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Prenatal cocaine exposure: Direct and indirect associations with 21-year-old offspring substance use and behavior problems

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ABSTRACT

Background: Prenatal cocaine exposure (PCE) has been linked to child/adolescent behavior problems and substance use in several longitudinal cohort studies. It is unclear whether these effects extend into adulthood and influence young adult behavior problems and substance use and, if so, whether they are mediated by childhood and adolescent experiences.

Methods: These data are from an ongoing longitudinal study of individuals born to women who were recruited early in pregnancy. Trimester-specific data on prenatal drug exposure were obtained. Caregivers and offspring were assessed at delivery and at 1, 3, 7, 10, 15, and 21 years postpartum. This report is from age 21, when 225 offspring (52% females; 54% African American, 46% Caucasian) reported on behavior problems, emotion regulation, and substance use.

Results: There were significant direct associations between PCE and early initiation of marijuana, 21-year emotion regulation problems, arrest history, and Conduct Disorder. The relation between PCE and young adult internalizing behavior was mediated by adolescent mood symptoms. The association between PCE and 21-year marijuana use was mediated by early initiation of marijuana use.

Conclusions: PCE has both direct and indirect long-term associations with young adult development. Using statistical models that considered the complex interrelationships among PCE and adult outcomes, we demonstrated that the direct effects of PCE on young adult emotion regulation problems, arrest history, and Conduct Disorder are not completely explained by earlier adolescent behavior. Moreover, the analyses suggesting mediated pathways from PCE to young adult problems identify crucial variables to target interventions for exposed children and adolescents.

1. Introduction

Emerging or young adulthood is an important and distinct developmental life stage with increased stress and demands as young adults transition into adult roles (Arnett, 2000). This developmental stage may prove particularly challenging for those with prenatal cocaine exposure (PCE) because of the child/adolescent deficits associated with PCE. In our longitudinal study of PCE, we have found persistent associations between PCE and three domains of child and adolescent outcomes that may make the transition into young adulthood difficult. First, PCE predicted externalizing behavior problems (aggression and delinquency) at ages 1, 3, 7, 10, and 15 years (Richardson et al., 2009, 2011, 2015; Richardson et al., 2013a, 2013b), a finding replicated by many others (Bada et al., 2012; Bennett et al., 2013; Delaney-Black et al., 2000; Lambert et al., 2013; Min et al., 2014a, 2016; Minnes et al., 2010). Second, PCE predicted fussy and difficult infant temperament at 1 and 3 years (Richardson et al., 2008, 2009) and mood problems including internalizing behavior problems (Richardson et al., 2009, 2011) and depressive symptoms (Richardson et al., 2013a, 2015) through age 15. Most other studies have not found effects of PCE on mood or internalizing behavior problems (Accornero et al., 2006; Bada et al., 2011; Bennett et al., 2002; Delaney-Black et al., 2000; Min et al., 2014b; Minnes et al., 2010). Third, we and others found that PCE increases risk for early initiation of alcohol and/or marijuana use (Frank et al., 2011; Min et al., 2014a; Minnes et al., 2014, 2017; Richardson et al., 2013b) and cocaine use (Delaney-Black et al., 2011). What is not

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known is whether PCE will be associated with these same domains in young adulthood and, if so, whether the relations will be mediated by earlier effects.

We know that adult behaviors are affected by child/adolescent behaviors in each of these three domains. First, previous research has established that the externalizing behavior problems of adult aggression and criminal behaviors are associated with difficult temperament and conduct symptoms during childhood (Fergusson et al., 2000; Moffitt et al., 1996) and with lower socioeconomic status (SES), exposure to violence and child abuse, negative life events, and earlier aggression, delinquency, and substance use (Copeland et al., 2007; Eitle and Turner, 2002; Leschied et al., 2008; Mason et al., 2010). Second, predictors of adult internalizing problems (such as depression and anxiety) and temperament include lower SES, exposure to violence and child abuse, substance use, and child/adolescent mood symptoms such as depression and anxiety (Copeland et al., 2009; Kessler et al., 2010; Klein et al., 2011; Najman et al., 2010; Reinherz et al., 2003). Third, substance use is particularly salient in emerging adulthood when levels of substance use and abuse peak and then generally decline as individuals take on adult roles such as employment and parenthood (Bachman et al., 1997; Chen and Jacobson, 2012; Jessor et al., 1991). However, for some, substance use continues to escalate and interferes with their transition into adult roles (Ellickson et al., 2004; Green et al., 2010; Oesterle et al., 2011; Schulenberg et al., 2005; Slade et al., 2008; Staff et al., 2010). Previous research has found that emerging adult substance abuse is associated with child/adolescent behavior problems (Doherty et al., 2008; Fergusson et al., 2007; Hayatbakhsh et al., 2009) as well as with early initiation of substance use (Wells et al., 2004).

To date, there have been no investigations of the association of PCE with young adult behavior problems, temperament, and substance use and no consideration of earlier behaviors that may mediate this association. The relations between PCE and child/adolescent behavior problems and the associations of child/adolescent behavior with young adult behavior problems raise the question of whether the linkage between PCE and young adult behavior problems is mediated by earlier behavior problems. Similarly, the relation between PCE and young adult substance use may be mediated through adolescent substance use. To accurately understand these relations, we must also consider that individuals with PCE are more likely to be exposed prenatally to other drugs and to maternal substance use, lower SES, and violence and/or abuse during childhood/adolescence (Alati et al., 2006; Bada et al., 2011; Baer et al., 2003; Frank et al., 1988; Lester et al., 2002; Min et al., 2017; Minnes et al., 2017; Porath and Fried, 2005; Schwab-Stone et al., 2013; Sonon et al., 2015). Additional risk factors for poor young adult outcomes, such as negative life events, poor social support, depression, and family history of alcohol/drug problems must also be considered (Stone et al., 2012; Tucker et al., 2005).

This program of research is informed by multiple theoretical approaches. Aspects of the teratologic model that have informed our research include the importance of the specific developmental period of exposure, the range of developmental domains that can be affected, and the emergence of effects later in development (Vorhees, 1989). As we evaluate developmental pathways to adult functioning, early risk factors need to be examined when investigating the relation between PCE and young adult outcomes, particularly in low-income samples (Glantz and Chambers, 2006; Stone et al., 2012). We must consider both early (distal) consequences and correlates of PCE and current (proximal) environmental risk factors as illustrated by theories of developmental transition such as the Transition Overload model and the Increased Heterogeneity model (Schulenberg and Maggs, 2002; Schulenberg et al., 2004). These models predict increased vulnerability of the PCE-exposed offspring in their transition to adulthood (Transition Overload) and an increasing divergence from their non-exposed peers (Increased Heterogeneity).

The purpose of this report is to investigate whether PCE is related to adult development and whether any relations are mediated by earlier PCE-associated deficits using data from the 21-year follow-up of individuals whose mothers were recruited early in pregnancy. Based on previous findings (cited above), we investigated the roles of: adolescent delinquency on adult externalizing problems, adolescent mood on adult temperament and internalizing problems, and adolescent substance use on adult substance use. We used prospectively collected data from childhood, adolescence, and young adulthood to understand the direct and indirect associations between PCE and adult outcomes considering covariates associated with PCE and/or the outcomes (cited above).

2. Methods

2.1. Study design

This sample was recruited from the Magee-Womens Hospital prenatal clinic from 1988 to 1992. Pregnant women, at least 18 years of age, were approached by research staff. Informed consent was obtained prior to interviewing, and 90% agreed to participate. Medical chart reviews conducted on a random sample of those who refused revealed only 5% with a history of prenatal drug use. This research was approved by the University of Pittsburgh's Institutional Review Board. A Certificate of Confidentiality from the Department of Health and Human Services assured participants that their responses could not be subpoenaed.

During the initial interview (4^{th} or 5^{th} prenatal month), women were asked about cocaine/crack, alcohol, tobacco, marijuana, and other illicit drug use in the year prior to pregnancy and the first trimester. Any woman who reported any cocaine/crack use during the first trimester was enrolled. The next woman interviewed for recruitment purposes who reported no cocaine/crack use during both the year prior to pregnancy and the first trimester was also enrolled in the study. Women selected for the study (N = 320) were interviewed during the 7^{th} prenatal month about their 2^{nd} trimester substance use and in their hospital room after delivery about their 3^{rd} trimester substance use. Between enrollment and delivery, there were 25 women who were not seen (e.g., moved, refused, fetal loss). Offspring were examined at birth by research staff, and follow-up assessments were conducted at 1, 3, 7, 10, 15, and 21 years postpartum. At all follow-up phases, mothers (or caregivers) were interviewed about their past-year substance use, sociodemographic and psychosocial characteristics, and psychiatric symptoms. We report here on the age 21 phase (conducted from 2009 to 2014). At this phase, 13% of the women interviewed were non-maternal caregivers; for ease of presentation, we refer to maternal variables.

2.2. Participants

Seventy-six percent of the birth cohort of 295 mother/infant pairs (Richardson et al., 1999) completed the age 21 phase (N = 225). Seventy offspring were not included in the current analyses for the following reasons: died, placed for adoption and could not be located, incarcerated or in a rehabilitation facility, refused, moved out of the area, lost to follow-up. There were no differences in PCE, maternal sociodemographic (education, income, work, marital status), or newborn (gestational age, weight, length) characteristics between those who were and were not included in these analyses. The two groups differed only on gender (48% versus 73%, respectively, were male, $p < 0.001$) and maternal Center for Epidemiological Studies— Depression Scale (CES-D) (Radloff, 1977) depressive symptoms at delivery (mean 41.4 versus 44.2, respectively, $p < 0.05$; items scored 1–4).

2.3. Measures

2.3.1. Maternal measures

2.3.1.1. Maternal substance use. Maternal cocaine/crack, alcohol, tobacco, marijuana, and other illicit drug use were assessed during

confidential interviews at each phase. Usual, maximum, and minimum quantity and frequency of cocaine and crack use were reported in lines, rocks, or grams (see Richardson et al., 2008 for details). For the analyses, first, second, and third trimester cocaine use were analyzed as any versus no use during each trimester. The alcohol, tobacco, and marijuana variables were average number of reported drinks, cigarettes, or joints per day, respectively. Alcohol, tobacco, and marijuana use for each trimester of pregnancy and at the age 21 follow-up were used as continuous variables, with one exception: at the age 21 phase, too few mothers reported marijuana or cocaine use for them to be analyzed as continuous variables: maternal marijuana use was defined as any versus no use, and other illicit drug use was defined as any reported use of cocaine or other illicit drugs versus no use.

2.3.1.2. Other maternal measures. At the age 21 follow-up, mothers were asked structured questions about current sociodemographic, social support (how many people to turn to; how often see/talk to relatives/friends), and psychosocial characteristics. The *CES-D* (Radloff, 1977) was used to assess depressive symptoms (item scores ranged from 1 to 4), and the *Spielberger State-Trait Personality Inventory* (STPI) anger subscale (Spielberger, 1979) was used to measure hostility symptoms (e.g., I am quick tempered; I am a hotheaded person).

2.3.2. Offspring measures

2.3.2.1. Offspring substance use. At the 15- and 21-year phases, offspring were asked about their age of initiation of alcohol (beer, wine, liquor), tobacco, and marijuana. To minimize recall bias, age of initiation as reported at the 15-year follow-up was used in the analyses unless initiation had not yet occurred, in which case age of initiation as reported at age 21 was used. At ages 15 and 21, offspring past-year alcohol, tobacco, marijuana, and other illicit drug use were assessed using questions parallel to those described above. At age 21, we collected a urine sample to test for marijuana: 98% of those with positive screens reported current use.

2.3.2.2. Offspring behavior: Adult Self-Report (ASR) (Achenbach and Rescorla, 2003). At the age 21 phase, offspring completed the ASR, an extension of the Child Behavior Checklist (CBCL) (Achenbach, 1991). The following standardized measures of behavior problems were used: total, internalizing, and externalizing scores, as well as the individual syndrome scales: anxious/depressed, withdrawn, and aggression. Reliability and validity are well-established (Achenbach and Rescorla, 2003). In addition, we asked the offspring about their arrest history, which was dichotomized as no versus any arrests. *Adult Temperament Questionnaire (ATQ)* (Evans and Rothbart, 2007; Rothbart et al., 2000). We used the 19-item Effortful Control (EC) subscale from the ATQ as a measure of the capacity for self-regulation, given earlier findings on the relation between EC and alcohol/drug use (Piehler et al., 2012; Wong et al., 2006). The EC subscale consists of items regarding Activation ("I can keep performing a task even when I would rather not do it"), Attentional ("It is very hard for me to focus my attention when I am distressed" – reverse coded), and Inhibitory Control ("I usually have trouble resisting my cravings for food, drink, etc." – reverse coded). Higher scores indicate more control. Very good reliability and validity have been reported (Evans and Rothbart, 2007). *Difficulties in Emotion Regulation Scale (DERS)* (Gratz and Roemer, 2004). This is a 36-item assessment of regulation of negative emotional states including the following four subscales: lack of emotional awareness ("I pay attention to how I feel" – reverse coded); lack of emotional clarity ("I have no idea how I'm feeling"); difficulty engaging in goal-directed behavior while upset ("When I'm upset, I have difficulty concentrating"); and difficulty with impulse control ("When I'm upset, I lose control over my behaviors"). Higher scores indicate more difficulties. The scale has good test-retest reliability and high internal consistency (Gratz and Roemer, 2004).

Conduct Disorder was diagnosed using the *Diagnostic Interview Schedule* (DIS-IV; Robins et al., 1981, 2000), a widely used structured diagnostic interview that assesses current (12-month) and lifetime prevalence of DSM-IV disorders. Interviewers were trained to administer the computerized DIS-IV by a trained and experienced clinician. Reliability standards were met, and regular reliability checks were conducted throughout data collection.

2.3.2.3. Other offspring measures. The *Self-Reported Delinquency Scale* (SRD) (Loeber et al., 1998) was completed by the offspring at the age 15 follow-up. The SRD assesses antisocial behaviors such as purposefully breaking or damaging things, stealing, hitting, fighting, and running away from home. Higher scores indicate more delinquent behaviors. The status offenses subscale was used in analyses because it had the best internal consistency (Loeber et al., 1998). The *Revised Dimensions of Temperament Survey* (DOTS-R) (Windle and Lerner, 1986), also completed by offspring at 15 years, is a self-assessment of temperament or behavioral style. The mood subscale consisted of seven questions about happiness (laughing, smiling, cheerful) and was dichotomized to $\leq 25^{th}$ (coded as 1) versus $> 25^{th}$ (coded as 0) percentile due to its asymmetric distribution.

The *Childhood Trauma Questionnaire* (CTQ) (Bernstein and Fink, 1998) was completed by the offspring at the age 21 follow-up. The CTQ has been used to measure childhood and adolescence physical and emotional abuse and neglect and sexual abuse in a variety of populations, and good reliability and validity have been reported (Cammack et al., 2016). The 21-year-old offspring were also interviewed about their sociodemographic characteristics (education, income, work/school status), life events during the past year (*Recent Life Changes Questionnaire)* (Miller and Rahe, 1997), and their immediate family history (biological parents or siblings) of serious alcohol and/or drug problems.

2.4. Statistical analyses

The following outcome variables were transformed prior to the analyses due to their asymmetric distributions: young adult offspring's use of alcohol (none, < 1 drink/day, ≥ 1 drink/day); tobacco (none, < 5 cigarettes/day, ≥ 5 cigarettes/day); and marijuana (none, < 1 joint/day, ≥ 1 joint/day). Multiple stepwise regression was used for the continuous outcome variables, ordinal logistic regression for the trichotomous variables, and Cox proportional hazards regression analysis for the age of initiation variables. Analyses were conducted separately by trimester to assess the effects of exposure during each gestational period.

Table 1 presents maternal and offspring characteristics, including the covariates that were considered for inclusion in the analyses based on the literature and on their associations with the outcomes or PCE in initial bivariate analyses. In addition to carefully selecting variables for consideration based on our theoretical framework and the relevant literature, we used the bivariate analyses to select the most parsimonious set of covariates to include in the final multivariate models. Covariates were included if they were significantly related to either PCE or the outcome at $p \leq .05$. We also tested race by PCE interactions for the outcome variables where PCE was significant in the regression. None of the interactions were significant.

In the final models, the tolerance of each covariate was examined to assure that the estimated regression slopes were not unstable because of multicollinearity. Residuals and the modified Cook's statistic (Cook and Weisberg, 1982) were used to identify possible outliers and influential points. There were no outliers for any of the outcome variables. There was one influential case each for the ASR, ATQ, and DERS. The significant relations with PCE reported here did not change with removal of these cases.

For those outcomes for which PCE was a significant predictor, mediating analyses were conducted to determine whether age 15 behaviors (SRD for adult externalizing problems, DOTS-R mood for adult

Table 1
Sample characteristics by first trimester cocaine exposure (unadjusted values).

	No cocaine use 1st trimester n = 133	Cocaine use 1st trimester N = 92	p value[a]
First trimester maternal characteristics			
African American (%)	42.1	55.4	< .05
Age (yrs) (mean, SD)	24.1 (5.0)	26.5 (5.0)	< .001
Education (yrs) (mean, SD)	12.1 (1.4)	11.9 (1.2)	ns
Single (%)	70	89	< .001
Family income ($/mo) (mean, SD)	782 (614)	568 (683)	< .05
Drinks/day (mean, SD)	0.3 (0.6)	2.3 (3.0)	< .001
Cigarettes/day (mean, SD)	5.7 (8.9)	10.7 (9.0)	< .001
Joints/day (mean, SD)	0.06 (0.2)	0.5 (1.3)	< .001
Other illicit drugs (except cocaine) (%)	2.3	9.8	< .05
21-year maternal characteristics			
Education (yrs) (mean, SD)	13.0 (1.7)	13.2 (1.9)	ns
Family income ($/mo) (mean, SD)	2927 (2155)	2138 (2176)	< .05
Single (%)	59	70	ns
Current depressive symptoms (CES-D[b])	38.3 (10.3)	41.3 (9.1)	< .05
Current hostility (STPI[c])	14.9 (4.2)	15.7 (4.6)	ns
People to turn to (#)	4.8 (2.4)	4.4 (2.2)	ns
How often see/talk to relatives/ friends[d]	4.3 (0.6)	4.2 (0.7)	ns
Drinks/day (mean, SD)	0.7 (2.4)	1.8 (3.5)	< .05
Cigarettes/day (mean, SD)	5.5 (9.1)	6.4 (7.4)	ns
Marijuana (% any)	9.3	17.4	ns
Illicit drugs (cocaine & other) (%)	1.7	9.3	< .05
21-year offspring characteristics			
Age (yrs) (mean, SD)	21.3 (0.7)	21.3 (0.6)	ns
Male (%)	48.1	46.7	ns
African American (%)	47.4	63.0	< .05
Education (yrs) (mean, SD)	12.8 (1.5)	12.6 (1.4)	ns
Working (% yes)	56.4	59.8	ns
Attend school (% yes)	40.6	43.5	ns
Personal income ($/mo) (mean, SD)	661 (739)	914 (1213)	ns
Receive public assistance (% yes)	15.8	12.0	ns
Live with partner (%)	19.6	19.6	ns
≥ 1 child (%)	22.6	28.3	ns
Current life events (#)	5.5 (3.2)	6.3 (3.3)	ns
Drink alcohol (%)	90.2	95.7	ns
Drinks/day (mean, SD)	1.6 (3.3)	1.9 (3.1)	ns
Use ≥ 1 drink/day (%)	30.8	40.2	ns
Smoke cigarettes (%)	36.1	46.7	ns
Cigarettes/day (mean, SD)	2.8 (5.3)	3.5 (5.4)	ns
Smoke ≥ ¼ pack/day (%)	24.0	33.7	ns
Use marijuana (%)	49.6	68.5	< .01
Joints/day (mean, SD)	1.3 (5.7)	1.7 (4.0)	ns
Use ≥ 1 joint/day (%)	16.5	31.5	< .01
Use other illicit drugs (includes cocaine) (%)	15.0	20.7	ns
Family history alcohol problems[e] (%)	27	50	< .001
Family history drug problems[e] (%)	23	50	< .001
CTQ[f]	2.2 (0.8)	2.5 (1.0)	< .05
Ever arrested (% yes)	24	47	< .001
DIS[g] Conduct Disorder (%)	9	21	< .01
ASR[h] externalizing problems (t-score)	53.1 (10.8)	55.4 (10.1)	ns
ASR aggression (raw score)	6.2 (4.9)	6.8 (5.4)	ns
ASR internalizing problems (t-score)	52.7 (12.2)	53.1 (11.7)	ns
ASR withdrawn (raw score)	3.2 (3.2)	4.0 (3.2)	< .05
ASR anxious/depressed (raw score)	7.6 (6.7)	8.0 (7.0)	ns
ATQ[i] inhibitory control	3.5 (0.6)	3.3 (0.6)	< .05
ATQ attention control	3.5 (0.7)	3.4 (0.6)	ns
ATQ activational control	3.6 (0.6)	3.6 (0.6)	ns
DERS[j] lack of clarity	9.7 (3.7)	10.4 (4.3)	ns
DERS lack of awareness	13.7 (4.9)	15.4 (5.8)	< .05
15-year offspring mediators			
Early marijuana use (% < 15 years)	18.0	43.5	< .001
Status offenses	1.5 (1.4)	2.3 (1.5)	< .001
DOTS-R[k] mood (% ≤25th percentile)	18.8	31.5	< .05

[a] Based on *t*-test or Mann-Whitney for continuous variables and on Chi-square test for dichotomous variables.
[b] Center for Epidemiological Studies - Depression scale (Radloff, 1977) (items scored.1–4).
[c] State Trait Personality Inventory (Spielberger, 1979).
[d] 1 = Never to 5 = Very often.
[e] Any biological parent or sibling serious problem.
[f] Childhood Trauma Questionnaire (Bernstein and Fink, 1998).
[g] Diagnostic Interview Schedule (Robins et al., 2000).
[h] Adult Self-Report (Achenbach and Rescorla, 2003).
[i] Adult Temperament Questionnaire (Rothbart et al., 2000).
[j] Difficulties in Emotion Regulation Scale (Gratz and Roemer, 2004).
[k] Dimensions of Temperament Scale – Revised (Windle and Lerner, 1986).

temperament and internalizing problems, and early marijuana use (< 15 years) for adult substance use) were part of the pathway between PCE and the age 21 outcomes. These variables were chosen because they were significantly associated with PCE at age 15 (Richardson et al., 2013b, 2015). For the logistic and multiple regression models, mediation was evaluated with path analysis using the product of coefficients, and MacKinnon's z' distribution was applied to determine significance of the mediator (z' ≥ 0.97 corresponds to p ≤ 0.05; MacKinnon et al., 2002). Partial mediation was attributed when the direct effect of PCE remained significant after including the mediator in the model; complete mediation was attributed when the direct effect of PCE became non-significant after including the mediator.

3. Results

3.1. Sample characteristics

At delivery, mothers were, on average, 24.8 years old (range: 18–41), had 11.9 years of education (range: 9–16), 25% were primigravidous, 23% were married, and 52% were Caucasian (Richardson et al., 1999). In the first trimester, 41% reported using cocaine. Use decreased over pregnancy with 8% and 11% reporting cocaine use during the second and third trimesters, respectively. In those who used first trimester, 50% reported snorting powder cocaine only; the rest smoked crack. In those who continued to use in the third trimester, 20% reported snorting powder cocaine only, and 80% smoked crack.

The median age of the offspring at the age 21 assessment was 21.3 years (range: 20–24). Forty-eight percent were male, 46% were Caucasian, and 54% were African American. The mean educational level was 12.7 years (range: 8–16 years). The majority (85%) had graduated high school, half attended some college, less than 2% had graduated college, 42% were attending school, 58% were working, and 3% served in the military. Median personal income was $500/month (range: $0-8,000), and 14% reported receiving public assistance. Most lived with their parents or relatives, and only 35% lived on their own. Three percent were married, and 25% had at least one child (range: 0–3). At 21 years, 92% drank alcohol, 40% smoked cigarettes, and 56% used marijuana; 36% drank ≥1 drink/day, 5% smoked ≥1 pack/day, and 25% used ≥1 joint/day. Thirty-six percent, 41%, and 28% reported using alcohol, tobacco, and marijuana, respectively, prior to age 15.

3.2. Bivariate relations with PCE

As seen in Table 1, mothers who used cocaine during the first trimester were significantly more likely to be African-American, older, single, have lower family incomes, and to use more alcohol, tobacco, marijuana, and other illicit drugs than were first trimester non-users. At the age 21 phase, maternal income was lower, depressive symptoms were higher, and current use of alcohol and illicit drugs was greater in first trimester cocaine users compared to non-users. At age 21, there were no significant demographic differences between exposed and non-exposed offspring except for race: exposed offspring were more likely to be African American. Offspring exposed during the first trimester were significantly more likely to use marijuana and at heavier levels, to have immediate family members with a history of alcohol or drug problems, and to report more childhood trauma than non-exposed offspring. In unadjusted analyses, exposed offspring were more likely to have been arrested, be diagnosed with Conduct Disorder (CD), and to report more ASR withdrawn symptoms, less ATQ inhibitory control, and greater DERS lack of awareness than non-exposed offspring.

Based on the literature previously cited and the bivariate analyses, the following variables were selected for inclusion in the multivariate models: offspring race, gender, and current life events; maternal age; prenatal alcohol, marijuana, and tobacco; current maternal family income, alcohol, and other illicit drugs; CTQ; and family history of alcohol/drug problems. Table 2 shows the correlations among the outcomes and variables that were included in the regression models.

3.3. Regression analyses

As shown in Table 3, first trimester cocaine exposure was a significant predictor of age 21 ATQ inhibitory control and DERS lack of awareness. Third trimester cocaine exposure significantly predicted ASR withdrawn behavior and DERS lack of awareness. Prenatal exposure was associated with more withdrawn behaviors, poorer inhibitory control, and increased difficulty with emotion regulation. There was no significant relation between PCE and ASR externalizing behaviors.

The age 15 DOTS-R mood scale completely mediated the pathway from third trimester exposure to ASR withdrawn (z' = 1.66) (Fig. 1) and the pathway between PCE and ATQ inhibitory control (z' = -1.92). However, the DOTS-R only partially mediated the relation between PCE and DERS lack of awareness (z' = 1.38); PCE remained a significant predictor.

First trimester cocaine exposure was a significant predictor of age of marijuana initiation but not of age of alcohol or tobacco initiation (Table 4). Fig. 2 shows that the exposed offspring start to diverge from the non-exposed offspring at about age 12; by age 21, 87% of the exposed and 69% of the non-exposed had initiated marijuana use. The inclusion of family history of alcohol/drug problems and childhood trauma as covariates in the model did not change the significant relation between first trimester cocaine exposure and age of marijuana initiation.

First trimester cocaine exposure was also a significant predictor of past-year marijuana use at age 21 but not of alcohol and tobacco use (Table 4). The percentage of daily marijuana users among the exposed offspring is almost double that of the non-exposed offspring (Table 1). However, as shown in Fig. 3, early marijuana use (< 15 years of age) completely mediated the relation between PCE and offspring marijuana use at age 21 (z' = 2.62; 51% of the total effect was due to the indirect effect, 49% was due to the direct effect).

PCE was also significantly associated with ever being arrested (odds ratios ~3) and with a diagnosis of CD (odds ratio ~2) (Table 4). The relation to arrest history was only partially mediated by age 15 delinquency (SRD) (z' = 3.14); PCE remained a significant predictor. The SRD was not related to CD so was not tested as a mediator.

4. Discussion

This report is from an ongoing longitudinal study of PCE in a sample enrolled early in pregnancy. Prenatal cocaine use occurred at moderate levels, and most users decreased or discontinued use after the first trimester, which represents the most common pattern of prenatal drug use in non-treatment samples (Day et al., 1989, 1991). Extensive data were collected on maternal characteristics associated with prenatal exposure and on offspring characteristics associated with their substance use and behavior problems, which enabled statistical modeling of their influence on young adult behavior. With control for prenatal and current covariates, PCE was significantly related to withdrawn behavior, inhibitory control, and emotion regulation at age 21. However, the relations of PCE to withdrawn behavior and inhibitory control were mediated by an indirect pathway through adolescent mood. The relation between PCE and emotion regulation was only partially mediated by adolescent mood; the direct pathway remained significant, consistent with the teratologic model. The relations between PCE and young adult arrests and CD were direct and were not mediated by adolescent delinquent behaviors. Those who were prenatally exposed were three times more likely to have been arrested and twice as likely to be diagnosed with CD as those who were not exposed, which is consistent with Schulenberg's transition models that predict a divergence of exposed from non-exposed individuals during major life transitions. First trimester cocaine exposure was significantly associated with age of marijuana initiation. As shown in Fig. 2, those who were prenatally exposed had a different trajectory of marijuana initiation than those who were not exposed, which is also consistent with Schulenburg's models. However, the relation between PCE and past-year marijuana use was explained by early initiation of marijuana. We did not find direct relations between PCE and young adult's self-report of planning, attention, or goal-directed behaviors, which are more likely to be associated with cognitive functions rather than emotion regulation.

These findings are consistent with earlier reports of significant associations between PCE and adolescent substance use and externalizing behavior problems (Delaney-Black et al., 2000; Lambert et al., 2013; Min et al., 2014a; Minnes et al., 2017; Richardson et al., 2013b, 2015) and a lack of association with global cognitive functions (Buckingham-Howes et al., 2013; Ross et al., 2015). This is the first report to show that some of these associations persist into young adulthood and that young adult outcomes are not merely a result of earlier problems. We have shown the importance of both distal and proximal influences on young adult development as emphasized by Schulenberg's transition models of development. There is only one other report from the adult follow-up of a longitudinal study of PCE, in which there was no significant relation between PCE and a composite measure of adaptive function (Forman et al., 2017). Our reported associations between PCE and young adult emotion regulation and externalizing behavior are also consistent with findings from animal studies (Behnke et al., 2013; Ross et al., 2015), in which PCE has been shown to affect the development and function of reward circuitry in the brain by increasing the reward potency of cocaine in operant conditioning tasks such as drug self-administration (Keller et al., 1996; Lin and Kellogg, 1996; Rocha et al., 2002) and causing long-term changes in D1-dopamine receptor signaling (Tropea et al., 2008). Our findings of direct associations with PCE are consistent with the teratologic model, which states that an exposure can act directly on specific mechanisms of development, particularly functional abnormalities (Vorhees, 1989).

We found that emotion regulation problems and arrests were associated with both first and third trimester exposure, while Conduct Disorder was associated with first trimester exposure. Weese-Mayer et al. (1993) reported that prenatal cocaine exposure early in gestation in rabbits was associated with a reduction in striatal dopamine. Howard et al. (1997) found that postnatal cocaine administration in rats (equivalent to third trimester in the human) was associated with

Table 2
Correlations among young adult outcomes and variables used in regression models.[a]

	Arrests	Conduct Disorder	Offspring marijuana	ASR[b] external	ASR internal	ASR anx/dep	ASR withdrawn	ASR aggression	DERS[c] clarity	DERS awareness	ATQ IC[d]	ATQ ATT[e]	ATQ AC[f]
1 st trim. cocaine	**0.24**	**0.18**	**0.21**	0.11	0.02	0.03	**0.12**	0.06	0.09	**0.15**	**−0.15**	−0.04	−0.06
3rd trim. cocaine	**0.15**	−0.05	**0.18**	0.09	**0.15**	**0.14**	**0.19**	**0.14**	0.04	**0.14**	**−0.13**	−0.04	−0.10
1 st trim. alcohol	0.07	**0.16**	**0.16**	0.07	0.03	0.03	0.11	0.02	0.02	0.09	−0.10	0.02	0.01
1 st trim. tobacco	0.10	**0.13**	**0.13**	0.06	0.09	0.10	0.11	0.06	0.04	0.09	0.02	0.04	−0.04
1 st trim. marijuana	0.10	0.05	−0.001	0.04	−0.08	−0.04	−0.04	0.02	−0.05	−0.10	0.06	**0.12**	0.08
Offspring race	−0.05	0.06	**−0.14**	0.02	0.07	0.09	−0.06	−0.02	−0.02	0.09	−0.02	−0.01	**0.12**
Gender	**0.18**	−0.01	0.06	**−0.16**	**−0.20**	**−0.22**	−0.004	**−0.20**	**−0.15**	**0.13**	**0.14**	**0.19**	0.10
Maternal age	−0.03	0.01	−0.05	**−0.20**	**−0.19**	**−0.23**	−0.10	**−0.21**	**−0.25**	−0.11	0.07	0.05	0.02
Current family income	0.03	−0.01	−0.10	−0.04	−0.02	0.02	0.003	−0.03	−0.05	0.06	0.01	0.09	**0.12**
Current maternal alcohol	0.03	−0.02	**0.15**	0.05	−0.06	−0.04	−0.03	0.04	−0.01	0.07	−0.09	−0.00	−0.05
Current maternal illicit drugs	**0.17**	**0.32**	**0.17**	**0.14**	0.02	−0.03	0.04	0.09	0.06	0.06	−0.10	−0.07	−0.05
Offspring life events	**0.22**	**0.18**	**0.29**	**0.37**	**0.29**	**0.25**	**0.18**	**0.31**	**0.28**	−0.02	**−0.27**	**−0.22**	**−0.23**
Family history alcohol problems	**0.17**	**0.15**	**0.13**	**0.15**	**0.15**	**0.15**	0.08	**0.12**	**0.14**	0.06	**−0.14**	−0.07	−0.07
Family history drug problems	**0.17**	**0.15**	0.06	0.01	0.06	0.07	0.05	0.01	**0.15**	**0.13**	0.05	−0.04	−0.11
CTQ[g]	0.10	**0.23**	**0.17**	**0.38**	**0.38**	**0.38**	**0.34**	**0.40**	**0.36**	**0.22**	−0.06	**−0.21**	**−0.22**
Early marijuana use	**0.41**	**0.40**	**0.34**	**0.22**	**0.12**	0.11	**0.17**	**0.16**	**0.12**	0.09	**−0.12**	−0.10	**−0.13**
Status offenses (SRD[h])	**0.40**	**0.34**	**0.22**	**0.28**	**0.15**	0.11	0.11	**0.23**	0.10	0.10	**−0.19**	−0.11	−0.10
DOTS-R[i] Mood	0.04	0.06	0.02	**0.20**	**0.28**	**0.28**	**0.34**	**0.26**	**0.26**	**0.20**	**−0.21**	**−0.20**	**−0.16**

[a] Correlations indicated in bold are significant at $p < .05$.
[b] Adult Self-Report (Achenbach and Rescorla, 2003).
[c] Difficulties in Emotion Regulation Scale (Gratz and Roemer, 2004).
[d] Adult Temperament Questionnaire Inhibitory Control (Rothbart et al., 2000).
[e] Adult Temperament Questionnaire Attentional Control (Rothbart et al., 2000).
[f] Adult Temperament Questionnaire Activation Control (Rothbart et al., 2000).
[g] Childhood Trauma Questionnaire (Bernstein and Fink, 1998).
[h] Self-Reported Delinquency Scale (Loeber et al., 1998).
[i] Dimensions of Temperament Scale – Revised (Windle and Lerner, 1986) ($\leq 25^{th}$ percentile = 1).

Table 3
Factors associated with continuous 21-year outcomes, controlling for covariates[a] (multiple regression analyses).

Outcome variable	Total R^2	Significant predictors	Raw beta	Standardized regression coefficient	*p* value
ASR[b] withdrawn	0.13	CTQ[c]	1.09	0.32	< .001
		3rd trimester cocaine[d]	1.20	0.12	< .05
ATQ[e] inhibitory control	0.13	Offspring life events	−0.04	−0.24	< .001
		1st trimester cocaine[d]	−0.25	−0.21	< .001
		Family history drug problems	0.20	0.16	< .05
		Gender[f]	0.15	0.13	< .05
		Maternal age	0.01	0.12	< .05
DERS[g] lack of awareness	0.10	CTQ	1.15	0.19	< .001
		1st trimester cocaine	1.80	0.17	< .05
		3rd trimester cocaine	2.64	0.15	< .05
		Maternal age	−0.15	−0.15	< .05
		Offspring race[h]	1.53	0.14	< .05

[a] Covariates included in model: offspring race, gender, current life events; maternal age; prenatal alcohol, marijuana, tobacco; current maternal family income, alcohol, and other illicit drugs; CTQ; family history of alcohol/drug problems. Results are presented only for those outcomes where prenatal cocaine exposure was significant. Predictors are listed in order of standardized regression coefficient, an indication of the magnitude of the effect. Results were run separately by trimester but are shown together for ease of presentation.
[b] Adult Self-Report (Achenbach and Rescorla, 2003).
[c] Childhood Trauma Questionnaire (Bernstein and Fink, 1998).
[d] 0 = no use, 1 = use.
[e] Adult Temperament Questionnaire (Rothbart et al., 2000).
[f] 0 = Female, 1 = Male.
[g] Difficulties in Emotion Regulation Scale (Gratz and Roemer, 2004).
[h] 0 = Black, 1 = Caucasian.

changes in dopamine concentrations. These alterations in the monoaminergic system are thought to be potential mechanisms for the PCE-associated behaviors that are seen in humans (Dow-Edwards, 2011; Mayes, 2002; Ross et al., 2015). However, most research, both with humans and animals, reports PCE as an across-pregnancy average, so it is not possible to make further comparisons. In fact, both Buckingham-Howes et al. (2013) and Ross et al. (2015) recommend that more work is needed to investigate the timing of prenatal exposure.

In addition to the consistency with the PCE literature, we also found that childhood maltreatment and current life events were strong predictors of adult behaviors, consistent with many previous studies (as cited in the Introduction). Our finding that adolescent mood mediated the relationship between PCE and adult inhibitory control and withdrawn behaviors is indicative of a pathway showing the continuity of adolescent and adult internalizing symptoms (Hofstra et al., 2000).

There are potential limitations of this work. One, this is a sample of women who sought prenatal care early in pregnancy at a clinic that served low-income women. Thus, the findings may not apply to samples with different health care or socioeconomic characteristics. Two, we did not have biological verification of prenatal substance use, which might lead to misclassification. However, with careful interviewer selection and training and attention to question format, our maternal self-report substance use measures identified a higher percentage of users than did hospital urine screening (Richardson et al., 1999, 2006), a finding reported by others (Ashling et al., 1994; Fendrich et al., 2004; Lester et al., 2001; Rutherford et al., 2000). We did collect biological samples from the 21-year-old offspring, and those data also support this point: 98% of offspring with positive urine screens for marijuana reported current use. However, 40% of the offspring who reported marijuana use had negative urine screens and thus would not have been detected if we had used only biological measures of marijuana use.

There are also strengths of this research. One, follow-up rates have been consistently good across phases, with 76% of the birth cohort assessed at age 21. There were no SES or prenatal drug exposure differences between those who were and were not seen at 21 years. Two, this is one of the only samples with an equal representation of African

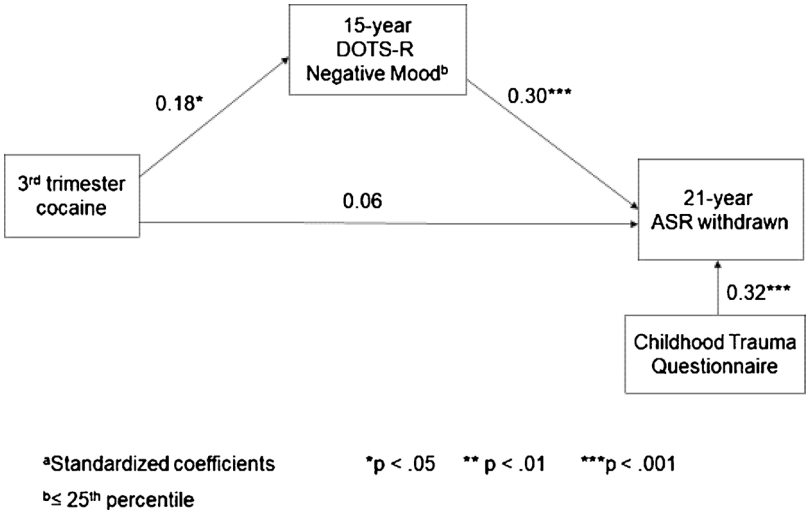

Fig. 1. Pathway from prenatal cocaine exposure to 21-year withdrawn behavior.

Table 4
Factors associated with categorical 21-year outcomes, controlling for covariates.[a].

	Coefficient	Hazard ratio (95% CI)	*p* value
Age of marijuana initiation[b]			
1st trimester cocaine[c]	0.49	1.62 (1.18-2.24)	< .005
Offspring life events	0.08	1.08 (1.03-1.14)	< .005
CTQ[d]	0.21	1.23 (1.03-1.48)	< .05
Current maternal illicit drug use[c]	0.89	2.43 (1.09-5.4)	< .05
	Coefficient	**Cumulative/Adjusted odds ratio (95% CI)**	***p* value**
Marijuana use in past year[e,f]			
Offspring life events	0.16	1.2 (1.1 - 1.3)	< .001
1st trimester cocaine	0.88	2.4 (1.4 - 4.2)	< .01
Maternal age	−0.06	0.95 (0.9 – 1.0)	< .05
Ever arrested[e]			
Offspring life events	0.16	1.2 (1.1 - 1.3)	< .001
1st trimester cocaine	1.04	2.8 (1.5 - 5.2)	< .001
Gender[g]	1.02	2.8 (1.5 – 5.2)	< .005
3rd trimester cocaine[c]	1.1	3.0 (1.2 – 7.7)	< .05
Conduct Disorder[e,h]			
CTQ	0.53	1.71 (1.13– 2.58)	< .01
1st trimester cocaine	0.87	2.39 (1.01 – 5.65)	< .05

[a] Covariates included in model: offspring race, gender, current life events; maternal age; prenatal alcohol, marijuana, tobacco; current maternal family income, alcohol, and other illicit drugs; CTQ; family history of alcohol/drug problems. Results are presented only for those outcomes where prenatal cocaine exposure was significant. Predictors are listed in order of *p* value, an indication of the magnitude of the effect. Results were run separately by trimester but are shown together for ease of presentation.
[b] Cox proportional hazards model.
[c] 0 = no use, 1 = use.
[d] Childhood Trauma Questionnaire (Bernstein and Fink, 1998).
[e] Ordinal logistic regressions.
[f] None; < 1 joint/day; ≥ 1 joint/day.
[g] 0 = Female, 1 = Male.
[h] Assessed by the Diagnostic Interview Schedule (Robins et al., 2000).

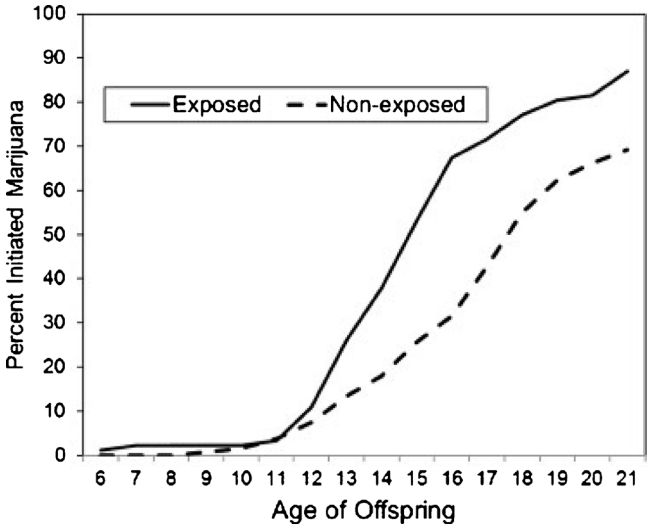

Fig. 2. Marijuana initiation as a function of prenatal cocaine exposure.

American and Caucasian women, which reflects the prenatal clinic from which they were recruited. Three, we have detailed assessments of all types of drug use both during pregnancy and in the postpartum. Four, we carefully measured the sociodemographic and environmental characteristics of both mothers and offspring, allowing control for associations with these characteristics. Five, this work with a predominantly non-college bound, diverse sample has added to our understanding of the transition into young adulthood. Six, by detecting adolescent mediators of the effects of PCE on common problems faced by young adults, we have identified crucial variables, such as early marijuana use and emotion dysregulation, to target interventions for exposed children and adolescents.

5. Conclusions

We found a consistent pattern of direct associations between PCE and young adult emotion regulation, arrest history, and Conduct Disorder. Of particular concern is the association of PCE with early initiation of marijuana use: 43.5% of the exposed and 18% of the non-exposed had initiated marijuana use prior to 15 years of age, and by 21 years, 69% of the exposed and 50% of the non-exposed had used marijuana in the past year. These rates are higher than the most recent NSDUH data, which show that ~35% of 18- to 25-year-olds reported use in the past year (SAMHSA, 2017). These associations with PCE were not explained by family history of alcohol/drug use, childhood environment, or adolescent behavior. These findings have implications for the continuity of risk among prenatally exposed individuals and for intergenerational patterns of illicit drug use. The results of this study support the need for interventions to prevent initiation of marijuana use targeted at children who have been prenatally exposed to cocaine. These findings also suggest a pathway from PCE to problems with emotion regulation, mood, and internalizing behavior problems that are apparent in adolescence and may continue unabated into young adulthood if not addressed at an earlier developmental phase. For example, both school- and parent-based programs designed to support and strengthen the development of emotional self-regulation in vulnerable youth through mentoring and skill development have been shown to be effective (Kohlhoff et al., 2016; Wyman et al., 2010) and could be used with children who have been prenatally exposed.

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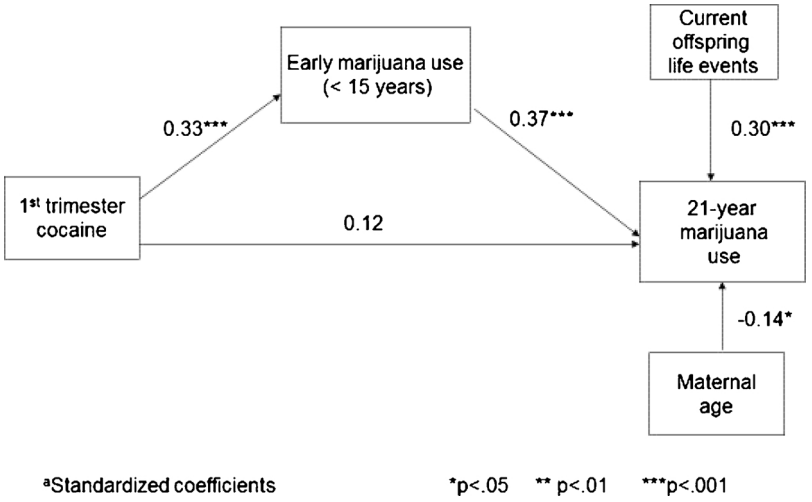

Fig. 3. Pathway from prenatal cocaine exposure to offspring marijuana use.

Principal Investigator). The study sponsor had no role in study design, collection, analysis, and interpretation of data, writing the report, or the decision to submit the report for publication. The content does not necessarily represent the official views of NIDA.

Contributors

GAR designed the study and wrote the protocol. LG conducted the statistical analysis. GAR wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors have no conflicts of interest to declare.

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