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Preschool blood lead levels, language competency, and substance use in adolescence

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ABSTRACT

Background: Elevated lead levels in children are a persistent public health problem, particularly in urban areas in the United States, yet few prospective studies have examined the association of childhood lead levels with substance use in adolescence.
Objectives: To determine the association of early lead levels with adolescent substance use and whether childhood IQ, language skills, and externalizing (aggressive and disruptive) behavior mediate the association, controlling for confounding biological and environmental factors.
Methods: The participants ($N = 265$) were a subsample of a prospective birth cohort study on the developmental effects of prenatal cocaine exposure in the Midwest United States. Blood lead levels (BLL) were assessed at age 4, IQ at age 11, language skills and externalizing behavior at age 12, and substance (alcohol, tobacco, marijuana) use and substance use-related problems at age 15. Biologic assays (hair, urine, bloodspots), along with self-report, were utilized to determine adolescent substance use. Path analyses were conducted to examine the direct and indirect associations of BLL with adolescent substance use.
Results: The children's mean BLL at 4 years of age was 7.07 (SD = 4.12) μg/dL. Approximately 31% of adolescents used tobacco or marijuana, 40% used alcohol, and 23% reported experiencing substance use-related problems at age 15.7 (SD = 0.28). Elevated BLL was related to a higher likelihood of substance use. Childhood language skills fully mediated the relationship of BLL with substance use-related problems. IQ was related to neither substance use nor substance use-related problems.
Discussion: Elevated BLL in preschool years is a risk factor for adolescent substance use and related problems. Early screening and intervention for language impairment may reduce substance use-related problems.

1. Introduction

Elevated lead levels in children are a persistent public health problem, particularly in urban, inner-city areas in the United States (US). Despite a steady decline in lead exposure over the last 40 years in the US (Egan et al., 2021), aged water pipes, dust and paint chips in old homes and buildings, and lead-tainted soil in playgrounds still remain, disproportionately threatening the development of children in industrial, urban communities (Koger et al., 2005). With no safe lead levels in children identified, the Centers for Disease Control and Prevention (CDC) currently uses a blood lead reference value of 5 μg/dL to identify children at risk for potential cognitive, behavioral, and academic problems.

Elevated childhood lead levels undermine brain growth and may trigger irreversible alterations in the structure and function of the central nervous system, particularly in the prefrontal cortex, hippocampus, basal ganglia, and cerebellum (Lidsky and Schneider, 2003). Specific effects on the disruption of glutamatergic transmission may foreshadow impairments in learning and memory. Disruption of dopaminergic neurotransmission, which modulates attention, memory, and executive

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functioning (NourEddine et al., 2005), may produce an array of behavioral problems (Lidsky and Schneider, 2003). Although the adverse relationship of early lead exposure with cognitive development and behavioral problems in children has been well-documented even with low lead levels (National Toxicology Program, 2012), few prospective studies have examined the association of childhood lead levels with later adolescent behavioral outcomes such as substance use (Desrochers-Couture et al., 2019; Dietrich et al., 2001). Substance use in adolescents is a critical public health priority (Degenhardt et al., 2016), as it may disrupt healthy transition to adulthood by increasing the risk of substance dependency (Behrendt et al., 2009; Guttmannova et al., 2012) and accompanying problems including academic failure (Yule and Prince, 2012; King et al., 2006), unemployment (Huang et al., 2011), greater mental health symptoms (Saban and Flisher, 2010), relationship difficulties (Fergusson and Boden, 2008; Brook et al., 2011), and incarceration (Slade et al., 2008; Bennett et al., 2008).

The purpose of the present study is to examine the long-term association of early blood lead level (BLL) with adolescent substance use. The impact of early BLL might manifest differently across different developmental periods. A lead-associated deficit in a developmental domain (e.g., cognition) at earlier ages might compromise another domain (e.g., behavior) over time, cascading to difficulties in subsequent areas and subjecting the exposed children to additional adverse developmental outcomes (Bellinger et al., 2016; Masten and Cicchetti, 2010). We previously reported inverse relationships between childhood BLL assessed at age 4 and cognitive functioning (Min et al., 2009) and language development (Lewis et al., 2018) across childhood in urban, primarily African American children with a history of prenatal substance exposure. Our previous studies indicated no differential association with outcomes when lead was combined with prenatal alcohol, tobacco, marijuana, or/and cocaine exposure (Min et al., 2009; Lewis et al., 2018).

Building on the previous findings, we modeled developmental processes that may lead to the emergence of substance use in adolescents with elevated BLL. We examined cognitive functioning and language skill as possible pathways mediating the relationship of BLL with adolescents' substance use and substance use-related problems, as cognitive functioning and language skill are related to educational achievement that may affect early substance use (Conti-Ramsden et al., 2009). Given the association of early BLL with childhood externalizing (aggressive and disruptive) behavior (National Toxicology Program, 2012) and the association of childhood externalizing behavior with subsequent substance use (Maughan et al., 2004; Minnes et al., 2017), we also examined childhood externalizing behavior as an additional mediator of BLL on adolescent substance use and substance use-related problems.

Elevated childhood BLL, especially in the context of an urban, inner-city environment, is often correlated with other factors that may contribute to cognitive and behavioral problems. These may include biological factors, such as prenatal substance (alcohol, tobacco, marijuana, cocaine) exposure (Bada et al., 2007; Min et al., 2021; Minnes et al., 2017), child birth weight, and head circumferences (Dietrich et al., 2001); maternal/caregiving factors, such as caregiver's verbal skills, education (Lewis et al., 2018), ongoing substance use (Min et al., 2018), psychological distress (Maughan et al., 2004), the quality of home environment (Min et al., 2014), and parental monitoring (Bohnert et al., 2012); and environmental factors, such as exposure to violence (Delaney-Black et al., 2002; Kobulsky et al., 2016) and non-kinship adoptive/foster care placement (Linares et al., 2006; Singer et al., 2008). Thus, we examined cognitive functioning, language skill, and child externalizing behavior as potential pathways mediating the relationship of BLL with adolescents' substance use and substance use-related problems, controlling for confounding factors of BLL. We hypothesized that higher BLL would be related to poorer cognitive and language development and higher externalizing behavior, which would in turn contribute to substance use and substance use-related problems.

2. Methods

2.1. Sample and procedure

The present study included 265 children (128 boys, 137 girls) for whom BLL were obtained at age 4. All children were recruited at birth (September 1994 to June 1996) from a metropolitan county hospital for a prospective study on the developmental effects of prenatal cocaine exposure (See Singer et al., 2004 for a complete description of sample recruitment). Pregnant women at high risk for drug use (self-admitted substance use, behavior suggesting intoxication, a lack of prenatal care, or a previous history with the Department of Human Services), underwent drug toxicology screenings at delivery. Women with HIV-positive status, chronic medical illness, a psychiatric history, or a diagnosis of intellectual disability, were excluded, as were infants with Down syndrome, fetal alcohol syndrome, or medical illness. A total of 647 women were screened; of them 54 were excluded, 155 refused to participate, and 21 didn't come to the enrollment visit. Thus, 415 infants and their mothers enrolled at birth in the parent study.

At 4 years, 376 children were assessed, and venous blood samples were obtained from 278 children. Ninety-eight children did not contribute blood samples due to parental refusal, child distress and sickness, or logistic difficulties. More African American and married mothers and fewer foster parents consented for blood collection. The present study utilizes data from 265 children with the 4-year lead data available and who completed cognitive assessment at 11 years (n = 265), language (n = 264), or behavioral assessments (n = 254) at 12 years, and substance use assessment (n = 265) at 15 years, representing a 95% retention rate for children with BLL at 4 years. Children and their caregivers were seen at the university-based developmental research laboratory by separate examiners blinded to both the mother and child's substance exposure status and BLL. Parental written informed consent and child assent (beginning at age 9) were obtained prior to data collection. The Institutional Review Board of the participating hospital approved the study. A Certificate of Confidentiality (DA-98-91) was obtained from the Department of Health and Human Services to protect against release of confidential health information from women participating in the study. All participants were compensated with a monetary stipend, lunch, and/or transportation costs for their time.

2.2. Measures

Blood lead level. Venous blood samples (~5 ml) were obtained at age 4 by trained pediatric phlebotomists from the affiliate University Hospital Laboratory Services accredited by the College of American Pathologists and in compliance with Clinical Laboratory Improvement Amendments regulations. BLL was determined by atomic absorption spectrophotometry using a graphite furnace and matrix modification to eliminate chemical interferences. BLL is reported in micrograms per deciliter (μg/dL). Details on the method of blood collection and analyses were described previously (Min et al., 2009; Nelson et al., 2004).

Substance use and substance use-related problems at age 15. Adolescent substance use was assessed at age 15 using biologic assays for drug metabolites (alcohol, tobacco, and marijuana) and self-report via The Youth Risk Behavior Surveillance System (Centers for Disease Control and Prevention, 2009). Samples of participants' hair, urine, and/or bloodspots were collected by research nurses from the university's NIH-funded Clinical Research Unit and sent to the United States Drug Testing Laboratory for analysis (See Minnes et al., 2014 for a complete description of adolescent drug use assessment). Respondents' positive result on either biologic assays or self-report for a particular drug were coded 1 (*yes*) for that drug. Substance use was specified as a latent variable (α = 0.72) with three indicators (alcohol, tobacco, and marijuana) for path analyses. Substance use-related legal and social problems (e.g., drunk driving, feelings of addiction, missed school) were assessed with the 17-item Substance Use and Abuse Scale from the Problem

Oriented Screening Instrument for Teenagers (Rahdert, 1991). Respondents endorsing any problem were coded 1 (*yes*) due to skewed distribution.

Mediators. Children's intelligence was assessed using the Wechsler Intelligence Scales for Children-Fourth Edition (Wechsler, 2003) Full Scale IQ scores at age 11. Children's receptive and expressive language skills were assessed via the Test of Language Development-Intermediate, 3rd edition (Hamill and Newcomer, 1997) Total Standard scores at age 12. Children's aggressive and disruptive behaviors were assessed with caregiver-rated externalizing behavior *T* score on the Child Behavior Checklist (CBCL) at age 12 (Achenbach, 1991).

Potential confounders. Child birth and medical characteristics (race/ethnicity, sex, gestational age, birth weight, length, head circumference, APGAR scores) and maternal characteristics (age, marital status, years of education) were extracted from hospital birth records. Prenatal cocaine exposure was coded as a dichotomous indicator (yes/no) based on infant meconium or urine, maternal urine or self-report. It was also quantified based on maternal report of the number of crack cocaine "rocks" consumed and amount money spent per day, which was converted to a standard "unit" of cocaine, referring to \$20 worth of cocaine. For tobacco, marijuana, and alcohol exposure, the average number of cigarettes per day, marijuana joints smoked per week, the number of drinks of beer, wine, or had liquor consumed per week, with each drink equivalent to 0.5 oz. of absolute alcohol, during the pregnancy were computed (Singer et al., 2004). Socioeconomic status (SES) was assessed via the Hollingshead 2-Factor Index (Hollingshead, 1971). Maternal receptive vocabulary was assessed using the Peabody Picture Vocabulary Test-Revised (PPVT-R; Dunn and Dunn, 1981) and updated using its third edition (PPVT-III; Dunn and Dunn, 1997) at later assessments. Maternal psychological distress was assessed using the Global Severity Index ($\alpha = 0.95$), a summary scale of the Brief Symptom Inventory (Derogatis, 1992), at all visits. At each visit, the child's placement (with either biological mother/relative or adoptive/foster caregiver) and changes (defined by a change in both primary caregiver and physical setting lasting longer than one month) were noted; data on the current caregiver were updated to provide concurrent assessment of caregiver vocabulary, psychological distress, and drug use. The quality of the caregiving environment was assessed via interview with caregivers using the Home Observation of the Environment-Early Adolescent (HOME; $\alpha = 0.83$; Caldwell and Bradley, 2003) at age 12. Parental monitoring ($\alpha = 0.74$) and lifetime frequency of exposure to violence, either as a direct victim or witness ($\alpha = 0.75$), were assessed at age 12 using The Assessment of Liability and Exposure to Substance Use and Antisocial Behavior, an illustration-based, audio, computer-assisted self-report for children ages 9–12 (Ridenour et al., 2009).

2.3. Statistical analyses

Structural equation model-based path analyses were conducted using Mplus 7.11 to evaluate the direct and indirect association of BLL with adolescent substance use. Since some of the endogenous variables (adolescent alcohol, tobacco, and marijuana use and substance use-related problems) were binary, the weighted least squares estimator with mean and variance adjustments (WLSMV) was used. Model fit was evaluated with the robust WLSMV chi-square, comparative fit index (CFI), Tucker-Lewis Index (TLI), root mean square error of approximation (RMSEA), and the weighted root mean square residual (WRMR). Values ≥ 0.95 for CFI and TLI, ≤ 0.06 for RMSEA (Hu and Bentler, 1999), and ≤ 0.90 for WRMR (Yu and Muthén, 2002) indicate a good model fit. Missing data on endogenous variables were estimated as a function of the observed exogenous variables. Variables correlated ($p <$ .10) with any of the seven endogenous variables were included as covariates (sex, race/ethnicity, prenatal cocaine, tobacco, marijuana exposure, head circumference at birth, maternal psychological distress, PPVT scores, and marital status, exposure to violence, HOME scores, non-kinship foster/adoptive care). Since the three mediators were assessed at the similar ages, correlations among them were specified. Similarly, as both substance use and substance use-related problems were assessed simultaneously, a correlation between these two outcome variables was included in the model. Direct paths from BLL to substance use and substance use-related problems were specified to indicate other unmeasured mediators of BLL. The derivatives difference test was used to compare competing nested models (Muthén and Muthén, 2012). The significance of indirect association were tested using a bootstrap approach (Preacher and Hayes, 2008). Two-sided $p < .05$ indicated statistical significance.

3. Results

3.1. Sample characteristics

The 265 adolescents and their mothers were predominantly African American and of low SES (Table 1). The mean (SD) number of maternal education years was 11.8 (1.55), with 39% without a high school diploma. Only 14% of the mothers were married at the child's birth. A majority of adolescents ($n = 227$, 86%) were prenatally exposed to at least one substance and two-thirds ($n = 176$) to ≥ 2 substances: 51% of their mothers ($n = 136$) used crack cocaine, 61% ($n = 157$) smoked tobacco, 76% ($n = 197$) drank alcohol, and 31% ($n = 79$) used marijuana during pregnancy.

The adolescents' mean (SD) BLL at 4 years of age was 7.1 (4.1) μg/dL (range 1.3–23.8), with 36% ($n = 95$) having BLL <5 μg/dL and 19% ($n = 51$) having ≥10 μg/dL (Table 2). The mean (SD) Full Scale IQ was almost 1 SD below the normative mean, with 86 (12.9) at age 11; the mean (SD) language score was more than 1 SD below the normative mean, with 76 (13.6) at age 12. The mean (SD) *T*-score of caregiver-rated externalizing behavior was 50 (12), with approximately 25% in the borderline/clinical range (>60). About 19% of the adolescents experienced non-kinship foster or adoptive care by age 12. At age 15, the majority reported being recipients of free lunch ($n = 221$, 88%). More than half of the adolescents ($n = 150$, 57%) used one of the target substances, with 23% reporting substance use related problems. Table 3 summarizes bivariate correlations among key observed variables included in the path model.

Table 1
Maternal and caregiver characteristics ($N = 265$).

	n (%) or Mean ± SD	Median (10%–90%)
Biological mother		
African American	229 (86.4)	
Low socioeconomic status	258 (97.7)	
Age at delivery	27.6 ± 5.23	27 (21–35)
Years of education	11.79 ± 1.55	12 (10–14)
Not completed high school	104 (39.3)	
Married	36 (13.6)	
Global Severity Index	0.62 ± 0.64	0.40 (0.08–1.47)
PPVT Standard Score	75.9 ± 14.4	74 (59–93)
Substance use during pregnancy[a]		
Alcohol drinks per week	197 (76.1)	2.95 (0.19–23.1)
Cigarettes per day	157 (60.6)	10 (2–20)
Marijuana joints per week	79 (30.5)	1.5 (0.12–7.0)
Cocaine units per week	136 (51.3)	7.87 (0.76–52.5)
Caregiver at child age 12		
HOME	48.4 ± 6.40	50 (39–56)
Global Severity Index	0.36 ± 0.41	0.23 (0.02–0.91)
PPVT Standard Score	77.6 ± 15.1	78 (61–97)
Substance use past 30 days[a b]		
Alcohol drinks per week	100 (37.7)	3.0 (0.75–14.0)
Cigarettes per day	122 (46.0)	10 (3–20)
Marijuana joints per week	11 (0.42)	2.25 (0.25–35)

PPVT, Peabody Picture Vocabulary Test; *HOME*, Home Observation for Measurement of the Environment.

[a] Median (10%–90%) are based on users (*n*) only. For example, 197 (76%) mothers used alcohol during pregnancy, with median of 2.95 drinks per week.

[b] No caregiver reported cocaine use in the past 30 days.

Table 2
Adolescent characteristics ($N = 265$).

	n (%) or Mean ± SD	Median (10%–90%)
Male	128 (48.3)	
African-American[a]	227 (85.7)	
Gestational age, weeks	38.1 ± 2.67	39 (35–41)
Prematurity (<37 weeks gestational age)	51 (19.25)	
Birth weight, g	2903 ± 677	3010 (2030–3730)
Birth length, cm	48.22 ± 3.77	48.5 (43.5–52.0)
Head circumference, cm	32.9 ± 2.25	33.0 (30.5–35.5)
APGAR score- 1 min <7	28 (10.7)	
APGAR score- 5 min <7	5 (1.9)	
Blood lead level at 4 years (μg/dL)	7.07 ± 4.12	6.1 (2.7–12.5)
< 5 μg/dL	95 (35.9)	
5 μg/dL - < 10 μg/dL	119 (44.9)	
≥ 10 μg/dL	51 (19.2)	
Iron deficiency anemia at 4 years	9 (3.4)	
Parental monitoring[b]	2.45 ± 0.62	2.60 (1.5–3.0)
Violence exposure[c]	0.58 ± 0.72	0.25 (0–1.75)
Full Scale IQ at age 11	85.84 ± 12.94	86 (70–104)
Language score at age 12	76.48 ± 13.57	75 (61–95)
CBCL Externalizing behavior at age 12	49.91 ± 11.96	50 (34–66)
Ever in non-kinship foster/adoptive care by age 12	51 (19.25)	
Receiving free lunch at school at age 15	221 (87.7)	
Substance use at age 15[d]		
Tobacco	81 (31.4)	
Alcohol	104 (40.0)	
Marijuana	82 (31.5)	
Substance related problem	59 (23.1)	

[a] The 38 adolescents who did not identify as African American are 25 Whites, 3 Hispanic/Latinx, 1 Asian, and 9 biracial.
[b] Youth-perceived parents' awareness of the youth's activities and whereabouts, 0 = *none of the time* to 3 = *all of the times*.
[c] Lifetime frequency, either as a direct victim or witness, 1 = *none* to 5 = *5 times or more*.
[d] Assessment age $M = 15.67$ ($SD = 0.28$).

3.2. Model estimation

Fig. 1 represents the final structural equation model-based path model generated from iterative model-fitting procedures. Our initial model included: 1) paths from BLL to all five endogenous variables (IQ, language, externalizing behavior, substance use latent variable, and substance use problems); 2) paths from all three mediators (IQ, language, externalizing behavior) to the two outcomes (substance use latent variable and substance use problems); 3) correlations among the three mediators and a correlation between the two outcomes; 4) paths from each exogenous confounding variable (sex, race/ethnicity, prenatal cocaine tobacco, marijuana exposure, head circumference at birth, maternal psychological distress, PPVT scores, and marital status, exposure to violence, HOME scores, non-kinship foster/adoptive care) to each of the five endogenous variables, creating a saturated model. Correlations were assumed for all exogenous variables in the model. This initial model (Model 1) indicated that the Full Scale IQ at 11 years was not related to either substance use latent variable or substance use problems ($p > .50$), suggesting no mediated relationship of BLL with the substance use outcomes via IQ, and the initial model (Model 1) was respecified without IQ. This respecified model (Model 2) produced a reasonable fit, χ^2 (32) = 58.84, $p = .003$, CFI = 0.925, TLI = 0.782, RMSEA = 0.053 (90% CI = 0.034 - 0.083), WRMR = 0.074. To achieve a more parsimonious model and to minimize the number of parameters to be estimated, paths coefficients of covariates with significance level of $p \geq .15$ were set to 0 (Model 3) (Hosmer and Lemeshow, 2000), χ^2 (64) = 73.46, $p = .20$, CFI = 0.974, TLI = 0.961, RMSEA = 0.025 (90% CI = 0.000 - 0.048), WRMR = 0.139, yielding insignificant differences from Model 2, $\Delta\chi^2$ (32) = 26.694, $p = .73$. Thus, Model 3 was selected as the

Table 3
Correlations (r) among key observed variables in the path model ($N = 265$).

	Covariates												Mediators			Substance use			
	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1. BLL	-.05	.21***	-.09	.04	-.05	-.14*	-.07	-.01	-.01	-.17**	.16**	-.09	-.21***	-.28***	.09	.06	.02	.10	.06
2. Male	–	-.08	-.07	-.05	-.01	.10	.15*	-.07	-.01	-.12	.11	.01	-.07	-.03	.07	-.03	.01	.03	.15*
3. African American		–	-.03	-.21***	-.13*	-.17**	-.12	-.21***	-.03	.10	.16**	-.05	-.21***	-.31***	-.04	-.24***	-.14*	-.04	-.07
4. Pre. Coc. exp.[a]			–	.52***	.27***	-.25***	-.12*	.24***	-.12*	-.09	.03	.36***	-.02	<.01	.08	.07	.10	.10	.12*
5. Pre. Cig. exp.[b]				–	.20***	-.23***	-.01	.25***	-.12	-.19**	.05	.16**	-.03	-.02	.10	.03	.12	.06	.03
6. Pre. Mar. exp.[b]					–	-.01	.05	.11	-.10	-.10	-.08	-.03	.11	.11	-.04	-.08	-.01	-.04	-.10
7. Head circumference						–	.05	-.10	.08	.02	.04	-.10	.19**	.11	.15*	-.02	<.01	.11	-.02
8. Maternal PPVT							–	-.06	-.01	.07	-.08	-.10	.28***	.29***	.02	.08	.08	.02	-.07
9. Maternal GSI								–	-.10	-.09	-.08	.20**	-.03	-.01	.13	.18**	.12	.09	.09
10. Maternal married									–	.04	.01	-.03	.06	.01	.03	.09	.16*	.19**	.06
11. HOME score										–	-.08	.02	.08	.15*	-.12	-.05	-.06	-.12	-.13*
12. Violence exp.											–	.02	-.14*	-.26***	.21**	-.02	.08	.17**	.10
13. Ever in non-kinship care												–	-.15*	-.06	.11	.15*	.14*	.14*	.19**
Mediators																			
14. Full Scale IQ													–	.73***	-.16*	.17**	-.01	-.06	-.19**
15. Language														–	-.12	.17**	-.03	-.08	-.23***
16. Externalizing behavior															–	.10	.21**	.22***	.19**
Substance use at age 15																			
17. Alcohol																–	.43***	.43***	.16*
18. Tobacco																	–	.54***	.35***
19. Marijuana																		–	.39***
20. Substance use problem																			–

$^*p < .05$, $^{**}p < .01$, $^{***}p < .001$.
[a] Dichotomous.
[b] Log-transformed.

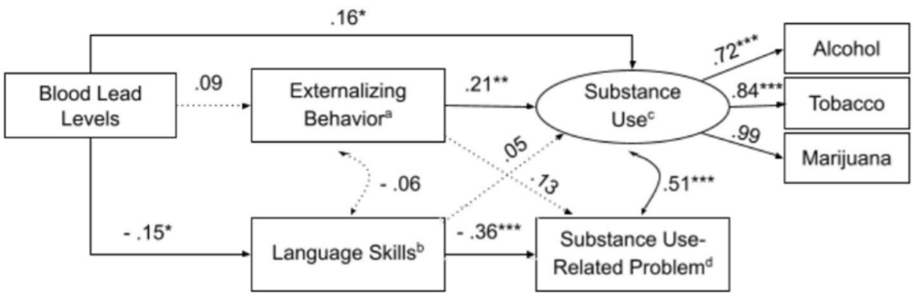

Fig. 1. The impact of preschool blood lead levels on adolescent substance use and substance use-related problems (N = 265). χ^2 (64) = 73.46, p = .20, CFI = 0.974, TLI = 0.961, RMSEA = 0.025 (90% CI = 0.000 - 0.048), WRMR = 0.139. Rectangles indicate observed variables, and ovals represent latent constructs. All path coefficients are standardized. Single-arrowed lines represent standardized path coefficients, whereas double-arrowed lines represent correlations. Solid lines indicate statistically significant coefficients (p < .05), whereas dotted lines indicate non-significant coefficients (p > .05). *p < .05, **p < .01, ***p < .001. Significant (p < .05) covariates for each endogenous variables are listed in *italics.* [a] Adjusted for *head circumference at birth,* prenatal cocaine exposure*, violence exposure,* and *biological maternal psychological distress*. [b] Adjusted for *child race/ethnicity, violence exposure,* HOME score, and *biological maternal PPVT standard score.* [c] Adjusted for child race/ethnicity, *prenatal cocaine exposure, biological maternal marital status,* and *ever in non-kinship foster/adoptive care by age 12.* [d] Adjusted for *child sex, child race/ethnicity, prenatal cocaine exposure*, prenatal cigarette exposure, and *ever in non-kinship foster/adoptive care by age 12.*

final path model (Fig. 1).

Fig. 1 indicates that, adjusting for relevant covariates, preschool BLL was directly related to substance use (β = 0.16; 95% CI, 0.004–0.327, p = .044) and indirectly to substance use-related problems via language skills (β = 0.054, 95% CI, 0.003–0.097, p = .036). Higher BLL at 4 years was related to lower language skills at age 12 (β = −0.149, 95% CI, −0.269 to −0.029, p = .015) and, in turn, to substance use-related problems at age 15 (β = −0.364; 95% CI, −0.522 to −0.205, p < .001). Substance use and substance use-related problems were correlated (r = 0.51; 95% CI, 0.316–0.707, p < .001) as expected, whereas no correlation was observed between externalizing behavior and language skill. Although no significant association was found between BLL and caregiver-rated externalizing behavior, greater externalizing behavior was related to subsequent substance use. In terms of covariates, greater head circumference at birth (β = 0.20; 95% CI, 0.062–0.341, p = .005) and higher maternal psychological distress (β = 0.20, 95% CI, 0.043–0.360, p = .013) were related to greater externalizing behavior; more frequent exposure to violence was related to both greater externalizing behavior (β = 0.22, 95% CI, 0.083–0.355, p = .002) and lower language skills (β = - 0.13, 95% CI, −0.254 to −0.001, p = .048); lower maternal PPVT scores (β = 0.27, 95% CI, 0.158–0.383, p < .001) and being African American (β = - 0.27, 95% CI, −0.410 to −0.129, p < .001) were related to lower language skills; being African American was also related to fewer substance use problems (β = - 0.22, 95% CI, −0.408 to −0.028, p = .024); a history of non-kinship care by age 12 was related to both substance use (β = 0.18, 95% CI, 0.019–0.333, p = .028) and substance use problems (β = 0.19, 95% CI, 0.025–0.358. p = .024); boys were more likely to experience substance use problems than girls (β = 0.27, 95% CI, 0.088–0.454, p = .004); and prenatal cocaine exposure was related to both substance use (β = 0.21, 95% CI, 0.006–0.404, p = .044) and substance use problems (β = 0.25, 95% CI, 0.026–0.474. p = .029). Approximately 25% and 34% of the variation in substance use and substance use-related problems were accounted for respectively in the final model.

4. Discussion

Higher BLL during preschool age was related to a greater likelihood of substance use at age 15 in a sample of low SES, urban, primarily African American adolescents. In addition, a significant indirect association of BLL, via childhood language skills, with substance use-related problems was found, identifying a risk process leading to adolescent substance use-related problems. Childhood IQ was not related to either substance use or substance use-related problems, despite a substantial correlation between childhood IQ and language skills. The present study is one of few prospective studies that documented the association of BLL with adolescent substance use and, to our knowledge, the first to examine multiple functional domains across developmental periods, illustrating that compromised function in one domain may cascade to difficulties in another.

Our findings are partially in line with previous studies. In a birth cohort study of 212 Inuit children, the relationship of BLL during childhood (median age of 11 years) with binge drinking and cannabis use in late adolescence (median age of 18 years) was fully mediated by concurrently assessed teacher-rated externalizing behavior (Desrochers-Couture et al., 2019). Another prospective birth cohort study of 195 urban, inner-city children found that prenatal and postnatal BLLs were associated with increased frequency of self-reported delinquent behaviors, including marijuana use, in adolescents aged 15–17 (Dietrich et al., 2001). However, this latter study did not examine marijuana use separately from other types of delinquent behaviors, preventing a direct comparison with the present study. We did not observe a significant relationship between BLL and caregiver-reported externalizing behavior at age 12. Given that about 25% of the study sample were in the borderline/clinical range of externalizing behavior, our sample may represent a clustering of overall high levels of externalizing behavior and may not have sufficient variability for identifying relationships with other measures. Alternatively, methodological differences in assessing externalizing behavior in terms of informants (teacher vs. caregiver), assessment age, operationalization of externalizing/delinquent behavior, and/or covariates, including prenatal drug exposure, adjusted with different operationalization, may explain the seemingly inconsistent findings.

Our study indicated that childhood language skill fully mediated the association of BLL with substance use-related problems, yet no such relationship was found for substance use. Poor language skills are associated with poor literacy skills, which affect academic achievement, and with more psychosocial problems (Kamhi and Catts, 2012). Early language impairment has been related to problems in social competence, adaptive functioning, emotional and self-regulation during the preschool years (Conti-Ramsden et al., 2013; St Clair et al., 2019), attentional difficulties during the school years (Snowling et al., 2006), anxiety disorders at young adulthood (Beitchman et al., 2001; Lewis et al., 2016), and to an increased risk of substance and alcohol abuse in late adolescence (Beitchman et al., 2001) and young adulthood (Armstrong et al., 2017). These findings collectively suggest interrelationships between elevated BLL, poor language competency in childhood, and problem behaviors including substance use problems in adolescence. Replication studies examining language competency in the context of BLL will further enhance our understanding of the role of language competency in a developmental sequence of risk processes that may lead to substance use-related problems.

It is noteworthy that greater violence exposure was related to lower language skills as well as to externalizing behavior. Adverse life experience may alter neuroendocrinological mechanisms, such as the hypothalamic-pituitary-adrenal axis, involved in regulating the stress response, affecting a child's ability to focus (Nemeroff, 2004) and interfering child language acquisition (Delaney-Black et al., 2002).

This study has limitations. First, we used a single BLL measured at age 4, which might compromise reliability and validity. While multiple BLL assessed across the developmental continuum may represent a more complete impact of lead exposure, BLL at 4 years reflects exposure during important developmental years and has been a sensitive/reliable measure in prior research (Lanphear, 2000). Second, although we utilized biologic assays to determine adolescent substance use, our measure of substance use-related problems relied solely on self-report, subject to social desirability bias and recall error, which might underestimate the influence of BLL. Third, given that BLL tends to confound with low SES, relative homogeneity of our study sample in terms of SES might not fully disaggregate the influences of lead from those of SES. However, our analytical model included HOME scores, maternal vocabulary scores, and non-kinship care, all of which are specific components of SES relevant to child development, allowing a more detailed and nuanced examination of the interrelationship between BLL and substance use in adolescents with low SES. Fourth, our observational design may not rule out the possibility of unmeasured genetic and/or other environmental confounders of BLL, especially given the nature of prenatal substance exposure. However, our study provides a unique opportunity to examine the influence of BLL within a natural context of prenatal substance exposure, which tends to co-occur in urban communities. Lastly, generalizability of the findings may be limited to a population of low SES, urban, predominantly African American children with a history of prenatal substance exposure, where prematurity and intrauterine growth retardation are likely to be prevalent.

The notable strength of the current study includes a prospective design from birth to 15 years of age, with a remarkable retention rate, allowing the longitudinal investigation of progression of BLL-related risks across developmental periods. An additional strength also includes simultaneous evaluation of multiple mediators and their interrelationships and a large number of covariates, enhancing the validity of the findings. In conclusion, elevated BLL in preschool years is a risk factor for adolescent substance use and related problems. Given the vulnerability of the developing adolescent brain to the effects of substance use (Jordan and Andersen, 2017), our findings raise added attention to the detrimental influence of lead on health. The mediating role of language skills observed in the present study reinforces current pediatric recommendations of early screening for language impairment as well as intervention for children at risk for elevated BLL to prevent further escalating the likelihood of lifelong psychological, social and health problems.

Credit author statement

Dr. Meeyoung O. Min conceptualized the paper, performed the statistical analyses, and wrote the initial and final draft. Dr. Barbara A. Lewis participated in the interpretation of data and reviewed the manuscript. Dr. Sonia Minnes designed the study, interpreted the data and reviewed the manuscript. Ms. Kwynn M., Gonzalez-Pons conducted literature review and summarized the findings. Dr. June-Yung Kim assisted the literature review and reviewed the manuscript. Dr. Lynn T. Singer participated in the study's conception and design, interpretation of data, and reviewed the manuscript. All authors read and approved the final manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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