to be risk factors for later alcoholism and illicit drug use (Felitti, 2002). Studies have shown that the relationship between ACEs and the risk of alcohol misuse and abuse in adulthood are independent of a history of parental alcoholism (Dube et al., 2006). Substance dependent parents, externalizing behaviors in adolescents, low commitment to school (Stone et al., 2012), poly-substance use in adolescence (Schmid et al., 2007) family conflicts, poor impulse control, living in a neighborhood with high crime rates or drug use (Ali et al., 2011), and victimization by violence (Doherty et al., 2012) may promote and perpetuate later drug dependence and problematic substance use in young adulthood.

Research conducted among children of alcoholics (King and Chassin, 2007) and more representative samples of the U.S. population (Chen et al., 2009; Grant and Dawson, 1998) found early initiation of cocaine and marijuana use in adolescence to be associated with an increased risk of later drug dependence (Chen et al., 2009; Grant and Dawson, 1998; King and Chassin, 2007) and alcohol dependence (Grant and Dawson, 1998). However, one study found early initiation of drug use may not predict later alcohol and drug dependence among 20th century Black populations (Grant and Dawson, 1998). Conversely several potential protective factors have been identified including close parental supervision and religiosity (Schulenberg et al., 2005; Stone et al., 2012).

Intrauterine exposures to alcohol and other psychoactive substances have been associated in prospective investigations with early initiation of licit and illicit substances. In a longitudinal study, intrauterine marijuana exposure (IUME) was found to be associated with marijuana initiation at age 14 (Day et al., 2006). Among 16 to 21 year olds, intrauterine tobacco exposure (IUTE) was associated with marijuana initiation (Day et al., 2006; Porath and Fried, 2005), while IUTE but not IUME was associated with tobacco initiation (Porath and Fried, 2005). In a prospective cohort of white and black adolescents, intrauterine cocaine exposure (IUCE), as well as a family history of alcohol problems and adolescent's history of exposure to violence were been found to be associated with early adolescent marijuana and alcohol use (Richardson et al., 2013). In contrast, Lester and colleagues (2012) found that there was no direct association between IUCE and age of substance use initiation once neurobehavioral disinhibition (based on a composite indicator of externalizing behaviors at ages 8, 9 years) was considered as a mediator (Lester et al., 2012).

Recent studies examining the relationship between IUCE and the offspring's cocaine use in adolescence yield mixed results. A prospective IUCE cohort study conducted in Detroit found a more than two-fold increased risk of cocaine use, measured using hair, sweat, or urine samples, at the age of 14 years among young adolescents with IUCE (Delaney-Black et al., 2011). In contrast, a prospective IUCE cohort study from rural Florida found no significant differences in pre-teen cocaine use, identified by positive hair specimens, between those with and without IUCE (Warner et al., 2011).

In both studies, the interpretation of adolescent cocaine use is somewhat uncertain because of reliance primarily on hair samples, which may not unequivocally differentiate the adolescent's own cocaine use from environmental contamination (Romano et al., 2001).

Standard criteria of substance use disorder as laid out in the Diagnostic and Statistical Manual-IV (DSM-IV) do not appear to have the same validity among adolescents as among adults (Winters et al., 2011). There are a number of complex factors to take into account with subsyndromic substance use that may cause physical or other harm in adolescent populations. These diverse potential negative consequences of use (Mason et al., 2007), have been evaluated by other researchers in varying composites with the more classic definitions of substance use disorders such as tolerance, addiction, or dependence under the rubric which we will also use of “problematic substance use” (Roelofs, 2001).

In addition to the obvious concern that mothers’ use of psychoactive substances in pregnancy may be a marker for genetic vulnerability to substance use disorders, the earlier initiation of psychoactive substance found in some, but not all, studies of adolescents with intrauterine substance exposures, raises concern that this may be a group at increased risk for problematic substance use by later adolescence.

Data regarding prenatal exposures and later problematic substance use (as opposed to early initiation of substance use) are sparse. Intrauterine alcohol exposure (IUAE) has been associated with an increased risk of alcohol problems at age 21 years in the U.S. (Baer et al., 2003), but not in an Australian cohort (Alati et al., 2005). Little is known about intrauterine exposures to illicit substances and later problematic substance use.

Taken as a whole, prior research findings suggest that linkages between intrauterine substance exposure and later problematic substance use have not yet been fully delineated, particularly with regard to the relative roles played by endogenous factors such as sex and intrauterine exposures and exogenous forces in the social environment.

In the current cohort, the association between intrauterine substance exposures (IUSE), environmental factors and the early initiation of substance use have been previously reported (Frank et al., 2011), with findings largely consistent with the subsequent reports of other investigators (Minnes et al., 2013; Richardson et al., 2013). We reported heavier IUCE and lighter IUME were both significantly associated with initiation of any substance use by the age of 16 (Frank et al., 2011). Adolescents in our cohort who reported higher levels of violence exposure were at increased risk of early initiation of any substance by 16 compared to adolescents who reported lower levels of violence exposure. In addition, marijuana use by a member of the adolescent’s household was associated with an increased risk of the adolescent’s own marijuana use (Frank et al., 2011).

The goal of the current analysis is to extend our previous work on age of substance initiation to evaluate whether there are direct or indirect associations between levels of IUCE and IUME and problematic substance use by late adolescence (16–18) after controlling for relevant covariates.

2. METHODS

2.1. Sample recruitment

As has been previously reported in greater detail (Frank et al., 1999; Tronick 1996), sample recruitment occurred 8–72 hours after delivery during post-partum hospitalization at Boston City Hospital (now Boston Medical Center) between October 1990 and March 1993, with screening for eligibility conducted 7 days a week with the exception of major holidays or interviewer illness. Mother and infant medical records, interviews conducted by trained research staff, biological measures and infant physical examinations were assessed to identify the following inclusion criteria: infant gestational age ≥ 36 weeks; no neonatal intensive care; no obvious major congenital malformations; no diagnosis of fetal alcohol syndrome in the neonatal record; no positive HIV history noted in the mother's or infant's medical record; no indication by neonatal or maternal urine toxicology screen or history in medical record of mother's use during pregnancy of illegal opiates, methadone, amphetamines, phencyclidine, barbiturates, or hallucinogens; mother aged 18 years or older (which was considered at that time as the minimum age for valid informed consent); and mother's ability to communicate fluently in English. These criteria were established to exclude subjects with known risk factors (such as premature birth) that might have confounded the effects, if any, of intrauterine cocaine exposure on later outcomes of interest, and to permit consistent administration of later study measures most of which at that time were only available in English.

Of the 192 mothers identified clinically as cocaine users and invited to join the study 64% agreed to participation, while 21% of 646 mothers not clinically identified as cocaine users also agreed. Within the cocaine exposed group no statistically significant differences were found in mothers' age, parity, ethnicity or mode of payment for medical care among those who were recruited, refused, or not approached by research staff. Within the non-exposed group those recruited were significantly ($p=.03$) more likely to be primiparous than those who refused or were not approached, but did not differ on other parameters. At the beginning of the study, 252 birth mothers provided informed consent and provided baseline data for analysis.

The Institutional Review Board of Boston Medical Center has approved this study each year since its inception. A Certificate of Confidentiality was obtained from the federal government to protect researchers from being compelled by subpoena to release data regarding study participants.

If a child's caregiver changed between study contact points, informed consent was obtained from the new caregiver who was also interviewed regarding the child's current environment. Assent was first obtained from the children at the 8-year visit.

2.2. IUCE classification

For all subjects in the study, IUCE status was confirmed by at least one biological marker, either urine from mother or infant or meconium from the infant. Research assistants also administered the Addiction Severity Index (McLellan et al., 1980) in order to identify mothers' patterns of use of psychoactive substances during pregnancy. In order to be

classified as “unexposed,” mothers had to deny the use of cocaine during the interview and all available biological markers from both the mother and infant needed to be negative for cocaine metabolites.

For some mothers in the study, urine tests for metabolites of illicit drugs were conducted at the discretion of health care professionals during pregnancy, results of which were extracted from medical records when available. After recruitment and informed consent following delivery, urine samples were collected from all participating mothers for analysis of benzoylecognine, opiates, amphetamines, benzodiazepines, and cannabinoids by radioimmunoassay using commercial kits (Abuscreen RIA, Roche Diagnostics Systems, Inc, Montclair, NJ). Meconium specimens were also sought from all enrolled newborns to be analyzed by radioimmunoassay for benzoylecognine (a cocaine metabolite), opiates, amphetamines, benzodiazepines, and cannabinoids.

Among cocaine users in this sample, the mean days of self-reported cocaine use during pregnancy was 20.6 days (range: 0 – 264 days). The mean meconium concentration was 1143 nanogram (ng) of benzoylecognine per gram (g) of meconium (range: 0 – 17950 ng of benzoylecognine/ g of meconium). Composite a priori definitions of “heavier” and “lighter” cocaine use were created before the data were analyzed. The top quartile of meconium concentration for cocaine metabolites (3314 ng of benzoylecognine/g of meconium) and/or the top quartile of self-reported days of use (>61 days) during the entire pregnancy were used to define “heavier” cocaine use. Any other cocaine use was classified as “lighter.” As has been described in earlier reports (Frank et al., 1999), in cases when meconium levels and self-report did not agree, the measure that indicated a higher level of exposure was used to categorize a subjects exposure level.

2.3. Other intrauterine substance exposure determined during the neonatal period

IUME was also analyzed according to an a priori, composite index including results from the urine assay, meconium assay, and maternal self-report. For a subject to be classified as unexposed to marijuana, the urine and meconium assays and the mother’s self-report all had to be negative. “Heavier” marijuana use was categorized as a positive meconium or assay or positive urine at delivery or the top quartile of self-reported days of use (>8 days during pregnancy). “Lighter” marijuana users were categorized as those positive by self-report or gestational urine assay but who did not meet criteria for inclusion in the heavier group. This classification scheme was significantly associated with the use of alcohol, cigarettes, and cocaine during pregnancy ($p<0.0001$) and with the infants’ mean birth weight – Marijuana Unexposed 3211 g (s.d. 477), “Lighter” 3069 g (s.d. 464), and “Heavier” 2943 g (s.d. 511), $p=0.02$). Further details regarding this marijuana classification scheme and its justification are reported elsewhere (Frank et al., 2011).

Identification of intrauterine alcohol and tobacco use was by self-report. At the time the study was initiated, there was no established biomarker for gestational alcohol exposure and cotinine assays for tobacco metabolites were too expensive to be utilized. Therefore, the Addiction Severity Index (McLellan et al., 1980) was supplemented with study specific questions regarding alcohol and tobacco use during the index pregnancy. These included the self-reported average daily volume of alcohol consumed per day in the 30 days prior to

delivery, recommended at the time and currently as one of the most sensitive and specific measures for use in pregnancy (Burns et al., 2010). Alcohol use was then categorized as “none,” “lighter” (<1 drink/day) or “heavier” (≥1 drinks/day) in the 30 days prior to delivery. IUTE was measured as the self-reported average number of cigarettes that mothers consumed per day while pregnant. Cigarette use was categorized as “none,” “lighter” (<11 cigarettes a day), or “heavier” (≥11 cigarettes a day) during pregnancy.

2.4. Procedures

2.4.1. Outcome measures: Problematic substance use—As noted above, we use the term problematic substance use as a composite encompassing DSM-IV indication of tolerance, abuse, and dependence on alcohol, marijuana, and tobacco and what others describe as “unhealthy use” (McCowan et. al. 2013) encompassing *any* use of more hazardous or stigmatized substances such as cocaine, glue, or opiates by self-report or urine assays. Problematic substance use was assessed at three study contacts at early adolescence (EA) 12 to 14, middle adolescence (MA) 14 to 16, and late adolescence (LA) 16 to 18 years. The assessment at the oldest age available was the outcome of interest. There was some overlap in study intervals since logistics and participants’ schedules caused contacts to occur earlier or later than initially planned. Problematic substance use indicators at LA (mean age of 17.04 years, s.d. of 1.73 years) were measured using the National Institute of Mental Health Diagnostic Interview Schedule for Children (DISC). The Voice DISC (V-DISC) is a self-administered automated version of the instrument that assesses common mental disorders, including substance use disorders among adolescents (Shaffer et al., 2000).

An adolescent was categorized as a problematic substance user if the V-DISC diagnosis was positive for abuse, lifetime dependence, or tolerance of alcohol or marijuana, ascertained by questions such as “In the last year, did you get into trouble at [school/work] or did you have problems [with your schoolwork/doing your job] because of marijuana?”

Problematic tobacco use was defined as lifetime dependence on tobacco. Other drug use was considered problematic if the adolescent responded with “yes” to the question of ever having used the drug or had a positive urine assay for cocaine, opiates, or amphetamines.

If the V-DISC assessment was not available from the most recent interview, then problematic substance use was derived from the last point in time at which the adolescent completed the Audio Computer Assisted Self-Interview (ACASI). The last assessment point for 11 adolescents was during the middle adolescent protocol, at age 16 years (mean age of 15.42 years, s.d. of 0.75 years) and six adolescents during the early adolescent protocol or at age 14 years (mean age of 14.46 years, s.d. of 0.56 years). The substance use related questions on the ACASI consisted of validated questions from the CDC’s 2005 Youth Risk Behavior Surveillance System (YRBSS; http://www.cdc.gov/healthyyouth/yrbs/questionnaire_rationale.htm) the Wisconsin Youth Risk Behavior Survey (YRBS), Middle School Questionnaire, the State and Local YRBS, and the Wisconsin YRBS High School Questionnaire (http://sspw.dpi.wi.gov/sspw_oyrbsindex; Eaton et al., 2006).

Urine samples were tested by the United States Drug Testing Laboratories, Inc. using the No-Excuse Urine Panel, a detection panel that uses the lowest validated concentrations of

metabolites. This urine panel is at 1/2 or 1/5th of SAMHSA-recommended screening concentrations depending on the drug class, maximizing detection of substance use during the past three to seven days. Drugs were tested using enzyme multiplied immunoassay (EMIT) and confirmed by GC/MS (or LCMSMS) using standard methodologies (USDTL, 2011–2012). Samples were tested for amphetamines, 3,4-methylenedioxymethamphetamine, cocaine, opiates, oxycodone, phencyclidine, marijuana, barbiturates, benzodiazepines, methadone, propoxyphene, and cotinine, and were validity-tested for creatinine.

2.4.2. Covariates—Caregiver/child dyads were scheduled for assessment at postnatal ages of six months, 1, 2, 4, 6, 8.5, 9.5, 11 years, EA, MA, and LA (Frank et al., 2011). Covariates were ascertained from interviews at birth and later interviews about child behavior and household substance use at ages specified below, from the participants' report of exposure to violence at age 9.5 years and every subsequent research visit, and from cognitive assessments, urine assays, face-to-face and Audio computer Administered Self-Interview (ACASI) interviews of adolescents at EA, MA, and LA.

2.4.3. Caregiver Measures—Caregiver demographics examined as potential confounders were maternal age, maternal race/ethnicity (categorized as Black vs. Other), and maternal education (categorized as less than high school vs. high school graduate). Level of birth mother's use of alcohol and tobacco in pregnancy were analyzed as potential covariates. Starting at 8.5 years through EA, MA, LA, the adolescent's post-natal exposure to adults' substance misuse was ascertained by the primary caregiver's (whether birth mother's, foster parent's, or kin caregiver's) report of alcohol use problems and of any illicit drug use by adults in the household other than the caregiver. The adults (other than the caregiver) in the household variable was ultimately selected for analysis because post-natal caregiver psychoactive substance use (by self-report and urine assay) was too highly correlated with pre-natal exposure to assess its independent effect and thus could not be controlled for in final analyses.

2.4.4. Adolescent Measures—Adolescent characteristics examined in analysis were sex and IQ as measured in EA using the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). In a few cases, IQ was missing during EA and the Wechsler Intelligence Scale for Children (WISCIII) from childhood at age 11 (4 cases) or the WASI from MA (11 cases) were substituted. We also tested as a potential mediating confounder the caregiver-reported Child Behavior Checklist (CBCL; Achenbach, 1992; 1991 <http://www.aseba.org/>). Internalizing and externalizing problem scores from the Child Behavior Checklist were measured repeatedly between 2 and 11 years of age and averaged over available observations. The adolescent's perception of parental supervision was elicited using the scale of Lamborn and colleagues (1991), which includes questions such as "How much does your parent/guardian *really* know where you go at night?" rated 1–3 on a Likert Scale of "doesn't know, knows a little, knows a lot."

Exposure to violence was categorized as ever having scored in the maximum quartile on the Violence Exposure Scale for Children – Revised (VEX-R; Fox and Leavitt, 1995, <http://www.ncsnet.org/content/violence-exposure-scale-children-revised>) designed to assess children's exposure to violence through self-report using a 21 item, cartoon-based interview.

The VEX-R yields a 4-point Likert scale (0 = never, 1 = once, 2 = a few times, 3 = lots of times) to determine how many times the child reports witnessing different types of violence (e.g., someone being yelled at, being beaten up, or stabbed with a knife) and how many times these violent things have happened to the child him/herself. Trained examiners administered the VEX-R face-to-face in the testing laboratory at ages 8.5, 9.5 and 11 years.

We then modified the VEX-R for the adolescence research visits by removing the cartoons and the questions related to spanking. The text of the remaining questions was administered by ACASI without cartoons. Questions for adolescents were time-specific to determine if the event took place within the past year or at any point in the respondent's lifetime.

The VEX-R was analyzed using a total score, calculated by simply adding up how many times the subject reported experiencing each violent event, without weighting for severity. Without attempting *a priori* weighting of violent events, we created quartiles by summing each subject's VEX-R score at each of the time points, and then subdividing those scores into 4 approximately equal groups. This approach addressed the non-interval scaling and the skewed nature of the VEX-R total score. The highest quartile obtained by each subject at each time point comprised the time-dependent variable used for our analyses, with the 4th quartile representing the highest level of violence exposure for age and the 1st quartile representing the lowest level of exposure. When data were missing at any protocol point, the last value for the VEX-R was carried forward. If no such value was available the closest later value for the instrument was substituted. Exposure to violence was analyzed in the path analysis in two epochs - from 8.5 years through EA, and at MA or LA.

2.5. Data analyses

2.5.1. Logistic regression models—Adolescents with no, lighter, and heavier IUCE were compared on maternal and adolescent characteristics using analysis of variance (for continuous measures) and the chi-square test of homogeneity (for categorical characteristics). Unadjusted associations between maternal and adolescent characteristics and problematic substance use by LA are described through odds ratios (OR) and 95% confidence intervals (CI). Multiple logistic regression models examined the association between IUCE and problematic substance use controlling for other intrauterine substance exposure (marijuana, alcohol, and tobacco), maternal characteristics (maternal age, education, and race/ethnicity), adolescent characteristics (gender, full scale IQ, childhood CBCL externalizing T score, and CBCL internalizing T score) and childhood and adolescent exposures (violence, household substance use). These logistic regression models were developed with a focus on both controlling for confounding of the IUCE association and on identifying other factors associated with problematic substance use. Given the limited number of problematic substance users in our sample, logistic regression only supports a few covariates in any single analysis. Therefore, multivariable models were developed in three steps. First, cocaine exposure and all covariates associated with problem substance use at $p < 0.10$ in bivariate analyses were entered into a multiple logistic regression model. Second, a series of separate logistic regression models were fit, individually adding each variable not in the model as a check on potential confounding for the cocaine effect (changing an odds ratio associated with a cocaine effect by 20%). We generated odds ratios

and 95% confidence intervals based on these logistic regression models. We designated as statistically significant results with two tailed p-values less than 0.05. Because our earlier work (Frank et al., 2011) identified a substance-specific association between IUME and early initiation of marijuana, we repeated these analyses to examine the association between IUME and problematic marijuana use.

2.5.2. Structural equations models (SEM)—To further examine the pathways from IUCE, household substance use, and violence exposure to age of substance use initiation to problematic use by LA, structural equation models (SEMs) examined direct and mediational pathways between these variables, linking a Cox survival model for early initiation to a logistic regression model for problematic substance use. Using this framework, we can examine early violence exposure (up to EA) as a risk factor for early initiation of substance use, as well as early substance initiation as a risk factor for later higher (MA and LA) violence exposure, and examined both early (ages 8- to age 11 years) and later (EA and MA) household substance use as risk factors for problematic substance use. Age of substance use initiation was treated as a time-to-event variable in these SEMs with censoring at age 16 (focusing on early initiation). Associations with age of initiation are described through hazard ratios (HR) in these SEMs. Problematic use and higher exposure to violence (top quartile of the VEX) each by LA are dichotomous variables and associations with these variables are described through odds ratios (OR) in these SEMs. Based on prior analyses, maternal age was included as a covariate for the problematic use and age of initiation associations. Goodness-of-fit measures for SEMs (CFI and RMSEA) cannot be calculated with time-to-event data, and we developed our model by first fitting the full model with all direct and indirect pathways and then using a stepwise approach to eliminate paths with $p > 0.20$; paths of key interest (e.g., IUCE to age of initiation, household substance use to problematic use) were included regardless of statistical significance.

3. RESULTS

3.1. Sample maintenance and retention

After each study visit, the caregiver and child were given store vouchers and/or age appropriate gifts for completion of the interview and assessment.

The initial neonatal sample consisted of 252 caregiver-child dyads. Sixty-two percent (157/252) of the initial sample were retained until adolescence. Nineteen withdrew or were lost to follow up in the first month of life. Over the subsequent 18 years, 76 others have been lost to follow up, including one who died in gang violence. Others have withdrawn consent, or remain in contact with the study, but have not participated in recent testing due to having moved out of state or being otherwise unavailable (e.g. in job corps, prison, or the military). When the 157 participants included in this analysis were compared to the 95 from the initially enrolled cohort who were not, no statistically significant differences between groups were found in mother's use of tobacco, alcohol, cocaine, or marijuana during pregnancy, mother's age and education, and participants' birth weight or sex. Those retained were more likely than those not retained to be Black as opposed to Other race/ethnicities (90% vs. 81%, $p = .049$).

The analysis sample of 157 is comprised of 140 subjects who were assessed at LA and 17 who were assessed at EA or MA but did not return for the later adolescent follow-up. Those seen at LA were compared to those who were seen in EA or MA but did not return in LA. There were no statistically significant differences among participants seen at LA and those who were tested at EA or MA but did not return during in LA with regard to birth mother's age or education, adolescent's sex, birth weight, race/ethnicity, levels of prenatal exposure to alcohol, cocaine, tobacco, or marijuana, or age of substance initiation.

3.2. Sample characteristics

Sample characteristics are summarized by level of IUCE in Table 1. Compared to adolescents with no IUCE, adolescents with lighter or heavier IUCE were more likely to have older mothers who were more likely to be born in the United States, who were more likely to smoked cigarettes, had higher alcohol intake in the 30 days prior to delivery, and who used marijuana heavily during pregnancy. Children with lighter or heavier IUCE compared to those with no IUCE were more likely to have lower birth weight, and 1st degree relatives with a drug problem reported by birth mother. Adolescents with heavier or lighter IUCE were more likely than adolescents with no IUCE to have a higher number of caretaker changes through LA and were less likely to currently live with the birth mother. There was a trend for any drug use by age 16, with those with heavier or lighter IUCE reporting more substance use by 16 years of age than those with no IUCE exposure ($p=0.09$). Maternal Education, race/ethnicity, and adolescents' gender, IQ, CBCL T scores, reports of violence exposure and problematic substance use did not significantly differ by IUCE level.

3.3. Bivariate associations with problematic substance use

Twenty percent (32/157) of the sample manifested problematic substance use by age 18 years, of whom the majority (22/157) acknowledged abuse, tolerance, or dependence on marijuana with or without other substances. Less than one percent (0.6%) had a tobacco only problem. Similarly, less than one percent (0.6%) had an alcohol only problem. Six percent had a marijuana only problem while two percent had an "other" substance only problem. Three percent had a problematic use of cocaine only. Eight percent of the sample (11 participants) reported problematic use of marijuana and another substance, including 2 participants who had problematic use of marijuana and of cocaine, and 9 participants who experienced problematic marijuana use with problematic use of alcohol, tobacco, or both.

As Table 2 shows, unadjusted analyses showed no significant association between level of IUCE and problematic substance use (heavier cocaine vs. no exposure, OR=1.06, 95% CI 0.39–2.89; lighter cocaine vs. no exposure, OR=0.47, 95% CI 0.18–1.23). Bivariate analyses of prenatal substance exposures other than cocaine also showed no statistically significant association between levels of intrauterine marijuana, alcohol or cigarette exposure, and problematic substance use (Table 2). Older maternal age and greater maternal education were significantly associated with lower odds of problematic substance use, while exposure to higher levels violence and more members of household with substance use were associated with higher odds of adolescent's problematic substance use. Child factors (sex, full scale IQ, internalizing and externalizing problem behavior scores on the CBCL), and

history of close caregiver supervision were not significantly associated with problematic substance use. Participant's religiosity data were too incomplete to analyze.

3.4. Multivariable analyses for any problem use

3.4.1. IUCE and problematic substance use—Table 3 presents adjusted odds ratios from our final multivariable logistic model for any problematic substance use. After including variables with suggestive ($p < 0.10$) associations with problem substance use in bivariate analyses, no other variable was suggestive ($p < 0.10$) in the model or changed the odds ratio for either lighter or heavier IUCE by 20%. There was no suggestion of an increase in the odds of problematic substance use for those with either heavier or lighter IUCE after controlling for maternal demographics, household substance use, and higher violence exposure. Household substance use increased the odds of adolescents' problematic substance use (adjusted odds ratio (aOR) = 3.77, 95% CI 1.04 – 13.75) and we found a trend for a similar effect of higher violence exposure (aOR = 2.37, 95% CI 0.97 – 5.77).

3.4.2. Structural equation modeling—Structural equation modeling was used to more fully describe the associations between IUCE, substance use initiation, and problematic substance use (Figure 1). We found no significant direct or indirect association between IUCE and problematic substance use. Older maternal age (HR = 0.86, $p = 0.005$) and adolescent's older age at substance use initiation (HR = 0.76, $p = 0.028$) were associated with decreased problematic substance use. Household substance use exposure through childhood up to age 11 (OR = 3.75, $p = 0.049$), but not while the respondent was in EA or MA, was a risk factor for problematic substance use. We found a complex relationship between exposure to violence and adolescent substance use, in that exposure to violence by EA was a risk factor for early substance use initiation (HR = 1.58, $p = 0.014$), while later substance use initiation was associated with decreased odds of later exposure to violence (OR = 0.79, $p = 0.003$). Exposure to violence in MA was a risk factor for later problematic substance use (OR = 5.69, $p = 0.001$).

3.5. IUME and problematic marijuana use

Bivariate analyses showed no significant association between IUME and problematic marijuana use (OR = 0.69, 95% CI 0.22–2.18). Evaluation of bivariate associations with other prenatal exposures, maternal characteristics, and child characteristics showed no significant associations between other prenatal exposures and problematic marijuana use. Older maternal age (OR = 0.85, 95% CI 0.76–0.95) and mother's high school education (OR 0.36, 95% CI 0.14–0.90) were significantly protective against problematic marijuana use while exposure to higher levels of violence (OR = 3.16, 95% CI 1.19–8.37) and to household marijuana use between 8 and MA (OR = 3.78, 95% CI 1.46–9.75) were significantly associated with higher odds of problematic marijuana use. In multivariable logistic regression analysis, the association between IUME and problematic marijuana use remained non-significant after controlling for potential confounders (Table 4).

In a structural equations model focusing on IUME and problematic marijuana use (Figure 2), we found a 'U-shaped' association between level of IUME and problematic marijuana use. Lighter, but not heavier, IUME was significantly associated with earlier initiation of

marijuana use ($HR=1.99$, $p=0.022$). Later marijuana initiation was significantly associated with decreased odds of problematic marijuana use ($OR=0.61$, $p=0.001$). Older maternal age was significantly associated with less problematic marijuana use ($OR=0.83$, $p=0.031$). Household marijuana use through the participant's age 11 was significantly associated with earlier initiation of marijuana use ($HR=2.13$, $p=0.001$) but not with problematic use. In contrast, household marijuana use while the participant was in EA or MA was significantly associated with problematic marijuana use ($OR=4.27$, $p=0.047$). Early exposure to violence by EA was a significant risk factor of initiation of marijuana use ($HR=1.61$, $p=0.036$) while later initiation of marijuana use was significantly associated with lower odds of violence exposure in MA ($OR=0.50$, $p=0.001$). Violence exposure in MA was significantly associated with problematic marijuana use ($OR=4.12$, $p=0.026$).

4. DISCUSSION

To our knowledge, no other studies have examined the association between IUCE and IUME and problematic substance use by LA. The prevalence of problematic substance use in this cohort where half the participants experienced IUCE, was almost identical to the national level of past year illicit drug or alcohol abuse and dependence recently reported (Substance Abuse and Mental Health Services Administration, 2011). In our cohort there does not seem to be a direct relationship between IUCE or IUME and problematic substance use in LA, whether in bivariate analyses or after consideration of potential covariates to rule out suppression of such a relationship. As in other samples unselected for intrauterine exposures (Chen et al., 2009; Doherty et al., 2012; Dube et al., 2006; Grant and Dawson, 1998; King and Chassin, 2007) earlier substance initiation, higher exposure to violence and household problem alcohol use and illicit substance use in general increased the risk of problematic substance use in LA. Being born to an older and, in the case of problematic marijuana use, being born to a mother with at least a high school education were partially protective. Close parental supervision in adolescence did not alter these relationships.

There are, however, some differences between our findings in the current analyses and results reported in our earlier work (Frank et al., 2011), which only followed participants until age 16. In both analyses we found that lighter IUME was associated with earlier marijuana use. In our earlier paper, we also reported that heavier IUCE was associated with earlier initiation of any substance use, while the current analysis does not show a significant association between IUCE and initiation of use. One explanation for this difference is in how household substance use was treated in the two studies. If we do not control for household substance use in the path model in Figure 1, there is a significant association between heavier IUCE and age of initiation of substance use ($HR=1.80$, $p=0.011$). In our earlier paper, household substance use was treated as a time-dependent covariate, which focused the association on concurrent household use at the time of the participant's substance initiation. In this earlier analysis, household substance use was not significantly associated with age of initiation, nor did it confound the association between IUCE and age of initiation. In this analysis, household substance use in childhood (ages 8.5 through 11 years) was found to be significantly associated with earlier age of initiation, but concurrent household substance use at the time of initiation was not. The current analysis leads to a similar conclusion with respect to problematic substance use in late adolescence, where it is

earlier (ages 8.5 through 11) but not later (ages 12 through 15) household substance use that is associated with problematic substance use. The current analyses make clear that there is no direct association between IUCE and later problematic use after accounting for the pathway through age of initiation.

4.1. Limitations

Our results must be interpreted with some caution. Because of sample attrition, relatively small sample size, and the limited number of problematic substance users, including cocaine users, in our late adolescent sample, the issue of power must be addressed. We thus examined the statistical power available in samples consistent in size with ours, based on findings of Delaney-Black et al. (2011) on youth cocaine use, which would by our definition *per se* (without regard to other substances) indicate problematic substance use.

Delaney-Black et al. (2011) compared cocaine use among young teens with and without IUCE and reported that 22% of unexposed and 43% of exposed teens reported personal cocaine use, with an odds ratio of approximately 2.5 for cocaine use among exposed teens. In our current sample we would have 80% power to detect a roughly similar odds ratio of 2.7 at LA as statistically significant at the 0.05 level between those who were IUCE exposed versus unexposed. Our null findings, therefore, cannot be attributed to a lack of statistical power to detect a relationship of similar magnitude to that found by others.

Our results differ in prevalence of late adolescent cocaine use (as noted above, by our definition, problematic use *per se*) from two published studies examining the association between IUCE and later cocaine use in teen years (Delaney-Black et al., 2011; Warner et al., 2011). This discrepancy may partially reflect the varying prevalence of cocaine use in the source populations from which subjects are drawn. Most of the present sample lives in Boston, Massachusetts. In 2009, 2.8% of Boston 12 to 17 year olds reported ever using cocaine in any form (Eaton et al., 2010). This is in contrast to the 4.9% of youth in Detroit who reported ever using any form of cocaine and 6.9% of Florida 12 to 17 year olds who reported any form of cocaine use in 2009. Thus, variations in the ecology of drug use from city to city may in part explain discrepant findings between the current report and other studies.

Additional limitations include unmeasured covariates. Particularly, we have no genetic measures and our family history of substance abuse was imprecise and derived from birth mothers' report, without direct assessment of other family members. Because of collinearity with prenatal use, we cannot rule out that caregiver's own substance use influenced results, as household use by other adults did. We cannot generalize the finding beyond low-income, urban, predominantly Black samples similar to those in our study sample.

Other differences in our findings from the work of other investigators may reflect recruitment strategy – all mothers were recruited after delivery rather than prenatally – introducing possible short term recall bias, but capturing mothers who did not present for prenatal care. Our findings can also not be generalized to preterm children or those who were also exposed prenatally to opiates.

4.2. Conclusions

Our data suggest an escalating cascade of childhood violence exposure, early youth substance initiation, and ongoing youth violence exposure contribute to adolescent problematic substance use. Intrauterine substance exposure contributed to problematic substance use only indirectly, through a younger age at substance initiation. Higher early life exposures to violence and to household members who had alcohol problems or illicit substance use were associated with younger age of initiation of any substance and of marijuana specifically. Earlier substance initiation predicted increased subsequent higher violence exposure, which then was associated with the higher likelihood of problematic substance use by LA.

4.3. Implications for policy and practice

While there is broad consensus on the need to help pregnant women decrease or eliminate use of psychoactive substances whether legal or illegal (Behnke, 2013), the current study also suggests that intrauterine exposures are not the sole or most powerful predictors of problematic substance use in offspring. Even in a sample such as ours with high levels of prenatal substance exposures, postnatal factors are crucial determinants of substance misuse. Thus, postnatal interventions may decrease the risk of problematic substance use. The association between earlier age of initiation of substance use, ongoing exposure to violence, and later problematic use in this cohort, as well as in many others, suggests that delaying initiation of psychoactive substance use might impact public health, not only in the population as a whole, but among young people such as those in this study who experienced intrauterine exposures. However, data currently only exist for populations unselected for intrauterine exposures. A cost-benefit analysis conducted by Miller and Hendrie (2008) reported that the implementation of effective prevention programming could delay initiation of use among 12 to 14 year olds by an average of 2 years and prevent use altogether in some youth. In addition, these authors estimate that universal prevention programming in 2002 would have delayed cocaine use among 247,000 youth and marijuana use among 389,000 youth. Evidence suggests that prolonged interventions, combined with environmental prevention strategies and sustained efforts across different domains in a child's life are most likely to result in positive health outcomes (Greenberg et al., 2003). The National Registry of Evidence-based Programs and Practices (www.nrepp.samhsa.gov) provides a database of programs and practices effective for adolescents in general that have been rated and reviewed by independent reviewers (SAMHSA, 2012). The registry provides a first step for communities interested in preventing substance abuse and violence and promoting mental health among unselected groups of adolescence, but elucidation of efficacy of such programs for youth at potentially higher risk because of intrauterine exposures, household substance use, or exposure to violence requires further research.

Violence exposure (being a witness or victim of a violent act), a risk factor for PTSD, depression, distress, aggression, and externalizing behaviors (Buka et al., 2001; Fowler et al., 2009), also clusters with other health risk behaviors, including substance use (Albus et al., 2004). Mediators of the effects of violence exposures on later health outcomes are an emerging area of research. For example, good parenting practices and greater family cohesion may help lessen the negative impact of community violence (Aisenberg and

Herrenkohl, 2008). The co-occurrence of PTSD and substance use among adolescents exposed to community violence suggests the substance use may represent a maladaptive coping mechanism (Margolin and Vickerman, 2007), a mechanism which, our data suggest, may involve the adolescent in subsequent increased exposure to violence and consequent increase in substance misuse.

In spite of earlier dire predictions in the popular media we did not identify a direct relationship between problematic substance use and IUCE or IUME, but we did find potentially modifiable post-natal risk factors also noted to be associated with problematic substance use in the population as a whole including earlier substance initiation, exposure to violence and to household substance use. Further work is needed to identify whether there are differences in efficacy of prevention/intervention efforts in youth with intrauterine substance exposures compared to demographically similar youth who did not experience a high level of intrauterine exposures.

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Figure 1.
 The Relationship between Intrauterine Cocaine Exposure and Problem Substance Use in Late Adolescence.

Figure 2.
The Relationship between Intrauterine Marijuana Exposure and Marijuana Problem Use at Late Adolescence.

Table 1

Demographics by IUCE^a (n=157)

	IUCE Level										p value
	Total Sample		None (n=75)		Light (n=54)		Heavy (n=28)				
	Mean	SD	Mean	SD	Mean	SD	Mean	SD			
Continuous Variables											
Maternal age (yrs) at infant's birth	26.49	5.29	25.18	5.48	28.27	5.24	26.58	3.80			0.004
Maternal education (yrs completed)	11.56	1.33	11.61	1.40	11.59	1.32	11.36	1.16			0.67
Infant birth weight (grams)	3158.24	480.63	3356.88	508.70	3039.91	372.61	2854.39	345.74			<.0001
Log of average daily cigarettes during pregnancy	1.09	1.23	0.52	1.06	1.42	1.16	1.98	1.00			<.0001
Log of average daily volume of alcohol in past 30 days	0.11	0.38	0.00	0.01	0.12	0.37	0.36	0.68			<.0001
Number of first degree relatives with drug or alcohol problems at intake	1.36	1.38	0.84	1.09	1.59	1.41	2.32	1.42			<.0001
Number of caretaker changes from birth to LA	1.73	2.35	0.80	1.88	2.56	2.43	2.64	2.42			<.0001
CBCL: Externalizing T Score (avg 2–10 yrs)	51.77	8.52	51.77	8.00	51.81	9.04	51.64	9.24			.99
CBCL: Internalizing T Score (avg 2–10 yrs)	48.00	6.64	48.82	6.28	47.24	7.29	47.16	6.24			0.36
Full Scale IQ at last available time point	92.22	12.31	91.80	12.40	91.40	13.02	94.82	10.66			0.46
Categorical Variables											
Male	N	%	N	%	N	%	N	%			
	80	51.0	40	53.3	27	50.0	13	46.4			0.81
Black	141	89.9	70	93.3	46	85.2	25	89.3			0.28
Intrauterine marijuana exposure (% Yes)	37	23.6	9	12.0	18	33.3	10	35.7			0.005
Prenatal marijuana exposure – 3 levels % exposed											0.005
None	120	76.0	66	88.0	36	67.0	18	64.0			
Light	20	13.0	7	9.0	9	17.0	4	14.0			
Heavy	17	11.0	2	3.0	9	17.0	6	21.0			
Mother is a high school graduate (% Yes)	98	62.0	50	66.7	34	63.0	14	50.0			0.3
U.S. born mother (% Yes)	139	89.1	60	80.0	51	96.0	28	100.0			0.002
Household substance use exposure from age 8.5 to LA ^b	107	68.6	50	66.7	33	62.3	24	85.7			0.09
History of close caregiver supervision (% Yes)	31	22.3	14	20.9	12	24.5	5	21.7			.0001
Ever in 4th VEX-Rc quartile from age 9.5 to EA ^d (% Yes)	64	42.7	30	42.3	20	39.2	14	50.0			0.65
Ever in 4th VEX-R ^c quartile from age 9.5 to LA ^b (% Yes)	79	50.3	37	49.3	26	48.2	16	57.1			0.72
In 4th VEXc quartile at Middle and Later Adolescence (MA ^e & LA ^b)	50	33.0	26	35.6	15	28.3	9	36.0			0.65

Continuous Variables	IUCE Level								p value
	Total Sample		None (n=75)		Light (n=54)		Heavy (n=28)		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Current Caretaker N (%)									<.0001
Birth mother	107	71.0	64	89.0	33	61.1	10	40.0	
Kinship	29	19.0	4	6.0	15	28.0	10	40.0	
Non-kinship	9	6.0	1	1.0	5	9.0	3	12.0	
Institution (DYS/DSS/)	6	4.0	3	4.0	1	2.0	2	8.0	
Any drug use by age 16 (% Yes)	114	72.6	49	65.3	41	75.9	24	85.7	0.09
Problematic substance use	32	20.4	18	24.0	7	13.0	7	25.0	0.25

^aIntrauterine Cocaine Exposure^bLate adolescence^cViolence Exposure Scale-Revised^dEarly adolescence^eMiddle adolescence^fDepartment of Youth Services/Department of Social Services (now Department of Children and Families)

Table 2

Bivariate associations with problematic substance use (n=157, 32 with problematic use)

	OR ^a	95% CI ^b	p-value
Intrauterine cocaine exposure ^c			
Heavier	1.06	(0.39 – 2.89)	0.916
Lighter	0.47	(0.18 – 1.23)	0.123
Intrauterine marijuana exposure ^c	0.70	(0.26 – 1.86)	0.474
Natural log ADV alcohol ^d	0.66	(0.17 – 2.54)	0.547
Natural log of average daily cigarettes ^e	0.99	(0.72 – 1.36)	0.958
Maternal characteristic			
Maternal age	0.88	(0.80 – 0.96)	0.005
Mother with a high school degree vs. less	0.44	(0.20 – 0.98)	0.045
Black vs. non-Black	0.52	(0.17 – 1.63)	0.261
Child characteristics			
Male vs. Female	1.23	(0.56 – 2.67)	0.605
Full scale IQ	0.99	(0.95 – 1.02)	0.357
Externalizing T score ^h	1.03	(0.98 – 1.08)	0.397
Internalizing T score ^h	1.01	(0.95 – 1.07)	0.813
Child Exposures			
Violence exposure ^f	2.88	(1.26 – 6.60)	0.013
Household substance use ^g	5.70	(1.64 – 19.76)	0.006
History of close caregiver supervision ⁱ	0.40	(0.11 – 1.42)	0.115

^a odds ratio^b confidence interval^c vs. unexposed^d average daily alcohol +1^e average daily cigarettes +1^f Ever in 4th quartile of violence exposure variable (VEX-R) through EA (early adolescence) vs. unexposed^g Any substance use in household up to and including LA (late adolescence) vs. unexposed^h Child Behavior Checklist (CBCL)ⁱ Yes vs. No in the 4th quartile

Table 3

Multivariable logistic regression model predicting problematic substance use (n=157 total, 32 with problematic use)

	aOR ^a	95% CI ^b	p-value
Intrauterine Cocaine Exposure ^{c,d}			
Heavier	0.82	(0.27 – 2.55)	0.735
Lighter	0.54	(0.18 – 1.65)	0.280
Maternal age	0.94	(0.85 – 1.05)	0.266
Mother with a high school degree vs. less	0.52	(0.21 – 1.26)	0.147
Violence exposure ^e	2.37	(0.97 – 5.77)	0.058
Household substance use ^f	3.77	(1.04 – 13.75)	0.044

^a adjusted odds ratio

^b confidence interval

^c vs. unexposed

^d Intrauterine Cocaine Exposure

^e Ever in 4th quartile of violence exposure variable (VEX-R) through EA (early adolescence) vs. unexposed

^f Any substance use in household up to and including LA (late adolescence) vs. unexposed

Table 4

Multivariable logistic regression model predicting problematic marijuana use (n=157 total, 22 with problematic use)

	aOR ^a	95% CI ^b	p-value
Intrauterine Marijuana Exposure ^c			
Heavier	1.10	(0.20 – 6.01)	0.911
Lighter	0.59	(0.10 – 3.32)	0.545
Maternal age	0.90	(0.80 – 1.01)	0.087
Mother with a high school degree vs. less	0.29	(0.10 – 0.84)	0.022
Violence exposure ^d	2.44	(0.85 – 7.03)	0.098
Household marijuana use ^e	4.01	(1.34 – 11.99)	0.013

^a adjusted odds ratio

^b confidence interval

^c vs. unexposed

^d Ever in 4th quartile of violence exposure variable (VEX-R) through EA (early adolescence) vs. unexposed

^e Any marijuana use in household up to and including MA (middle adolescence) vs. unexposed