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Effects of prenatal cocaine/polydrug exposure on substance use by age 15

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ABSTRACT

Objective: Examined effects of prenatal cocaine exposure (PCE) on tobacco, alcohol, marijuana and cocaine use by age 15.
Methods: Adolescent ($n = 358$; 183 PCE, 175 non-prenatally cocaine exposed; NCE) drug use was assessed using urine, hair, and/or blood spot samples and self-report (Youth Risk Behavior Surveillance System; YRBSS) at ages 12 and 15. Logistic regression assessed effects of PCE on drug use controlling for other drug exposures, environment and blood lead levels (BLL).
Results: Adjusted percentages of drug use (PCE vs. NCE) were: tobacco 35% vs. 26% ($p < .04$), marijuana 33% vs. 23% ($p < .04$), alcohol 40% vs. 35% ($p < .01$), and any drugs 59% vs. 50% ($p < .005$). PCE adolescents were twice as likely to use tobacco (OR = 2.02, 95% CI = 1.05–3.90, $p < .04$), 2.2 times more likely to use alcohol (OR = 2.16, 95% CI = 1.21–3.87, $p < .01$) and 1.8 times more likely to use marijuana (OR = 1.81, 95% CI = 1.02–3.22, $p < .04$) than NCE adolescents. A race-by-cocaine-exposure interaction ($p < .01$) indicated PCE non-African American adolescents had greater probability of tobacco use (65%) than NCE non-African American youth (21%). PCE was associated with any drug use (OR = 2.16, CI = 1.26–3.69, $p < .005$), while higher BLL predicted alcohol use ($p < .001$). Violence exposure was a predictor of tobacco ($p < .002$), marijuana ($p < .0007$) and any drug ($p < .04$).
Conclusions: PCE and exposure to violence increased the likelihood of tobacco, marijuana or any drug use by age 15, while PCE and higher early BLL predicted alcohol use. Prevention efforts should target high risk groups prior to substance use initiation.

1. Introduction

Adolescent substance use is a serious, persistent, public health problem in the United States. According to a 2011 National Survey on Drug Use and Health, 10.1% of youths aged 12 to 17 use illicit drugs and 13.3% of these youths use alcohol (Substance Abuse Mental Health Services Administration (SAMHSA) SAMHSA, 2012). These rates are considerably higher among at-risk, underprivileged youth (Buu et al., 2009; Reinherz et al., 2000; Tucker et al., 2012). For instance, rates of substance use among adolescents with substance-abusing parents, low socioeconomic status, and violence exposure have been reported to be 2–5 times higher than that of adolescents without such risk factors (Kelly et al., 2011; Kilpatrick et al., 2000). Previous studies suggest that early initiation of substance use is associated with an increased risk of substance dependency (Anthony and Petronis, 1995; Behrendt et al., 2009; Guttmannova et al., 2012) and accompanying problems including legal and relationship difficulties, incarceration, academic failure, unemployment and greater mental health symptoms (DuRant et al., 1999; Fergusson and Horwood, 1997; Gordon et al., 2004; Slade et al., 2008).

Substance use among teens and young adults is one of the leading preventable causes of morbidity and mortality due to associated medical illnesses (e.g., liver disease), accidents, suicide and overdose (Clark et al., 2008; Cornelius et al., 2008; Eaton et al., 2012; Windle and Windle, 1997). The number and severity of problems associated with substance dependence provide compelling support for accelerated efforts at prevention. Although a growing body of research has identified many risk factors for adolescent substance use, comparatively little consideration has been given to the unique role of intrauterine cocaine exposure, despite data indicating that children of substance-using parents are more likely to become dependent on substances (Glantz and Chambers, 2006). There are only a few studies that have investigated the effects of prenatal

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cocaine exposure on teen substance use. Although these studies controlled for confounds, the specific confounds differed by study and they did not include consideration of out-of-home placement and early lead level (Bennett et al., 2007; Delaney-Black et al., 2011; Frank et al., 2011; Richardson et al., 2013). This critical gap in our knowledge will need to be addressed in order to identify pervasive risk factors for early substance use and to develop effective, targeted, prevention strategies.

Maternal use of cocaine during pregnancy directly affects the fetus via the placenta and subsequent movement across the blood-brain barrier (Lee et al., 2008). Areas of the brain known to be rich in monoamines (e.g., dopamine, serotonin and norepinephrine), particularly the prefrontal cortex, are thought to be the target of neuronal cell damage in fetuses exposed to cocaine prenatally (Malanga and Kosofsky, 1999). Damage to the frontal areas of the brain have been implicated in problems of inhibitory control, attention, increased risk taking activity, and delinquent behavior, all significant risk factors associated with adolescent substance use (Elkins et al., 2007; Lester et al., 2012; Mason et al., 2007; Tarter et al., 2003). Further, prenatal cocaine exposure indirectly increases risk of early substance use through epigenetic factors and negative postnatal environmental conditions (Glantz and Chambers, 2006), including ongoing parental substance abuse (Weinberg et al., 1994), childhood maltreatment and exposure to violence (Kilpatrick et al., 2000), quality of parent-child relationships (Hans, 2002), and parent-child separation dictated by child protective services (Glantz and Chambers, 2006).

Preclinical animal studies investigating the relationship between prenatal cocaine exposure and offspring's substance use have indicated an inconsistent relationship between prenatally drug exposed animals and increased reward seeking behavior and self-administration of drugs (Malanga and Kosofsky, 2003). For example, Keller and colleagues (Keller et al., 1996) found that prenatal cocaine exposed rats showed higher rates of cocaine self-administration than saline exposed controls. Similarly, prenatal exposure to higher doses of cocaine increased the probability of cocaine self-administration in mice (Rocha et al., 2002). In contrast, reduced conditioned place-preference for cocaine (Malanga et al., 2007), and for high doses of cocaine in particular (Estelles et al., 2006), have been reported in adult mice with prenatal cocaine exposure compared to unexposed controls. In animals, a predisposition to substance use has also been found for prenatal exposure to alcohol, tobacco, and opiates, providing further evidence that the increased vulnerability is independent of factors such as genetic variability, parenting influences and environmental effects (Glantz and Chambers, 2006).

To date, human studies investigating the effects of prenatal cocaine exposure on adolescent substance use indicate increased use of one or more substances of abuse, compared to control groups. However, these studies also have inconsistencies, primarily in the type of drugs in which increased use was found. Differences in findings are likely due to a lack of consistency in control variables selected, with some studies controlling for current caregiver drug use, exposure to violence, placement in foster or adoptive care or early blood lead levels, while others did not. In a small sample ($n = 149$), Frank and colleagues (Frank et al., 2011) found that heavier intrauterine cocaine exposure increased the risk for early initiation (before age 17) of any substance use (licit or illicit), as well as marijuana and alcohol use specifically, in a predominantly African American/African Caribbean urban sample. Exposure to violence between ages 8 and 16, investigated in this cohort, was also found to be independently associated with drug use. Similarly, Delaney-Black et al. (2011) found that prenatal cocaine exposure was related to teen use of cocaine at age 14 years in a large, prospective longitudinal cohort ($n = 316$). As in the Frank study, teen community violence exposure and caregiver negativity were also independent predictors of adolescent cocaine use. Richardson et al. (2013) reported that prenatally cocaine exposed adolescents, using self-report data only, were two times more likely to have initiated marijuana and alcohol use by age 15. While behavior problems and depression at age 10 did not mediate the relationship, exposure to violence partially mediated the relationship. However, prenatal cocaine exposure remained a significant predictor. A study of substance use related problems and externalizing behaviors in a cohort of 15.5 year old subjects indicated that higher amounts of prenatal cocaine exposure were associated with 2.8 times higher rates of substance use related problems than adolescents not prenatally exposed to cocaine (Min et al., 2013). Unlike other studies of adolescent substance use among prenatally cocaine exposed individuals, this study controlled for early blood lead levels and for the effects of placement in foster/adoptive care. Neither of these variables predicted substance use related problems, nor did they diminish prenatal cocaine exposure's effect, strengthening the findings. Gender effects, with cocaine exposed males having higher rates of early substance use, have been found in only one study (Bennett et al., 2007) to date, indicating that further investigation of gender effects is necessary. Previous research has highlighted the importance of considering multiple confounding factors when examining adolescent substance use in prenatally cocaine exposed cohorts. Prenatal exposure to alcohol (Baer et al., 2003) and other drugs, including marijuana (Day et al., 2006) and tobacco (Cornelius et al., 2000; Goldschmidt et al., 2012; Monshouwer et al., 2011), are associated with adolescent substance use and these substances are known to be used at high levels by cocaine-using pregnant women (Behnke et al., 2002; Singer et al., 2000). Postnatal environmental variables such as parent/caregiver substance use (Chassin et al., 2004; Ohannessian and Hesselbrock, 2008), exposure to violence (Frank et al., 2011; Vermeiren et al., 2003) and elevated lead levels (Dietrich et al., 2001; Lane et al., 2008) have also been linked to increased risk of adolescent substance use and often co-occur with prenatal cocaine exposure. In the cohort under investigation, placement in foster or adoptive care has been shown to have a protective effect for some cognitive outcomes (Lewis et al., 2011) and negative or no effects for other outcomes (Linares et al., 2006; Minnes et al., 2013, 2010). Careful consideration of these multiple risk factors will aid in determining if prenatal exposure to cocaine exerts a specific and additive effect on the propensity for adolescent substance use. Of interest in our analyses was whether prenatal cocaine exposure had a specific negative influence on the percentage of youth who had begun using substances by age 15.5, once protective and potentially negative influences on substance use had been taken into account. It was hypothesized that prenatal cocaine exposure would have a direct negative effect on substance use among 15 year old adolescents, controlling for other prenatal drug exposures and environmental conditions. It was further hypothesized that higher amounts of prenatal cocaine exposure would increase the likelihood of substance use by age 15.

Prenatally cocaine exposed (PCE) children placed in foster/adoptive care were expected to have less substance use by 15 years compared to PCE children in biologic/relative care due to better quality caregiving and home environment. Preschool blood lead level and exposure to violence were also expected to have independent negative effects on drug use regardless of prenatal cocaine exposure status.

2. Methods

2.1. Subjects

Participants in this study were 358 (183 PCE/175 non-prenatally cocaine exposed; NCE) 15.5 year old adolescents who participated in a longitudinal study examining the developmental effects of prenatal cocaine exposure since their births between September, 1994 and August, 1996. The number of subjects at age

15.5 represents 89% of the living sample. The participants were primarily African American (85%) and of low socioeconomic status (SES; 98%).

Subjects were recruited from a high risk maternal population screened for drug use during pregnancy via urine analysis at a Midwestern, urban, county, teaching hospital. The high risk population was prospectively defined as women who did not receive prenatal care, showed behaviors suggesting intoxication at the time of delivery, had previous involvement in the child welfare system or self-admitted drug use to hospital staff. Maternal and infant urine samples, ordered by the medical staff, were obtained immediately before or after labor and delivery. Urine was tested for metabolites of illicit drugs, including cocaine, barbiturates, cannabinoids (THC), opiates, phencyclidine, amphetamines, and benzodiazepines. The Syva Emit method (Syva Co, Palo Alto, California) was used for urine analyses, and positive analyses were followed up by confirmatory gas chromatography. In addition to urine analysis, infant meconium (which begins to accumulate during the last 4.5 months of fetal development) was collected by the research staff from infant's whose mothers agreed to participate in the study. Meconium was screened for cocaine and other drug metabolites, including benzoylecgonine (BZE), meta-hydroxybenzoylecgonine (m-OH-bze), and cocaethylene, which form after maternal ingestion.

PCE was determined based on any one of the following: maternal self-report of cocaine use during pregnancy to medical staff, or a positive result on urine (maternal or infant) or meconium analyses conducted at the time of birth. NCE status was determined if negative results were obtained on all measures. Four hundred fifteen (218 PCE and 197 NCE) mothers of the 647 approached by a research nurse shortly after childbirth agreed to participate in the study. One hundred fifty-five women refused to participate (49 cocaine-positive and 106 cocaine-negative), 23 women (9 cocaine-positive, 14 cocaine-negative) did not come to the enrollment visit and 54 were excluded (20 PCE and 34 NCE). Exclusion from the study was due to lack of meconium (15), infant Down syndrome (2), maternal psychiatric history (16), primary heroin use (2), maternal HIV positive status (5), maternal low IQ (1), fetal alcohol syndrome (1), maternal age less than 19 years (2), infant illness (3), maternal chronic illness (4) and other (3). Since birth, 12 children died (9 PCE and 3 NCE). Causes of death for the children with PCE were sudden infant death syndrome (4), cardiopulmonary arrest (1), pneumonia (1), accidental asphyxia (1), and respiratory distress syndrome (1) and unknown illness (1). Causes of death for the NCE children were sudden infant death syndrome (2) and respiratory distress syndrome (1). Four hundred and three children were available for assessment at 15.5 years of age. Of those 403 children, 359 came to the 15.5 year study visit. All but one subject finished the self-report drug use survey. Demographic, caregiver, and prenatal drug exposure variables were compared separately for those PCE and NCE subjects who had substance use data ($n = 358$) versus those that did not ($n = 45$). Among the PCE subjects, those who had substance use data had caregivers with higher nonverbal reasoning scores than children who did not have drug use data ($p < .008$). Among the NCE subjects, those who had substance use data were more likely to be African American ($p < .0004$), had less prenatal cigarette exposure ($p < .04$) and were less likely to be microcephalic (<10th percentile head circumference) at birth ($p < .03$). If not specifically mentioned all other assessed variables were not different between those included in the analyses and those not included for either the PCE or NCE groups.

2.2. Procedures

Informed consent, approved by the participating hospital's institutional review board, was completed at the time of infant birth and prior to each assessment point in the longitudinal follow-up. A research assistant interviewed all available mothers, shortly after their child's birth, about prenatal drug use patterns. This information was used to further quantify drug use during pregnancy. Women were asked to recall frequency and amount of drug use in the month prior to becoming pregnant and during each trimester of pregnancy. The number of tobacco cigarettes smoked per day, and the number of marijuana "joints" smoked and drinks of beer, wine, or hard liquor consumed per week were computed, with each drink equivalent to 0.5 oz. of absolute alcohol. For cocaine, since the majority of mothers (>90%) in our study primarily used the crack cocaine form, the number of "rocks" consumed and/or the amount of money spent per day were noted to calculate the average units of use over the pregnancy. For each drug, frequency of use was recorded on a Likert-type scale ranging from 0 (not at all) to 7 (daily use), converted to reflect the average number of days per week a drug was used, except for cigarettes which was recorded as number smoked per day. Frequency was multiplied by the amount used per day to compute an average use score for the month prior to pregnancy and for each of the three trimesters. This amount was then averaged across the pregnancy to obtain average use during pregnancy for each drug.

Ten women from the sample did not self-report cocaine use during pregnancy but tested positive on meconium analyses, therefore an estimate of cocaine use per week was made. (Arendt et al., 1999). First a level of cocaine use classification was determined via meconium screen or self-report using the 70th percentile as the break point between heavy (≥70th percentile) versus light (<70th percentile) cocaine use. For infants whose meconium screens were positive but maternal self-report was unavailable, estimates were made by assigning the median score for the group (heavy/light) to which they were assigned based on meconium metabolites. Drug use information was updated at each follow-up visit for current caregivers and assessed for use in the past 30 days prior to the assessment appointment.

A trained research assistant, unaware of the adolescent's cocaine or other prenatal drug exposure status, administered a battery of cognitive and behavioral assessments at the child development lab at subject age of 15.5 years. Adolescents were taken to the affiliated hospital's National Institute of Health (NIH) supported Clinical Research Unit for hair, urine and/or bloodspot samples, collected by trained research nurses.

Caregivers were given a $35 stipend at the post-birth assessment, during which baseline demographic information, maternal pregnancy drug use and psychological distress were assessed. Caregiver screening measures of receptive vocabulary and non-verbal reasoning were administered one time up to 15 years, but were updated upon any change of caregiver. At the 15.5 year assessment, caregivers were given $50 and children were given $100 for their participation, with an additional $10 for biologic drug use samples.

A summary of caregiver assessment data used for describing the sample, covariates considered for the analyses, as well as child substance use outcome measures, are listed below.

2.3. Measures

2.3.1. Assessment of adolescent drug use. To ensure that anyone who had initiated substance use by age 15 was included in the analyses, multiple assessments of substance use were acquired. These included self-report data collected at 12 years and/or 15.5 years of age and biologic assays collected at 15.5 years. If results were positive on any one of these assessments for a particular drug, a positive code for that drug was recorded. To be coded as negative, all assessment types at age 15.5 and prior at age 12 had to be negative for a given drug. If a subject was positive on any one drug, at either time point, they were considered positive for a variable named "any drug use."

2.3.2. Self-report. The *Youth Risk Behavior Surveillance System* (YRBSS; Centers for Disease Control and Prevention, 2009). The YRBSS assesses adolescent health risk behaviors associated with death, disability, and social problems, including drug use (tobacco, alcohol and other drugs), and risky dietary, violent, and sexual behaviors. Drug use behavior, including age of initiation and frequency of tobacco, marijuana, and other illicit drug use was recorded at age 15.5 years and 12 years. The number of assessments (one per individual subject) for this measure was $n = 358$.

Violence exposure was assessed at age 12 using the computerized Illustration-Based Assessment of Liability and Exposure to Substance Use and Antisocial Behavior (ALEXSA Ridenour, 2003). The ALEXSA Violence Exposure subscale consists of 8 items ($\alpha = 79$) (Ridenour et al., 2009) assessing experiences of violence that have been inflicted directly on the respondent (e.g., "*How many times have you been beaten up?*" "*How many times have you been robbed or mugged?*"), as well as violence that the respondent has witnessed (e.g., "*How many times have you seen in person somebody get beat up* (*remember this does not count T.V. or movies?*" "*How many times have you seen in person someone being robbed or mugged?*"). Children rated the frequency of violence exposure using a 5-point Likert scale (0 = 0 *times* to 5 = 5 *times or more*), with higher scores indicating greater exposure. The number of assessments for this measure was $n = 293$.

2.3.3. Biologic samples. Study participants were asked to voluntarily submit any of the following biologic samples at age 15.5, urine, hair, and/or bloodspots, with the assistance of research nurses from the university's NIH-funded Clinical Research Unit. Two hundred and forty two (242) subjects submitted at least one of the biologic measures. Each participant received $10 for agreeing to give a biologic sample, regardless of the number of specimens (hair, urine, blood) that were able to be collected. All biologic samples were analyzed by the United States Drug Testing Laboratory (USDTL; Des Plaines, IL, USA).

Urine specimens were analyzed by USDTL for cannabinoids, cotinine, and ethyl glucuronide (Etg) using ThermoFisher Microgenics DRI immunoassay reagents on an Olympus AU640 analyzer. Presumptive positive cannabinoids were confirmed using an Agilent 5971 gas chromatography/mass spectrometry and presumptive positive ethyl glucuronide specimens were confirmed using an API 2000 liquid chromatography/tandem mass spectrometry system. A positive assessment for ethyl glucuronide indicates drinking approximately 2–3 drinks in the past 3–4 days and a positive assessment for THCA indicates marijuana use within the past 1–5 days. The total number of usable urine samples was $n = 222$.

Hair specimens were analyzed on an API 3200 liquid chromatography/tandem mass spectrometry system for amphetamines, benzodiazepines, cocaine, opiates, and ethyl glucuronide. Hair samples yield information regarding drug use in approximately the past 3 months. For valid analyses, about 1/4 inch diameter of untreated hair collected from the head, under arms or legs is required. The number of hair samples collected was low ($n = 61$) due primarily to chemically treated hair, particularly for girls, or lack of volume, particularly for boys.

Bloodspots (3.1 mm punches × 3) were analyzed for phosphatidylethanol using an API 5500 liquid chromatography/tandem mass spectrometry system. Phosphatidylethanol, a series of abnormal phospholipids, formed only in the presence of phospholypase D and ethanol, is incorporated into the phospholipid membranes of the blood cells and is detectable for 2–4 weeks following risky alcohol drinking behavior (i.e. binge drinking). The total number of bloodspots collected was $n = 210$.

Table 1
Child demographics ($N = 358$).

Demographics	PCE ($n = 183$)		NCE ($n = 175$)		p
	M	SD	*M*	SD	
Male, *n* (%)	81	44.26	84	48.00	.48
African-American, *n* (%)	150	81.97	144	82.29	.94
Test age	15.69	0.27	15.67	0.27	.50
Gestational age	37.73	2.86	38.46	2.90	.02
Hobel Neonatal Risk score	7.71	16.77	5.90	16.11	.30
Birth length (cm)*	47.21	3.96	49.11	3.79	<.0001
Head circumference (cm)*	32.26	2.17	33.48	2.40	<.0001
Birth weight (grams)*	2700.38	654.52	3100.03	704.06	<.0001
Microcephaly, *n* (%)	27	15.00	7	4.05	.0005
Small for gestational age, *n* (%)	25	13.81	4	2.30	<.0001
2 years and/or 4 years Lead Level**	7.06	4.16	8.16	4.64	.03
Violence Exposure†	0.63	0.77	0.59	0.81	.54
Adopted/Foster Care at 15 years, *n* (%)	44	24.04	6	3.43	<.0001

* p-value is adjusted for prematurity.
** Sub-sample size included 142 PCE and 136 NCE.
† Assessed at 12 years old.

At ages 2 and 4 years, children were asked to participate in a separate study of elevated blood lead and iron deficiency anemia. The numbers of subjects with valid blood measurements at ages 2 and 4 years were 143 and 274, respectively. For 122 subjects with two blood samples, values were averaged. Samples were not obtained from some children due to parental refusal, inability to draw blood without undue stress, child illness, or logistical difficulties. A greater percentage of African-American and married women and a lower percentage of foster parents consented to child blood collection. Blood lead was reported and analyzed using microgram per deciliter.

2.3.4. Demographic, caregiver variables and potential covariates. Demographic information and medical characteristics were extracted from hospital birth records and included infant birth weight, head circumference, length, gestational age, race, maternal age, parity and number of prenatal care visits. Maternal education in years, work history, and socioeconomic status based on the Hollingshead classification system (Hollingshead, 1957) was collected via research interview.

Drug use history was collected using the Maternal Post-Partum Interview and Update (Singer et al., 2008; Streissguth, 1986). This semi-structured interview assessed amount and frequency of drug use during the month prior to and each trimester of pregnancy and during the last 30 days at follow-up assessments. It included summary measures of average cigarette (per day), alcohol (drinks per week), marijuana (joints per week) and cocaine (units per week) use during the month prior to and during each trimester of pregnancy. The Brief Symptom Inventory (BSI; Derogatis, 1992) was administered to mothers post-partum and to caregivers at the 15.5 year follow-up to assess current caregiver distress. Receptive vocabulary was assessed using the Peabody Picture Vocabulary Test-Revised (PPVT-R; Dunn and Dunn, 1981) and an estimate of non-verbal IQ was assessed using the Wechsler Adult Intelligence Test-Revised (WAIS-R) Block Design and Picture Completion subtests (Wechsler, 1981).

Quality of the home caregiving environment was assessed using an adapted interview format of the Home Observation for Measurement of the Environment (HOME; Caldwell and Bradley, 1984).

2.4. Statistical analyses

Demographic and other potential covariates were transformed by $\log_e(x+1)$ if not normally distributed. Means and standard deviations are reported based on the original distribution, but the test statistics are based on normalized data. All continuous data (potential covariates and demographics) were compared by cocaine group status using *t*-tests or the Wilcoxon-Mann–Whitney test. Pearson chi-square tests or Fisher's Exact tests were used for categorical variables.

2.4.1. Selection of potential covariates or independent predictors. Potential covariates, including over 20 caregiving, environmental and other prenatal drug exposure variables, were considered for inclusion in the logistic regression analyses. Variables included for evaluation were average prenatal alcohol, marijuana and tobacco exposure, caregiver current drug use, psychological distress, education, receptive vocabulary ability, estimate of non-verbal reasoning, child placement status, quality of the home environment and child exposure to violence. If any one of these variables was different by the dichotomized adolescent substance use variables at $p < .2$ they were further evaluated in the multivariate analyses. Race and gender were evaluated in every model if they were correlated with the outcome because of their well-established association with substance use habits among teenagers (Chen and Jacobson, 2012).

Multiple logistic regression analyses were used to assess the effects of prenatal cocaine exposure on tobacco, alcohol, marijuana, cocaine, and any drug use. Cocaine exposure was considered a significant predictor of the outcome if it remained significant ($p < .05$; two tailed test) after control for confounding variables. Covariates were retained in the model if they were significant at $p < .1$ or changed the unstandardized regression estimate for cocaine by 10%.

Quality of the home environment, biologic mother age at infant birth, parity, education, prenatal care, SES and current caregiver characteristics (PPVT-R, WAIS-R Block Design and Picture Completion) were entered separately in the model if they met the evaluation criteria. Next, prenatal exposure and current caregiver cigarette, alcohol and marijuana use were entered separately. Current caregiver cocaine use was not evaluated in the model because nearly every person asked about current use denied it, resulting in no variability. If cocaine group status was a significant predictor of the substance use outcome, interactions with race and gender were evaluated, as well as caregiver type (PCE biologic/relative, PCE foster/adoptive care and NCE). Additionally, if cocaine group status was significant in the final model, amount of cocaine use (average cocaine units per week) was examined to determine if there was a dose-response relationship. Blood lead data and average violence exposure data were evaluated separately after each final model was established due to their reduced sample sizes.

3. Results

3.1. Participant and caregiver demographic data

Birth outcome and demographic data for participants in this study were compared by cocaine group status. Results indicate that children with PCE weighed less, were shorter and had smaller head circumference, controlled for gestational age, at the time of birth (see Table 1) than NCE children. They were also more likely to be of lower gestational age, small for gestational age, microcephalic (<10%) and placed in non-relative foster or adoptive care. NCE individuals had higher blood lead levels at 2 and/or 4 years of age than the PCE group. Groups were not different in quality of the home environment, Hobel risk score, gender, race or exposure to violence.

Among birth mothers in the study, those who used cocaine prenatally were older, had more children, and had more psychological distress (BSI-Global Severity Index (GSI) scores) at birth than non-cocaine-using women (see Table 2). They also had fewer prenatal care visits, fewer years of education, lower receptive vocabulary scores and were less likely to have been married. Over their pregnancy, cocaine-using women on average used more average tobacco, alcohol and marijuana than their non-cocaine-using counterparts, as well as during the month prior to pregnancy and during every trimester. The average amounts of use of each drug generally declined over the course of pregnancy in both groups. The percentage of cocaine-using women who also used alcohol, tobacco and marijuana was also greater during the month prior to pregnancy and during each trimester of pregnancy compared to non-cocaine-using women. Eighty three percent (83%) of cocaine-using women self-reported cocaine use in the month prior to pregnancy, 80%

Table 2
Maternal characteristics ($N = 358$).

Demographics	PCE ($n = 183$)		NCE ($n = 175$)		p
	M	SD	*M*	SD	
Mother's age at birth	29.70	4.99	25.52	4.74	<.0001
Parity	3.50	1.83	2.77	1.87	.0002
Number of prenatal visits	5.18	4.59	8.69	4.85	<.0001
Maternal years of education	11.55	1.65	11.93	1.38	.02
PPVT Standard Score	73.12	14.09	77.32	14.66	.007
WAIS-R Block Design Scale	6.86	2.12	7.18	2.02	.15
WAIS-R Picture Completion	6.70	2.14	6.88	2.31	.44
BSI Global Severity Index	0.82	0.74	0.50	0.53	<.0001
Married, n (%)	14	7.65	28	16.00	.01
Low SES, n (%)	178	97.80	171	97.71	.96
African-American, n (%)	151	82.51	145	82.86	.93
Age of starting any drug use (years)	14.44	3.10	14.38	3.42	.86
Prenatal drug use	*M* (*n*)	SD (%)	*M* (*n*)	SD (%)	*p*
Prenatal Cigarette Use Average[a]	11.50 (154)	11.16 (86.52)	3.74 (67)	6.89 (39.88)	<.0001
Month prior cigarettes	13.05 (151)	12.27 (84.83)	5.15 (63)	9.36 (37.50)	<.0001
1st trimester cigarettes	12.43 (149)	12.27 (83.71)	3.92 (55)	7.80 (32.74)	<.0001
2nd trimester cigarettes	10.74 (143)	11.62 (80.34)	2.96 (46)	6.34 (27.38)	<.0001
3rd trimester cigarettes	9.51 (136)	11.08 (76.40)	2.90 (47)	5.79 (27.98)	<.0001
Prenatal Drinks Average [b]	9.79 (142)	17.73 (80.23)	1.39 (70)	4.68 (41.67)	<.0001
Month prior drinks	12.66 (122)	22.60 (68.93)	2.53 (60)	7.94 (35.71)	<.0001
1st trimester drinks	11.87 (112)	23.79 (63.28)	1.32 (34)	3.93 (20.24)	<.0001
2nd trimester drinks	8.20 (87)	19.97 (49.15)	0.55 (17)	3.03 (10.18)	<.0001
3rd trimester drinks	6.41 (87)	17.33 (49.15)	1.15 (22)	8.01 (13.10)	<.0001
Prenatal Marijuana Use Average [c]	1.37 (77)	3.51 (43.50)	0.62 (16)	3.58 (9.52)	<.0001
Month prior marijuana	1.66 (60)	3.86 (34.29)	1.60 (16)	10.27 (9.52)	<.0001
1st trimester marijuana	1.53 (50)	4.12 (28.74)	0.60 (10)	3.84 (5.95)	<.0001
2nd trimester marijuana	1.32 (34)	4.33 (19.32)	0.19 (4)	1.74 (2.38)	<.0001
3rd trimester marijuana	1.00 (32)	3.89 (18.29)	0.10 (4)	0.77 (2.38)	<.0001
Cocaine per week [d]	22.73(181)	38.24 (98.91)	–	–	–
Month prior cocaine	29.98 (152)	58.02 (83.06)	–	–	–
1st trimester cocaine	32.00 (147)	65.10 (80.33)	–	–	–
2nd trimester cocaine	25.35 (127)	63.59 (69.40)	–	–	–
3rd trimester cocaine	12.60 (134)	27.67 (75.71)	–	–	–

[a] Average number of cigarettes smoked per day.
[b] Average drinks of beer, wine, or hard liquor per week, each equivalent to .5 mL absolute alcohol.
[c] Average joints of marijuana per week.
[d] Average units of cocaine per week.

during the first trimester, 69% during the 2nd trimester and 75% during the 3rd trimester. Current caregivers of PCE participants at age 15 were more likely to smoke cigarettes (see Table 3). However, caregiver-reported alcohol, marijuana and cocaine use and caregiver psychological distress (BSI-GSI) did not differ between groups at subject age 15.

3.2. YRBSS self-report drug use data

Table 4 describes drug use habits by cocaine group status. There were no significant differences by group in terms of age of first drug use, number of drinks on occasion of alcohol use, and number of days of use in the past 30 days for cigarettes, alcohol and marijuana for those that reported drug use.

3.3. Effects of prenatal cocaine exposure on drug use by age 15 years

Unadjusted percentages for each drug used and for any drug use by adolescent subjects are reported in Table 5. PCE adolescents were more likely to have used marijuana, but not other drugs of abuse, compared to NCE adolescents. Table 6 summarizes the effects of PCE on substance use after controlling for covariates. PCE adolescents were 2 times more likely to have used tobacco (OR = 2.02, 95% CI = 1.05–3.90, $p < .04$). Figure 1 reflects a race by

Table 3
Current caregiver characteristics ($N = 358$).

Demographics	PCE ($n = 183$)		NCE ($n = 175$)		p
	M	SD	*M*	SD	
HOME score (15 years)	47.63	6.87	48.71	6.16	.12
BSI Global Severity Index (15 years)	0.35	0.42	0.34	0.47	.45
Cigarettes per day[a]	4.82	7.19	3.46	6.57	.01
Drinks per week[b]	1.83	4.56	2.01	4.67	.49
Marijuana per week[c]	0.54	5.48	0.46	3.10	.61
Cocaine per week[d]	0	0	0	0	NA

[a] Average number of cigarettes smoked per day.
[b] Average drinks of beer, wine, or hard liquor per week, each equivalent to .5 mL absolute alcohol.
[c] Average joints of marijuana per week.
[d] Average units of cocaine per week.

Table 4
Summary of substance use on YRBSS by cocaine group status.

Substance (yes)	N*	PCE (n = 183)		NCE (n = 175)		X^2	p
		n	%	n	%		
Using cigarettes at or younger than 12 years	67	31	79.49	19	67.86	1.16	.28
Using cigarettes more than 1 per day in last 30 days	39	3	11.54	1	7.69	0.14	.71
Using alcohol more than 2 days in lifetime	133	6	8.33	9	14.75	1.36	.24
Using alcohol at or younger than 12 years	135	49	64.47	37	62.71	0.04	.83
Using alcohol more than 2 days in last 30 days	43	0	0	0	0	–	–
Using marijuana more than 2 times in lifetime	106	22	34.38	15	35.71	0.02	.89
Using marijuana at or younger than 12 years	108	33	50.77	25	58.14	0.57	.45
Using marijuana more than 2 times in last 30 days	63	11	26.83	7	31.82	0.17	.68
Using cocaine more than 2 times in lifetime	5	0	0	0	0	–	–
Using cocaine more than 2 times in last 30 days	2	0	0	0	0	–	–
Using other drug more than 2 times†	11	1	12.50	2	66.67	3.23	.07

Test age	M	SD	M	SD	t	p
	15.69	0.27	15.67	0.27	−0.71	.50

* The total number of subjects using substances reported on the YRBSS.
† Any drug other than tobacco, alcohol, marijuana, cocaine, opiates, benzodiazepines, amphetamines, or MDMA.

Table 5
Unadjusted frequencies of outcomes by cocaine group status.

Any drug use (yes)	PCE (n = 183)		NCE (n = 175)		X^2	p
	n	%	n	%		
Tobacco	64	35.16	47	27.17	2.64	.10
Alcohol	72	39.34	64	36.57	0.29	.59
Marijuana	64	34.97	43	24.57	4.62	.03
Cocaine	11	6.01	10	5.71	0.01	.91
Opiates	1	0.55	1	0.57	0.001	.97
Benzodiazepines	1	0	0	3.57	1.20	.27
Amphetamines	1	0.55	2	1.14	0.38	.54
MDMA	2	1.09	2	1.14	0.002	.96
Other	8	4.37	3	1.71	2.12	.15
Any drug	106	57.92	90	51.43	1.52	.22

Table 6
Adjusted association of substance use with cocaine group status.

Any drug use (yes/no)	OR	95%CI	p
Tobacco[a]	2.02	1.05, 3.90	.04
Alcohol[b]	2.16	1.21, 3.87	.01
Marijuana[c]	1.81	1.02, 3.22	.04
Any drug[d]	2.16	1.26, 3.69	.005

Note: The significant covariates are italicized.
[a] Adjusted for *mother's age at birth*, *marital status*, *maternal BSI Global Severity Index*, prenatal average cigarette use, prenatal alcohol exposure month prior and *violence exposure*.
[b] Adjusted for mother's age at birth, maternal education, marital status, prenatal average alcohol use, 2nd trimester marijuana exposure and *race*.
[c] Adjusted for *HOME*, *marital status*, maternal BSI Global Severity Index, *gender* and *violence exposure*.
[d] Adjusted for *marital status*, prenatal average alcohol exposure and *violence exposure*.

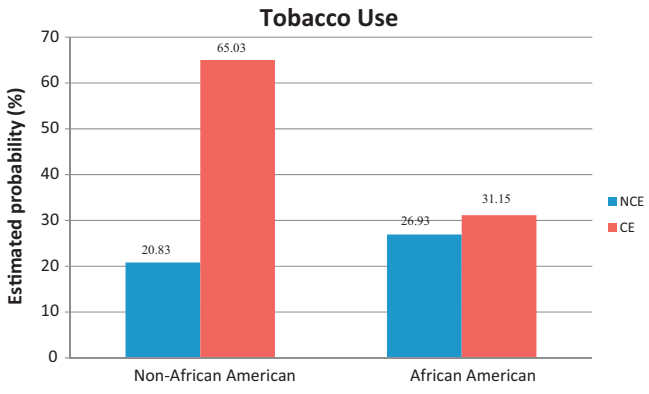

Fig. 1. Probability of tobacco use by race and cocaine interaction.

cocaine exposure interaction ($p < .01$) indicating that this cocaine effect was primarily among non-African American individuals. The PCE group had 150 African American and 33 non-African American subjects; the NCE group had 144 African American and 31 non-African American subjects. Non-African American PCE adolescents had 65% estimated probability of tobacco use compared to 21% among non-African American NCE individuals ($p < .002$). The greater amount of cocaine exposure, the more likely non-African American (OR = 2.56. 95%CI = 1.27–5.16, $p < .009$), but not African American (OR = 0.99. 95%CI = 0.79–1.25, $p < .96$), individuals were to use tobacco by age 15.

Adolescents with PCE were 2.2 times more likely to have used alcohol (OR = 2.16, 95% CI = 1.21–3.90, $p < .01$) by age 15 than NCE adolescents. PCE was also related to the use of marijuana (OR = 1.81, CI = 1.02–3.22, $p < .04$) and the use of any drug (OR = 2.16, CI = 1.26–3.69, $p < .005$). The number of subjects who had confirmed cocaine use by 15.5 years was small (PCE = 11; NCE = 10) and therefore logistic regression was not completed. For 21 subjects positive for cocaine use, 18 came from biologic measures, 2 came from self-report, and 1 came from both biologic and self-report measures.

There were no differences in the likelihood of drug use for cocaine exposed adolescents who were placed in foster or adoptive care versus those in biologic or relative care. Table 7 illustrates this finding by presenting the percentage of adolescents who had begun using tobacco, alcohol, marijuana or any drug, by exposure and caregiver status. While not statistically significant, PCE children in foster or adoptive care had higher percentages of tobacco, alcohol and any drug use, despite the lowest lead levels and highest quality of home environment.

3.4. Other significant predictors of substance use by age 15

Race was an additional independent predictor of alcohol use (OR = 0.38, 95%CI = 0.21–0.69; $p < .002$), with the adjusted probability of 58% for non-African American versus 33% for African American adolescents. Gender was a significant predictor of marijuana use (OR = 1.55; 95%CI = 1.04–3.14; $p < .04$), with the adjusted probability of 36.4% for boys versus 24.7% for girls. Older maternal age at the time of the child's birth predicted lower odds of adolescent tobacco use ($p < .02$), and being married at the time of infant birth increased the odds of current adolescent tobacco use ($p < .01$), marijuana use ($p < .01$) and any drug use ($p < .03$) by age 15 years. Higher maternal psychological distress after childbirth increased

Table 7
Comparisons of key covariates and adolescent substance use by exposure and caregiver status.[a]

	PCE		NCE	F/χ^2	p	Pair-wise difference
	Group 1: biologic/ relative (n = 139) M (SD)	Group 2: adoptive/ foster (n = 44) M (SD)	Group 3 (n = 175) M (SD)			
PCE, units per week	20.97(36.36)	28.30 (43.63)	–	1.16	.28	
WISC-IV Full Scale IQ at 15	81.01 (11.56)	80.77 (11.73)	83.74 (13.99)	1.91	.15	
Key covariates						
Child sex, male, n (%)	62 (44.60)	19 (43.18)	84 (48.00)	0.53	.77	
Child race, African American, n (%)	115 (82.22)	35 (79.55)	144 (81.87)	0.24	.88	
Marital status, married, n (%)	12 (8.89)	2 (4.56)	28 (16.37)	6.65	.04	
Maternal education	11.65 (1.72)	11.23 (1.38)	11.93 (1.38)	4.07	.02	2 ≠ 3
Birth maternal age	29.46 (5.06)	30.45 (4.74)	25.52 (4.74)	33.68	<.0001	3 ≠ 1,2
Maternal BSI-GSI at birth	0.81 (0.77)	0.85 (0.65)	0.50 (0.53)	12.06	<.0001	3 ≠ 1,2
Prenatal alcohol exposure month prior	11.39 (20.28)	16.76 (28.72)	2.53 (7.94)	35.74	<.0001	3 ≠ 1,2
Prenatal average cigarette use	10.21 (10.02)	15.64 (13.56)	3.74 (6.89)	58.38	<.0001	2 ≠ 1,3
2nd trimester marijuana exposure	1.14 (3.96)	1.90 (5.35)	0.19 (1.74)	8.98	.0002	3 ≠ 1,2
HOME score	46.69 (6.67)	51.00 (5.86)	48.78 (6.10)	8.85	<.0002	1 ≠ 2,3
Violence Exposure	0.66 (0.77)	0.50 (0.78)	0.59 (0.81)	1.45	.24	
Lead exposure[a]	7.34 (4.24)	5.82 (3.58)	8.16 (4.64)	4.46	.01	2 ≠ 3
Elevated lead (≥10 μg/dL)[b], n (%)	24 (20.7)	2 (7.7)	37 (27.2)	5.18	.07	
Adolescent substance use						
Any tobacco (n, adjusted %)	47 (50.22)	17 (54.96)	47 (13.19)	9.47	.009	3 ≠ 1,2
Any alcohol (n, adjusted %)	54 (44.92)	18 (48.64)	64 (27.92)	8.65	.01	3 ≠ 1,2
Any marijuana (n, adjusted %)	52 (32.66)	12 (27.24)	43 (21.53)	3.64	.16	
Any drug final (n, adjusted %)	80 (61.92)	26 (65.49)	90 (45.90)	7.12	.03	3 ≠ 1,2

[a] Key covariates include only those variables that met the criteria for evaluation in logistic modelling.
[b] Sub-sample of 116 PCE biological/relative care, 26 PCE adoptive/foster care, and 136 NCE.

the odds of tobacco use (p < .04) and higher quality home environment decreased the odds of marijuana use (p < .0002) by age 15.

Higher lead levels during the preschool years also independently predicted current adolescent use of alcohol (p < .009). No other substance use categories were predicted by early lead levels. Violence exposure was an independent predictor of the likelihood of tobacco use (OR = 1.47, CI: 1.15–1.88, p < .002), marijuana use (OR = 1.55, CI: 1.20–1.99, p < .0007) and use of any drug (OR = 1.24, CI: 1.01–1.52, p < .04). In all of these models the effects of prenatal cocaine exposure remained significant at p < .04–.005.

4. Discussion

4.1. Summary of results

Adolescents with PCE were more likely to use alcohol, tobacco, marijuana, and any drug by the age of 15 years compared to their non-exposed peers. This relationship does not appear to be dose-dependent. An interaction effect between PCE and race indicated that non-African American PCE adolescents used tobacco at almost three times the rate of non-African American NCE adolescents. There was a significant independent effect of race on alcohol use, with non-African American adolescents having a higher adjusted probability of use. Gender was a significant predictor of marijuana use, with boys having a greater probability of marijuana use than girls. With the exception of a relatively small number of other variables, primarily marital status and mother's age at infant birth, measures of environmental stress such as maternal psychological distress, quality of the home environment, other prenatal drug exposures, and current caregiver use of drugs added little explanatory value. Specifically, adolescents whose mothers were older at their births used less tobacco, but those with mothers who were married at the time of their birth had an increased likelihood of tobacco, marijuana or any drug use by age 15 years. Level of blood lead at age 2 or 4, which has not typically been investigated simultaneously with prenatal cocaine exposure, was also an independent additive factor related to increased odds of using alcohol. This finding raises special concern for those individuals that have the co-occurrence of PCE and elevated blood lead. In addition, violence exposure was an independent predictor of increased odds of tobacco, alcohol and any drug use.

4.2. Relationship of findings to existing research

The associations of prenatal cocaine exposure to later substance use found in this study are consistent with preclinical findings of underlying damage to the monoamine-rich areas of the brain thought to underlie poor inhibitory control and increased risk taking behavior among PCE individuals (Malanga and Kosofsky, 1999). Most notably, the present findings are similar to that of Frank et al. (2011) who found a dose dependent effect of PCE on increased risk of any licit or illicit substance use, as well as alcohol and marijuana use specifically, and to that of Richardson et al. (2013) who found an effect of first trimester PCE on alcohol and marijuana use. However, in this study a dose-dependent effect of PCE was only found in non-African American adolescents who used tobacco. A potential reason for the lack of a more pervasive dose-dependent response for drug use outcomes may have been that there is a threshold effect. For example, most subjects in the PCE group were exposed to an amount of cocaine necessary to increase the odds of substance use by 15 years. However, gradients of exposure did not have an effect on use or no use by age 15. These data add support to the findings of Frank et al. (2011) and Richardson et al. (2013) who also found independent effects of violence exposure on initiation of substance use.

Several other studies, both preclinical (Keller et al., 1996; Rocha et al., 2002) and with human adolescents (Delaney-Black et al., 2011), have found that prenatal cocaine exposure is related to increased rates of cocaine use. However, the rates of cocaine use by age 15 in this study were too small to complete statistical analyses (<10% of the sample, 6% of both the PCE and NCE group were identified as having used cocaine).

When substance use data from this sample is compared to the 2011 National Survey on Drug Use and Health (NSDUH; SAMHSA,

2012) data for 16–17 year olds, the closest reference point for our 15.5 year old subjects, both the PCE and NCE groups in this sample use drugs at a considerably higher rate than the overall population. For example, 39% of the PCE and 36% of the NCE groups reported or were identified as having used alcohol, whereas only 25.3% of NSDUH 16–17 year olds reported being current alcohol users. Similarly, 15.4% of surveyed 16–17 year old individuals reported past month tobacco use, whereas in the current sample 35% and 27% of the PCE and NCE youth were identified as having used tobacco. While these results are not directly comparable due to differences in determining substance use initiation and use of control variables, they do indicate that prenatally cocaine/polydrug exposed individuals have significantly greater risk of early drug use compared to both a high risk control group and the general population.

The finding that higher blood lead levels during the preschool years are associated with increased alcohol use is consistent with previous literature (Dietrich et al., 2001). It is widely thought that the association of elevated blood lead and propensity for drug use occurs via lead's disruption of central nervous system physiology concerned with regulation of impulse control and reward seeking (Dietrich et al., 2001; Lane et al., 2008). Researchers should not ignore this important variable in adolescent substance use research among high risk youth, since elevated lead levels are more likely to occur in high risk, poly-substance exposed populations. Additional research is required, however, because in this sample those individuals with the highest amounts of prenatal cocaine exposure were placed out of home in foster or adoptive care, where the risk of environmental lead was reduced due to greater economic resources compared to that of cocaine exposed children or non-cocaine exposed children living with biologic mothers or relatives.

Another particularly interesting finding is that placement of PCE adolescents in higher quality home and caregiver settings (foster or adoptive care) did not exert a protective effect as hypothesized. The enriched homes provided in these foster/adoptive care settings have had some protective effects in cognitive outcomes in our study cohort (Lewis et al., 2011; Singer et al., 2004) but do not appear to have had the same protective effect on behavioral outcomes that have been assessed thus far (McLaughlin et al., 2011; Minnes et al., 2013, 2010). Additional research is needed to understand why a better quality home environment was not a protective factor for substance use by age 15. One could speculate that the neurotoxic effects of cocaine or genetic transmission of substance use is stronger than the enriched environments of the foster or adoptive placements on this type of adolescent risk taking behavior. Adolescents in this study that were placed in foster/adoptive care had higher amounts of average prenatal cocaine and tobacco exposure, presumably accounting for added prenatal stress, that could not be overcome by higher quality home environments.

4.3. Strengths and limitations

Limitations of the study should be considered. Generalizability of results is limited to a high-risk, urban, low SES population who primarily used crack cocaine. In addition, a high percentage of women in this study continued to use cocaine throughout all three trimesters of pregnancy (69–83%) making this sample generalizable only to studies with similarly high rates of prenatal cocaine exposure throughout gestation. Interview data obtained from mothers about their prenatal drug use was collected retrospectively and thus subject to the possibility of recall error and social desirability bias. Adolescent drug use was measured dichotomously and information about severity cannot be inferred, limiting our understanding of the severity of their use. Continued study can ascertain whether or not the early use of drugs by age 15 will lead to long-term problems.

There are also considerable strengths to this study, including the prospective, longitudinal design and the multiple method assessment of current adolescent substance use, as well as the birth classification of exposure, increasing the accuracy of group status, and exceptional retention rate, with 89% of the original surviving cohort assessed at age 15. A large number of potential confounders were evaluated, including blood lead levels, available for a large proportion of subjects. The ability to evaluate whether the cocaine effect was dose dependent was another significant strength.

4.4. Conclusions

At age 15, adolescents who were exposed to cocaine prenatally were significantly more likely to use tobacco, alcohol, marijuana and any drug, after control for multiple confounding factors. As early drug use is associated with increased risk of lifetime drug dependence as well as mental health, physical health and other life problems, this increased risk among adolescents with prenatal cocaine exposure indicates the need for early, targeted prevention services as well as early screening for problem drug use.

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Contributors

Dr. Sonia Minnes participated in the study's conception, design, coordination, statistical analyses, interpretation of the data, and drafted the manuscript. Dr. Lynn Singer participated in the study's conception and design, interpretation of data, and helped to draft the manuscript. Dr. Meeyoung O. Min performed the statistical analyses, participated in the interpretation of data, and helped to draft the manuscript. Dr. Adelaide Lang participated in the coordination of the study, performed the measurements, and helped to draft the manuscript. Ms. Miaoping Wu provided data management, performed statistical analyses, participated in interpretation of data, and helped to draft the manuscript. Ms. Susan Yoon assisted in the literature review, drafting, and proofing the manuscript.

All authors read and approved the final manuscript.

Conflict of interest

No conflict of interest declared.

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