Systematic Review of Prenatal Cocaine Exposure and Adolescent Development

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KEY WORDS

prenatal cocaine exposure, adolescent development

ABBREVIATIONS

HPA—hypothalamic pituitary adrenal

IEP—Individualized Education Plan

NCE—non-cocaine exposure

ODD—oppositional defiant disorder

PCE—prenatal cocaine exposure

WNL—within normal limits

Dr Buckingham-Howes was responsible for idea formation and conception, literature searches, reading articles, abstracting information from articles, drawing parallels and finding differences between conclusions in studies, and the majority of manuscript writing; Dr Berger was responsible for idea formation and conception, literature searches, reading articles, abstracting information from articles, and some manuscript writing; Ms Scaletti was responsible for reading articles, abstracting information from articles, reconciling disagreements, data analysis, some manuscript writing, and providing valuable feedback during the manuscript writing process; and Dr Black was responsible for obtaining funding, idea formation and conception, some manuscript writing, and providing valuable guidance and feedback during the manuscript writing process.

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abstract

BACKGROUND AND OBJECTIVE: Previous research found that prenatal cocaine exposure (PCE) may increase children's vulnerability to behavior and cognition problems. Maturational changes in brain and social development make adolescence an ideal time to reexamine associations. The objective was to conduct a systematic review of published studies examining associations between PCE and adolescent development (behavior, cognition/school outcomes, physiologic responses, and brain morphology/functioning).

METHODS: Articles were obtained from PubMed, PsycInfo, Web of Science, and CINAHL databases through July 2012 with search terms: prenatal drug, substance, or cocaine exposure; adolescence/adolescent; and in utero substance/drug exposure. Criteria for inclusion were nonexposed comparison group, human adolescents aged 11 to 19, peer-reviewed, English-language, and adolescent outcomes.

RESULTS: Twenty-seven studies representing 9 cohorts met the criteria. Four outcome categories were identified: behavior, cognition/school performance, brain structure/function, and physiologic responses. Eleven examined behavior; 7 found small but significant differences favoring nonexposed adolescents, with small effect sizes. Eight examined cognition/school performance; 6 reported significantly lower scores on language and memory tasks among adolescents with PCE, with varying effect sizes varied. Eight examined brain structure/function and reported morphologic differences with few functional differences. Three examined physiologic responses with discordant findings. Most studies controlled for other prenatal exposures, caregiving environment, and violence exposure; few examined mechanisms.

CONCLUSIONS: Consistent with findings among younger children, PCE increases the risk for small but significantly less favorable adolescent functioning. Although the clinical importance of differences is often unknown, the caregiving environment and violence exposure pose additional threats. Future research should investigate mechanisms linking PCE with adolescent functioning. *Pediatrics* 2013;131:e1917–e1936

Prenatal drug exposure is a public health concern, with estimates of 4.4% of pregnant women aged 15 to 44 using illicit substances during pregnancy.¹ Prenatal cocaine exposure (PCE) has received national attention since the presumed “crack baby epidemic” of the 1980s. PCE may act through both biological and environmental mechanisms. Not only does it cross the blood-brain barrier to the fetus and act as a stimulant by blocking the reuptake of dopamine, serotonin (5-HT), and norepinephrine,² but the drug-using environment, often characterized by poverty, violence, a lifestyle of acquiring and using drugs, can undermine child development.^{3–5}

Several reviews and meta-analyses have examined PCE through early childhood. Prenatal growth is often restricted in utero, resulting in shortened average gestation and lower birth weight.^{6,7} Compared with nonexposed children, children with PCE may demonstrate less optimal motor performance, reflexes, and orientation through 3 to 4 weeks postpartum⁸ and lower scores on measures of neurobehavioral functioning,⁹ attention and emotional expressivity,¹⁰ and speech and language development through ages 4 to 6 years.¹¹ Effect sizes are often small, particularly after covariates, including prenatal alcohol/tobacco exposure and family/community factors, are introduced.^{11,12}

A review on school-age children with PCE found negative associations with sustained attention and behavioral self-regulation but few associations with cognition, language, or growth.¹³ Another review through age 13 years found associations with behavior problems, attention, language, and cognition.¹⁴ Little is known about PCE and adolescent functioning.¹⁴ Adolescence is a transitional period characterized by increased social and cognitive demands, together with increasingly complex executive functioning abilities (eg, abstract

reasoning).¹⁵ It is plausible that the small effects found in attention and emotion regulation among children with PCE early in life may increase during adolescence.⁹ Although many adolescents are capable of complex reasoning, their decisions are often influenced by psychosocial factors (eg, impulsivity), putting them at risk for adverse developmental outcomes.¹⁶ Adolescence is also a time of neural rewiring and potential recovery from earlier neural assaults (ie, PCE).¹⁷ This review was designed to examine how PCE relates to adolescent behavior, cognition/school performance, physiologic responses (cardiovascular or hypothalamic-pituitary-adrenal [HPA] axis), and brain morphology and function using neuroimaging.

METHODS

Selection Criteria

Criteria used to select articles included (1) PCE as the primary independent variable; (2) nonexposed comparison group; (3) peer-reviewed, English-language; (4) adolescent (ages 11–19) outcomes; and (5) published in print by July 2012. Eight studies included both prenatal cocaine and opiate exposure,^{18–25} recognizing their frequent co-occurrence.^{26,27}

Data Sources

Articles were obtained from PubMed, PsycInfo, Web of Science, and CINAHL databases with the following search terms: prenatal drug, substance, or cocaine exposure, adolescence/adolescent, and in utero substance, drug, or cocaine exposure. No additional articles were identified after searching references of selected articles.

Procedures

Each article was reviewed independently by 2 authors who documented (1) sample composition, (2) drug exposure

(eg, definition, frequency), (3) design, (4) independent and outcome variables, (5) covariates, (6) results, and (7) adolescent outcome (eg, behavioral, cognitive/school, physiologic responses, and brain morphology and function using neuroimaging). A third author compiled the independent reviews and investigated discrepancies. Discrepancies were discussed among authors until agreement was reached.

Effect Sizes and Clinical Importance

Effect sizes were used to compare significant associations across studies. If effect sizes were not reported, we contacted the authors either to confirm our calculations based on existing data or to request data to calculate effect sizes. Because the analyses yielded multiple types of effect sizes (eg, η^2 , f^2 , d , etc.), we reported numeric and categorical effect sizes (eg, small [0.20–0.30], medium [0.50], large [0.80]) based on standard criteria (Tables 1, 2, 3, and 4).^{28–31}

To examine the clinical importance of the findings for behavior and cognition/school performance, we compared the scores with standardized scores, when available. Scores within 0.5 SD of the standardized mean were within normal limits (WNL), scores 0.5 to 1.0 SD above the mean were high-WNL, scores 0.5 to 1.0 SD below the standardized mean were low-WNL, and lower scores were deficient. Data were extracted only for outcomes of interest and discussed only if scores were high-WNL, low-WNL or deficient.

RESULTS

Study Characteristics

We identified 27 articles that met selection criteria representing 9 unique cohorts (Tables 1, 2, 3, and 4). Covariates ranged from none to >20 and were organized into 7 categories:

TABLE 1 Description of Studies by Outcome: Behavioral Problems

Author ^a	Sample composition			PCE Determination Methods	PCE Level of Exposure	Additional Predictors/ Covariates ^b	Outcome Variable(s)	Main Finding	Effect Size ^{c,d}
	N	Age (y)	Ethnicity (%)	Gender (%)					
Bada et al, 2011 ²²	962 ^e	11, 13	79.9% AA ^e	51% male ^e	Self-report, meconium, 12% exposed to opiates	High: ≥ 3 times/wk in first trimester. Some: less exposure Any vs none	SF, CC, CE, YC, VE Behavior problems: • Teacher Report Form (TR) • CBCL (CR)	PCE > NCE externalizing score "trends."	$r^2 = 0.00001 - 0.597$ (small to large)
Buckingham-Howes et al, 2012 ²³	114; PCE: 76; NCE: 38	14	PCE: 99% AA; NCE: 100% AA	PCE: 49% male; NCE: 47% male	Self-report, medical records, UT; 13% exposed to heroin, 54% exposed to both heroin and cocaine	Any vs none	YC, VE, CC, CE Peer victimization: • Strengths and Difficulties Questionnaire (OR and YR); Emotion dysregulation: • CBCL (CR)	PCE > NCE in peer victimization (adolescence). Anxiety/depression, not aggression (middle childhood) mediated PCE and peer victimization association.	OR = 2.01 (small/medium)
Delaney-Black et al, 2011 ¹⁸	316 ^e	14	100% AA	49.5% male ^e	UT, meconium, self-report, medical records, retrospective report; some exposed to opiates ^e	For analyses: none/any variable.	CC, CE, YB, YC, VE Age 14 cocaine use: • hair, sweat, urine samples	PCE > NCE cocaine use. No gender differences.	$d = 0.25$ (small)
Frank et al, 2011 ¹²	149; PCE: 80; NCE: 69	14, 16	PCE: 86% AA; NCE: 93% AA	PCE: 49% male; NCE: 54% male	Self-report, UT, meconium	Heavy: ≥ 61 d of use throughout pregnancy, top quartile of metabolites in meconium. Light: less exposure.	CE, CC Licit/illicit substance use initiation (YR-ACASI): • Hooked on Nicotine Checklist, CDC's 2005 YRBSS; • Wisconsin YRBS Middle School Questionnaire; • State and Local YRBS; • Wisconsin YRBS High School Questionnaire	Heavy and light PCE > NCE adolescent substance use initiation.	HR = 2.1, 2.07, and 2.1 (small/medium)
Gerteis et al, 2011 ¹⁸	93; PCE: 47; NCE: 46	11, 12.5, 14.5	88% AA ^e	PCE: 60% male; NCE: 59% male	Self-report, UT, meconium	Heavy: ≥ 61 d of use throughout pregnancy, top quartile of metabolites in meconium. Light: less exposure.	YC, CC, CE Delinquent behaviors (YR-ACASI): • National Longitudinal Study of Adolescent Health	PCE = NE in delinquent behaviors.	n/a
Greenwald et al, 2010 ²¹	416; PCE: 86; NCE: 330	14	100% AA	50% male ^e	Self-report, UT, meconium, medical records, retrospective report; some exposed to opiates ^e	Heavy: For analyses: heavy/persistent and some/none.	CC, CE, VE, YB, YC Behavioral sensitivity to social provocation: • Point Subtraction Aggression Paradigm	PCE > NCE respond to social provocation with escape (negative reinforcement).	$d = 0.33$ (small)

TABLE 1 Continued

Author ^a	Sample composition			PCE Determination Methods	PCE Level of Exposure	Additional Predictors/Covariates ^b	Outcome Variable(s)	Main Finding	Effect Size ^{c,d}
	N	Age (y)	Ethnicity (%)						
LaGasse et al. ¹⁹ 2006 ¹⁹	517 (PCE = 44%) ^e	11	83% AA ^e	Self-report; meconium; 8% exposed to opiates	High: ≥ 3 times per week in first trimester. Some: any other level of exposure.	CC, CE, VE, YB, YC	Delinquency, early drug use, depression, attention-deficit/hyperactivity disorder, oppositional defiance disorder/conduct disorder (YR)	PCE=NCE in adolescent problem behaviors.	n/a
Warner et al. ¹² 2011 ¹²	263; PCE: 129; NCE: 134	12.5	PCE: 81% AA; NCE: 83% AA	Self-report, UT	For analyses: any vs. none	BF, YC, YB, VE, CC, CE	Done Adolescent use of cocaine • hair samples	PCE=NCE in adolescent cocaine use.	n/a
Whitaker et al. ²⁰ 2011 ²⁰	1081; PCE: 470; NCE: 611	11, 12	PCE: 84% AA; NCE: 79% AA	Self-report, Meconium; 7% exposed to opiates	High: ≥ 3 times per week in first trimester. Some: any other level of exposure.	SF, YC, CC, CE	Behavior problems (CR) • Pediatric Symptom Checklist	Heavy PCE>NCE to have attention, externalizing, and internalizing problems.	$f^2 = 0.007$ to 0.034 (small)

>, more likely than; <, less likely than; =, no significant differences; AA, African American; PCE, Prenatal cocaine exposure; NCE, Non-prenatal cocaine exposure; ACASI, Audio Computer Assisted Self Interview; CBCL, Child Behavior Checklist; CDC, Centers for Disease Control and Prevention; HR, hazard ratio; n/a, not applicable; TR, teacher report; UT, urine toxicology; YR, youth report; YRBSS, Youth Risk Behavior Surveillance System. CR, caregiver report; OR, odds ratio.

^a All studies included in this table are longitudinal.

^b Violence exposure (VE): community violence, home violence, community drug use, child abuse. Caregiving environment (CE): parental strictness, parental nurturance, foster care, caregiver changes, stimulation, home environment quality, postnatal caregiver drug use, depression, psychiatric problems. Caregiver characteristics (CC): socioeconomic status, marital status, employment, IQ, race, incarceration. Youth characteristics (YC): Head Start, pre-kindergarten, gender, race, IQ, age. Birth factors (BF): head circumference, birth wt, birth length, gestational age, obstetric complications. Youth behaviors (YB): health risks, internalizing, externalizing, current drug use, behavioral problems. Study factors (SF): site, assessment number, clinic, intervention status.

^c Effect sizes from nonsignificant findings were not reported.

^d η^2 : 0.01 = small, 0.06 = medium, 0.14 = large; f^2 = small, 0.15 = medium, 0.35 = large 2; d : 0.2–0.3 = small, 0.4 = medium, 0.8 = large.

^e No breakdown provided of PCE vs NCE.

violence exposure, caregiving environment, caregiver characteristics, youth characteristics, birth factors, youth behaviors, and study factors (Tables 1, 2, 3, and 4). Covariate categories indicate that the study included at least one of the variables listed in that category or a variable similar to it (see footnotes to Tables 1, 2, 3, and 4). Prenatal exposure to tobacco, alcohol, and marijuana was cataloged (Table 5). All studies included a non-cocaine exposure (NCE) comparison group, matched on individual and environmental characteristics, with frequent prenatal exposure to alcohol, tobacco, and/or marijuana.

Setting, Design, and Sampling

All articles represented low-income, predominantly African American samples. With the exception of 1 rural sample,³² all samples were urban. Most studies presented longitudinal data ($n = 19$); others analyzed the adolescent phase of longitudinal data sets ($n = 8$). Ages of participants ranged from 11 to 17 years. Several studies examined children aged <11, but only the adolescent results are reported here. All studies defined cocaine exposure through maternal and/or infant toxicology reports (urine, meconium) and/or self-reported prenatal drug use. Definitions differed across studies (Tables 1, 2, 3, and 4). The cohorts were relatively evenly distributed across adolescent outcomes (Fig 1).

Definition of PCE

Definitions varied across cohorts. Sixteen studies from 7 cohorts defined cocaine exposure dichotomously: “exposed” versus “nonexposed”^{18,23,24,32–43} or “heavy/persistent” versus “some/none.”²¹ Six studies from 1 cohort defined “heavy” as first trimester use ≥ 3 times per week.^{19,20,22,25,44,45} Four studies from 1 cohort defined “heavy” as at

TABLE 2 Continued

Author ^a	Sample Composition			PCE Determination Methods	PCE Level of Exposure	Additional Predictors/Covariates ^b	Outcome Variable(s)	Main Finding(s)	Effect Size ^{c,d}
	N	Age (y)	Ethnicity (%)	Gender (%)					
Landi et al, 2012 ⁴⁵	153; PCE: 107, NCE: 46	13	PCE: 91% AA; NCE: 67% AA	PCE: 52% male; NCE: 59% male	Any vs none	CC	Spatial cognition: • Line Orientation, • Mental Rotation; Visual cognition: • Visual Object and Space Perception Battery-Shape Determination, • Mooney's Test of Visual Closure-Face Perception; Memory: • Incidental Face Learning; • Incidental Word Learning Speech processing ability: • Event-related potentials, • Clinical Evaluation of Language Fundamentals II (CELF) Special education services: • Individual Education Plan (IEP) enrollment (school records)	PCE=NCE in language function on CELF. PCE had atypical responses in phonologic processing. PCE>NCE to have an IEP. Level of cocaine exposure not significant. Oppositional defiant disorder (ODD) moderated association between PCE and IEP enrollment PCE=NCE on executive functioning.	$d = 0.39$ (small) $\eta^2 = 0.04$ and 0.05 (medium) OR = 1.52 and 1.63 (small)
Levine et al, 2012 ⁴⁵	498; PCE: 205, NCE: 293	11	PCE: 87% AA; NCE: 78% AA	PCE: 51% male; NCE: 52% male	High: ≥ 3 times/wk in first trimester. Some: any other level of exposure.	CC, CE, YC, YB, BF, SF	Executive functioning: • Delis-Kaplan Executive Function System: Color-Word Interference, Design Fluency, Trail Making, Word Context, Tower		
Rose-Jacobs et al, 2011 ⁴⁸	137; PCE: 75, NCE: 62	12–14	PCE: 85% AA; NCE: 94% AA	PCE: 49% male; NCE: 52% male	Heavy: ≥ 61 d of use throughout pregnancy; top quartile of metabolites in meconium. Light: any other level of exposure	YC, YB, CE			n/a

> more likely than; < less likely than; =, no significant differences; AA, African American; PCE, prenatal cocaine exposure; NCE, non prenatally cocaine exposed CBC, Child Behavior Checklist; OR, caregiver report; n/a, not applicable; Reg. coeff., regression coefficient; TR, teacher report; UT, urine toxicology; YR, youth report; OR, odds ratio.

^a All studies included in this table are longitudinal.

^b Violence exposure (VE): community violence, home violence, community drug use, child abuse. Caregiving environment (CE): parental strictness, parental supervision, parental nurturance, foster care, caregiver changes, stimulation, home environment quality, postnatal caregiver drug use, depression, psychiatric problems. Caregiver characteristics (CC): socioeconomic status, marital status, employment, IQ, race, incarceration. Youth characteristics (YC): Head Start, pre-kindergarten, gender, race, IQ, age. Birth factors (BF): head circumference, birth wt, birth length, gestational age, obstetric complications. Youth behaviors (YB): health risks, internalizing, externalizing, current drug use, behavioral problems. Study factors (SF): site, assessment number, clinic, intervention status.

^c Effect sizes from nonsignificant findings were not reported.

^d η^2 : .01 = small, .06 = medium, .14 = large; r^2 = .02 = small, .15 = medium, .35 = large 2; d: 2–3 = small, .4 = medium, .8 = large.

TABLE 3 Description of Studies by Outcome: Neuroimaging

Author	Sample Composition			PCE Determination Methods	PCE Level of Exposure	Additional Predictors/ Covariates ^a	Neuroimaging Method	Outcome Variable(s)	Main Finding	Effect Size ^b
	N	Age	Ethnicity (%)							
Avants et al, 2007 ^{c,33} Hurt et al, 2008 ^{c,38}	49; PCE: 25; NCE: 24	14	PCE: 96% AA; NCE: 100% AA	UT, self-report	Any vs none; all heavily exposed	Individual brain vol	T1 weighted MRI	Caudate vol	PCE < NCE left, right, and total caudate volume.	No report
	34; PCE: 17; NCE: 17	14	PCE: 88% AA; NCE: 100% AA	Self-report, UT	Any vs none. mothers with ≥ 2 trimesters cocaine use	SF, YC	Block design	Prefrontal cortex activation	PCE = NCE on working memory task or brain activation patterns during working memory task.	n/a
	56; PCE: 33; NCE: 23	14	Primarily AA ^d	Self-report, UT	Any vs none	YC, BF	Block design	Amygdala activation; Prefrontal activation	PCE = NCE on behavioral performance on working memory task. NCE > PCE to have suppression of neural activity in bilateral amygdalae of caudate when cognitive demands increased.	Partial η^2 = 0.069 (medium), 0.106 (medium/large), and 0.167 (large)
									PCE/NCE differences in prefrontal activity when memory load differed.	
Li et al, 2011 ^{c,39}	56; PCE: 33; NCE: 23	14	Primarily AA ^d	Self-report, UT	Any vs none	YC, BF	Factorial block design	Brain activity in the DMN: • resting, task-activated	Resting: PCE > NCE functional connectivity in DMN. Working memory task: PCE < deactivation in DMN and functional MRI signaled increases with emotional arousal	Partial η^2 = 0.05–0.24 (moderate to large)
									PCE = NCE in the subregions of the corpus callosum.	n/a
Liu et al, 2011 ^{c,e,42}	40; PCE: 20; NCE: 20	13–15	PCE: 70% minority; NCE: 50% minority ^f	Self-report, meconium	Any vs none	SF; other covariates not specified	Diffusion Tensor Imaging	Sensation seeking; DTI measures in subregions of the corpus callosum: • mean diffusivity, fractional anisotropy		
Rao et al, 2007 ^{c,41}	49; PCE: 25; NCE: 24	14	PCE: 96% AA; NCE: 100% AA	Self-report, UT	Any vs none; majority exposed to 3 trimesters	YC, head motion, global CBF, total gray matter	Structural and perfusion functional MRI	Resting CBF, cerebral vol	PCE < NCE in global CBF (esp. in occipital cortex and thalamus). Relative CBF higher in frontal and superior regions	f^2 = 0.13–0.36 (small/medium)

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¹ >: more likely than; <: less likely than; =: no significant differences; AA, African American; PCE, prenatal cocaine exposure; NCE, non prenatally cocaine exposed; DMN, default mode network; UT, urine toxicology; fMRI, functional magnetic resonance imaging; DTI, diffusion tensor imaging.

² Caregiving environment (CE): parental strictness, parental supervision, parental nurturance, foster care, caregiver changes, stimulation, home environment quality, postnatal caregiver drug use, depression, psychiatric problems. Youth characteristics (YC): Head Start, pre-kindergarten, gender, race, IQ, age. Study factors (SF): site, assessment number, clinic, intervention status. Birth Factors (BF): head circumference, birth wt, birth length, gestational age, obstetric complications.

³ Effect sizes from nonsignificant findings were not reported; Avants et al 2007 was unable to provide effect sizes due to logistical reasons.

⁴ Adolescent phase only study.

⁵ No breakdown provided of PCE versus NCE.

⁶ Authors did not list all covariates.

⁷ This study is a subsample of the Maternal Lifestyle Study, which includes predominantly AA participants. The authors did not define "minority."

⁸ Longitudinal study.

⁹ The fMRI portion of the study included a subset of 52 participants. The authors also conducted analyses on cognitive measures using a larger sample of 138.

TABLE 4 Description of Studies by Outcome: Physiologic Responses

Author	Sample Composition			PCE Determination Methods	PCE Level of Exposure	Additional Predictors/ Covariates ^a	Outcome Variable(s)	Main Finding(s)	Effect Size ^b	
	N	Age	Ethnicity (%)							Gender (%)
Bauer et al, 2011 ^{c, 25}	725; PCE: 246, NCE: 479	11	PCE: 87% AA; NCE: 80% AA	PCE: 52% male; NCE: 51% male	Self-report, meconium, 7% exposed to opiates	High: ≥ 3 times/wk in first trimester. Some: any other level of exposure.	BF, SF, CE, VE, CC	HPA response: • Diurnal salivary cortisol	PCE=NCE in basal evening or morning cortisol. High PCE>low PCE and NCE had smaller increases (blunting) in cortisol from evening to morning and more likely to demonstrate an atypical change.	OR = 2.06 (small to medium)
Chaplin et al, 2010 ^{d, 34}	82; PCE: 49, NCE: 33	14.5–16	PCE: 94% AA; NCE: 85% AA	PCE: 51% male; NCE: 46% male	Self-report, UI, meconium	Any vs none	YC, CC, CE, BF	HPA response: • Salivary cortisol; Cardiovascular response (heart rate and blood pressure); Critikon Dinamap 120 Patient Monitor; Emotional response (anxiety, fear, sadness) (YR): • Self Report of Emotion Scale, • Differential Emotions Scale Revised	PCE>NCE to have altered stress response moderated by gender. PCE>NCE had higher cortisol levels before and after stress. PCE girls>NCE girls had higher anxiety in response to stress. PCE=NCE in fear, sadness, heart rate, or systolic blood pressure.	$d = 0.27$ – 0.62 (small to medium)
Lester et al, 2010 ^{e, 44}	743; PCE: 320, NCE: 423	11	PCE: 83% AA; NCE: 81% AA	PCE: 52% male; NCE: 51% male	Self-report, meconium	High: ≥ 3 times/week in first trimester. Some: any other level of exposure	SF, YC, CE, VE	HPA response: • Salivary cortisol	PCE>NCE to have blunted cortisol response to stress	No report

>, more likely than; <, less likely than; =, no significant differences; AA, African American; PCE, prenatal cocaine exposure; NCE, non prenatally cocaine exposed; OR, odds ratio; DMN, default mode network; YR= Youth report; UT, urine toxicology

Quality of life, postnatal caregiver drug use, depression, psychiatric problems. Caregiver characteristics (CG): socioeconomic status, marital status, employment, IQ, race, incarceration. Youth characteristics (YC): Head Start, pre-k, gender, race, IQ, age. Birth factors (BF): head circumference, birth wt, birth length, gestational age, obstetric complications. Study factors (SF): site, assessment number, clinic, intervention status.

Effect sizes from nonsignificant findings were not reported; Lester et al 2010 was unable to provide effect sizes for logistical reasons.

Longitudinal study.

Adolescent phase only study.

TABLE 5 Description of Prenatal Tobacco, Marijuana, and Alcohol Exposure by Study

Author	Prenatal Tobacco		Prenatal Marijuana		Prenatal Alcohol	
	Measurement	Covariate	Measurement	Covariate	Measurement	Covariate
Behavior problems						
Bada et al, 2011 ²²	Average no. cigarettes/d	Yes	No. joints/d	Yes	Ounces absolute alcohol/d	Yes
Buckingham-Howes, et al 2012 ²³	Any vs none	Yes	Not examined	No	Any vs none	Yes
Delaney-Black, et al 2011 ¹⁸	14-d recall of no. cigarettes smoked/d and averaged across pregnancy	Yes	14-d recall of no. joints smoked/d and averaged across pregnancy	Yes	14-d recall average ounces absolute alcohol/d, ounces absolute alcohol/drinking d, proportion of drinking d, vol, pattern indices	Yes
Frank et al, 2011 ¹²	≥1/2 pack/d	Yes	Heavier exposure: self report and/or meconium or urine and positive urine at delivery or top quartile of self-reported use. Lighter exposure: self report or assay who did not meet heavier group criteria.	Yes	≥0.5 drinks/d	Yes
Gerteis et al, 2011 ⁴⁶	Lighter use: <1/2 pack/d; Heavier use: ≥1/2 pack/d	Yes	Any vs none	Yes	Lighter use: <0.5 drinks/d; Heavier use: ≥0.5 drinks/d	Yes
Greenwald et al, 2010 ²¹	14-d recall of no. cigarettes smoked/d and averaged across pregnancy	Yes	14 d recall of no. joints smoked/d and averaged across pregnancy	Yes	14-d recall average ounces absolute alcohol/d, ounces absolute alcohol/drinking d, proportion of drinking days, vol, pattern indices	Yes
LaGasse et al, 2006 ¹⁹	Avg. no. cigarettes/d	No	No. joints/d	No	Ounces absolute alcohol/d	No
Warner et al, 2011 ³²	no. cigarettes/d	Yes	No. joints/d	Yes	Ounces absolute alcohol/d	Yes
Whitaker et al, 2011 ²⁰	Avg. no. cigarettes/d	Yes	No. joints/d	Yes	Ounces absolute alcohol/d	Yes
Cognition/School outcomes						
Bandstra et al, 2011 ⁴⁹	Self-report composite: no. weeks used × usual d/week and usual dose/d	Yes	Self-report composite: no. wk used × usual d/wk and usual dose/d	Yes	Self-report composite: no. weeks used × usual d/week and usual dose/d	Yes
Batancourt et al, 2011 ³⁶	Any vs none	Yes	Any vs none	Yes	Any vs none	Yes
Bridgett et al, 2011 ³⁵	Any vs none	Yes ^a	Any vs none	Yes ^a	Any vs none	Yes ^a
Hurt et al, 2009 ³⁷	Any vs none	Yes	Any vs none	Yes	Any vs none	Yes
Landi et al, 2012 ⁴³	Any vs none	No	Any vs none	No	Any vs none	No
Levine et al, 2012 ⁴⁵	No. cigarettes/d	Yes	No. joints/d	Yes	Ounces absolute alcohol/d	Yes
Rose-Jacobs et al, 2011 ⁴⁸	Heavier use: ≥10 cigarettes/d; lighter use: <10 cigarettes/d	Yes	Heavier use: positive urine, self-reported days of use in top quartile of sample, >8 d during pregnancy; lighter use: negative urine, self-reported d of use below top quartile	Yes	Heavier use: ≥0.5 drinks/d; lighter use: <0.5 drinks/d	Yes
Neuroimaging						
Avants et al, 2007 ³³	Any vs none	No	Any vs none	No	Any vs none	No
Hurt et al, 2008 ³⁸	Any vs none	No	Any vs none	No	Any vs none	No
Li et al, 2009 ⁴⁰	No. cigarettes/week ^b	Yes	No. joints/week ^b	Yes	Ounces absolute alcohol/d	Yes
Li et al, 2011 ³⁹	No. cigarettes/week ^b	Yes	No. joints/week ^b	Yes	Ounces absolute alcohol/d	Yes
Liu et al, 2011 ⁴²	Any vs none	Yes ^c	Not examined	No	Any vs none	No
Rao et al, 2007 ⁴¹	Any vs none	Yes ^d	Any vs none	Yes ^d	Any vs none	Yes ^d

TABLE 5 Continued

Author	Prenatal Tobacco		Prenatal Marijuana		Prenatal Alcohol	
	Measurement	Covariate	Measurement	Covariate	Measurement	Covariate
Riggins et al, 2012 ²⁴ Rivkin et al, 2008 ⁴⁷	Any vs none Any vs none	Yes Yes	Not examined Any vs none	No Yes	Any vs none Any vs none	Yes Yes
Physiologic responses Bauer et al, 2011 ²⁵	Avg. no. cigarettes/d	Yes	Avg. no. joints/d	Yes	Average ounces absolute alcohol/d	Yes
Chaplin et al, 2010 ²⁴ Lester et al, 2010 ⁴⁴	≥2 d use/mo High: ≥10 cigarettes/d; some: <10 cigarettes/d	Yes Yes	≥2 d use/mo High: ≥0.5 joint/d; some: <0.5 joint/d	Yes Yes	≥2 d use/mo High: ≥0.5 oz. absolute alcohol/d; some: <0.5 oz. absolute alcohol/d	Yes Yes

Under "Covariate," "No" indicates the exposure(s) (1) is not mentioned, (2) is reported only as percentages of how many participants were exposed to that drug, or (3) is reported only as differences in each exposure between prenatally cocaine exposed and nonexposed groups. "Yes" indicates (1) authors examined the exposures as potential covariates but exposures did not meet their own criteria for inclusion in their models or (2) authors included them as covariates in models.

^a Models were rerun to determine if prenatal tobacco, marijuana, and alcohol had any effect on the outcomes, but all models were determined to be a poor fit.

^b Number of cigarettes per week and number of joints per week were combined into 1 variable of number of cigarettes/joints per week because use was highly correlated.

^c Study design included grouping based on tobacco exposure.

^d Performed additional comparisons between PCE and non-PCE groups by only exposed subjects without a given type of drug exposure and between subjects with and without a given type of drug exposure within the PCE group. They detected similar patterns, and they concluded that the results were attributable to PCE rather than polydrug exposure.

least 61 days of use and the top quartile of meconium metabolites.^{12,46–48} One cohort calculated a latent variable, based on maternal self-report in each trimester and quantitative and qualitative cocaine metabolite assays.⁴⁹ Even though many studies identified high versus low PCE, many collapsed variables into any vs. none variables for analyses (see Tables 1, 2, 3, and 4). Twelve of the 16 studies that dichotomously defined PCE and 3 of the 11 that defined PCE dosage exposure reported significant findings.

Covariates

The most widely used covariates were other prenatal exposures (alcohol, tobacco, and marijuana), the caregiving environment, and violence. Almost all studies considered ≥1 other prenatal drug exposure ($N = 23$), but measurements differed (Table 5).

The caregiving environment (examined in 20 studies) included caregiver stability, quality of the home environment, caregiver-child relationships, postnatal caregiver drug use, and caregiver depression/psychopathology (Table 6). Violence was examined in 16 studies and included witnessed/experienced community or domestic violence, sexual/physical abuse, community drug use, and violent friends (Table 6).

Behavior

Eleven studies described behavioral problems. Nine examined externalizing/internalizing behaviors and/or drug use. Two examined behavior problems in the context of cognitive outcomes³⁵ or physiologic responses³⁴ and are included in both sections (Cognition/School and Physiologic Responses, Table 1).

Eight studies examined externalizing/internalizing behaviors,^{19–23,34,35,46} with mixed findings (Table 1). Two found no association between PCE and youth-reported behavioral problems,^{19,46} 1 found associations between Stroop

FIGURE 1

Distribution of study cohorts across each adolescent outcome construct. The number of studies totals 30 because 3 studies are counted twice: Chaplin et al 2010 is counted twice under Physiologic Response and Behavioral Problems; Bridgett et al is counted twice under Behavioral Problems and Cognition/School Outcomes; and Riggins et al 2012 is counted twice under Neuroimaging and Cognition/School Outcomes. Cohort 1 = Bada et al 2011, LaGasse et al 2006, Whitaker et al 2011, Lester et al 2010, Levine et al 2012, Bauer et al 2011, Liu et al 2011. Cohort 2 = Frank et al 2011, Gerteis et al 2011, Rose-Jacobs, et al 2011, Rivkin et al 2008. Cohort 3 = Bridgett et al 2011, Chaplin et al 2010, Landi et al 2012. Cohort 4 = Avants et al 2007, Hurt et al 2008, Hurt et al 2009, Rao et al 2007, Betancourt et al 2011. Cohort 5 = Li et al 2009, Li et al 2011. Cohort 6 = Greenwald et al 2010, Delaney-Black et al 2011; Cohort 7 = Warner et al 2011; Cohort 8 = Bandstra et al 2011; Cohort 9 = Riggins et al 2012, Buckingham-Howes et al 2012.

errors at 7.5 years and caregiver-reported aggression at 14 years, regardless of PCE status,³⁵ and one found that the PCE group was more likely than the NCE group to respond to a laboratory social provocation paradigm with escape, rather than aggression.²¹ The remaining 4 found significant differences favoring the NCE group. Heavy PCE was associated with attention problems and externalizing/internalizing behaviors,²⁰ PCE youth had higher teacher- and caregiver-reported externalizing problems,²² girls in the PCE group had more adolescent-reported anxiety than nonexposed girls,³⁴ and anxiety/depression, but not aggression, in middle childhood mediated the association between PCE and adolescent peer victimization.²³

Four studies examined adolescent drug use (Table 1).^{12,18,19,32} One found that PCE was associated with adolescent cocaine use (measured by hair, sweat, and urine).¹⁸ Another study found that heavy PCE was associated with youth-reported marijuana and

alcohol use.¹² The other 2, among younger adolescents, did not find associations between PCE and adolescent cocaine use (measured by hair)³² or any drug use (adolescent reported).¹⁹

Covariates

One study did not mention other prenatal exposures,¹⁹ 1 examined only alcohol and tobacco,²³ and the others examined prenatal tobacco, alcohol, and marijuana exposure (Table 5).^{12,18,20–22,32,34,35,46} Ten studies examined the caregiving environment and violence exposure, primarily postnatal/current caregiver drug use ($N = 7$), quality of the home ($N = 3$), caregiver stability ($N = 4$), caregiver depression/psychopathology ($N = 5$), community violence ($N = 8$), and home violence ($N = 7$; Table 6). One study found the relationship between heavy PCE and behavioral problems was mediated by caregiver changes.²⁰ Another found that PCE, together with current caregiver cocaine use, caregiver negativity, community violence exposure, and prenatal

tobacco exposure, was associated with adolescent cocaine use¹⁸; another reported associations between heavy prenatal tobacco exposure (but not PCE) and violence, with delinquent behaviors.⁴⁶ Five studies found that postnatal caregiver drug use/drugs in the home^{18,20–22,32} and caregiver psychiatric/depressive symptoms^{18–20,22,32} were associated with adolescent behavior problems. Another study found an association between community violence and peer victimization.²³ Associations were direct and did not interact with PCE.

Effect Sizes and Clinical Importance

Seven of the 11 studies reporting behavior had significant findings; 3 reported small effects,^{18,20,21} 3 reported small-moderate effects,^{12,23,34} and 1 reported small-large effects.²² Based on teacher-reported and caregiver-reported Child Behavior Checklist scores at ages 11 to 13, both exposure groups had high-WNL scores on externalizing, attention, and total problems.²² Means for other behavioral measures were WNL or not reported.

Cognition/School

Eight studies addressed cognition/school performance (Table 2).^{24,35–37,43,45,48,49} Three examined language,^{36,43,49} 4 examined neurocognitive and executive functioning (1 included here and in Neuroimaging),^{24,35–37} and 1 evaluated school outcomes.⁴⁵

One study found an enduring relationship between PCE and lower language performance scores.⁴⁹ Another found atypical language processing among the PCE group.⁴³ The third found no relationship with receptive language.³⁶ Five studies examined neurocognitive and executive functioning, with mixed results (Table 2).^{24,35–37} Two found no association between PCE and neurocognitive functioning (ie, cognitive control, working memory, reward processing, memory spatial cognition, visual cognition)³⁷ or

TABLE 6 Description of Caregiving Environment and Violence Exposure by Study

Author	Caregiving Environment			Violence Exposure		
	Construct	Measures	Findings	Construct	Measures	Findings
Behavior problems						
Bada et al, 2011 ²²	Postnatal caregiver drug use; quality of home environment; caregiver depression	Caregiver report of postnatal drug use; HOME; Beck Depression Inventory	Postnatal tobacco use and caregiver depression associated with externalizing, internalizing and attention problems; postnatal alcohol use associated with internalizing and attention problems. HOME associated with teacher-reported externalizing internalizing, and attention problems.	General violence exposure	Survey of Exposure to Violence	Community violence associated with externalizing problems.
Buckingham-Howes et al, 2012 ²³	Caregiving stability, postnatal caregiver drug use	Number of caregiver changes through age 7; Addiction Severity Index	Caregiver changes not related to peer victimization.	Community violence	Things I've Seen and Heard	Community violence (age 7) associated with adolescent peer victimization. PCE=NCE in violence exposure.
Delaney-Black et al, 2011 ¹⁸	Postnatal caregiver drug use; parenting style; caregiving stability; caregiver psychopathology	Biological specimens and self-report; Parenting Styles and Dimensions Questionnaire; change in caregiver; Personality Diagnostic Questionnaire—4th ed; Symptom Checklist-90-R Anxiety	Postnatal cocaine use associated with adolescent cocaine use; caregiver psychopathology related to teen drug use	Community violence; community drug use; PTSD (adolescent)	Things I've Seen and Heard; Survey of Exposure to Violence; Children's Report of Exposure to Violence; Checklist of Children's Distress Symptoms (CR); Schedule for Affective Disorders and Schizophrenia for School Age Children; Post-Traumatic Stress Disorder Reaction Index	Community violence, community drug use, and caregiver negativity associated with adolescent cocaine use
Frank et al, 2011 ¹²	Postnatal caregiver drug use; familial drug use; caregiving stability; food insecurity; caregiver supervision	Caregiver report of postnatal drug use; urine samples; family drug use; US Department of Agriculture Food Security Scale; Lamborn's adolescent perception of parenting	Familial drug use, caregiving stability, food insecurity, and caregiver supervision excluded from final models because did not change relationship between PCE and outcome. PCE > NCE to experience multiple caregiver changes. PCE=NCE in strict parenting and violence exposure.	General violence exposure	Violence Exposure Scale for Children—Revised	Violence exposure in the third or fourth quartiles associated with initiation of any substance.
Gerteis et al, 2011 ⁴⁶	Caregiver style; caregiver changes	Lamborn's adolescent perception of parenting; number of caregiver changes	Early adolescent delinquent behavior not associated with strict supervision. Caregiver changes not associated with delinquent behavior.	General violence exposure	Violence Exposure Scale for Children—Revised	Early adolescent delinquent behavior associated with higher violence exposure.
Greenwald et al, 2010 ²¹	Quality of home environment; postnatal caregiver drug use; biological caregiver status	HOME; caregiver report of postnatal drug use; hair analysis; caregiver report if caregiver was biological mother (Y/N)	Quality of home environment not associated with outcomes. Postnatal caregiver alcohol use associated with greater escape responding.	Community violence; general violence exposure	Things I've Seen and Heard; Survey of Exposure to Violence; Children's Report of Exposure to Violence	Community violence exposure not associated with outcomes.
LaGasse et al, 2006 ¹⁹	Relatedness to parents; caregiver psychiatric symptoms	Relatedness Questionnaire; Brief Symptom Inventory	Positive relatedness to others reduced incidence of CD/ODD school delinquency and depression. Caregiver psychiatric symptoms	Community violence; domestic violence; physical or sexual abuse involving	Survey of Community Violence; Things I've Seen and Heard; Caretaker report of physical or sexual abuse (for child);	Community violence associated with crimes against people and early drug use. History of physical or sexual abuse

TABLE 6 Continued

Author	Caregiving Environment			Violence Exposure		
	Construct	Measures	Findings	Construct	Measures	Findings
Warner et al, 2011 ³²	Postnatal caregiver drug use; access to drugs in the home; quality of home environment; attachment to caregiver; caregiver depression	Add Health Survey; Addiction Severity Index; HOME; Inventory of Parent and Peer Attachment; Center for Epidemiologic Studies—Depression Scale	associated with increased depression, ADHD, ODD, CD Cocaine hair positive youth > cocaine hair negative youth to have more drugs in the home, caregivers more alcohol problems and depression, lower HOME scores, less positive attachment scores	Child Protective Services; violent friends Community violence	History of child abuse; Things My Friends Have Done Things I've Seen and Heard; Neighborhood Survey From Add Health Survey	associated with depression. Domestic violence associated with CD/ODD. PCE=NCE in community violence exposure and neighborhood characteristics.
Whitaker et al, 2011 ²⁰	Caregiving stability; postnatal caregiver drug use; caregiver depression	Number of caregiver changes; caregiver continued use of marijuana, tobacco, alcohol; Beck Depression Inventory	Number of caregiver changes mediated association between high PCE and total Pediatric Symptom Checklist (PSC) scores, some PCE and total PSC scores. Postnatal tobacco exposure associated with total PSC scores, attention, externalizing, and internalizing problems. Postnatal marijuana exposure associated with total PSC scores and externalizing problems. Caregiver depression: higher PSC scores	Domestic violence	Reported abuse of the child or caregiver (child or caregiver report)	Higher domestic violence associated with higher PSC scores; externalizing, and internalizing problems.
Cognition/School outcomes						
Bandstra et al, 2011 ⁴⁹	Quality of home environment; caregiver stability; postnatal caregiver drug use	HOME; caregiver changes; caregiver drug use obtained from a structured psychosocial interview	PCE=NCE on expressive language, and HOME	NA/NR	NA/NR	NA/NR
Betancourt et al 2011 ³⁶	Quality of home environment; caregiver stability; caregiver depression	HOME, Caregiver Nurturance and Environmental Stimulation subscales; foster care placement (yes/no); Beck Depression Inventory II	Environmental stimulation related to increased language skills. No association with caregiver nurturance or depression.	NA/NR	NA/NR	NA/NR
Hurt et al 2009 ³⁷	Quality of home environment; caregiver stability; postnatal caregiver drug use; caregiver depression	HOME, Caregiver Nurturance and Environmental Stimulation subscales; Foster home placement; Current caregiver cocaine use; Beck Depression Inventory II	Environmental stimulation associated with neurocognitive function. Postnatal caregiver drug use, nurturance, stability, and depression not associated with neurocognitive function.	NA/NR	NA/NR	NA/NR
Levine et al 2012 ⁴⁵	Quality of home environment; postnatal caregiver drug use;	HOME; Caretaker Inventory of Substance Use; Beck Depression Inventory;	PCE>NCE to be exposed to postnatal caregiver substance use, more caregiver changes. IEP associated	Domestic violence; child abuse	Report of physical or sexual abuse. Caregiver interview and child protective service interactions.	PCE>NCE to experience child abuse.

TABLE 6 Continued

Author	Caregiving Environment			Violence Exposure		
	Construct	Measures	Findings	Construct	Measures	Findings
Rose-Jacobs et al 2011 ⁴⁸	caregiver depression; caregiver stability NA/NR	number of caregiver changes NA/NR	with any caregiver changes and chronic caregiver depression. NA/NR	General violence exposure	Violence Exposure Scale for Children, Revised	Violence exposure not associated with any substance exposure.
Neuroimaging Li et al 2009 ⁴⁰	Caregiving stability	List of questions addressing caregiving environment	PCE > NCE to have caregiver changes and involvement from the Division of Family and Children Services. PCE > NCE in caregiver changes.	Child abuse/neglect	List of questions addressing caregiving environment	PCE > NCE to have involvement from the Division of Family and Children Services.
Li et al 2011 ³⁹	Caregiving stability	List of questions addressing caregiving environment	PCE > NCE in caregiver changes.	Child abuse/neglect	List of questions addressing caregiving environment	PCE > NCE to have involvement from the Division of Family and Children Services.
Riggins et al 2012 ²⁴	Caregiving stability; caregiver depression	Number of caregiver changes through age 7; Center for Epidemiologic Studies Depression Scale	PCE > NCE to have caregiver changes than NCE group. No group differences in caregiver depression. PCE findings attenuated early environment variables in model.	Child abuse	Child Abuse Potential Inventory	No group differences
Physiologic responses Bauer et al 2011 ²⁵	Caregiving stability; caregiver depression; postnatal caregiver drug use	Caregiver changes and foster care; Beck Depression Inventory; caregiver report of postnatal drug use	Caregiver depression: PCE > NCE had atypical pattern of change in diurnal cortisol (blunted), PCE > NCE associated with caregiver changes, foster care placement, and caregiver use of alcohol, tobacco, and binge drinking. Caregiver-child relationship quality did not moderate relationship between PCE and any outcomes. Poorer relationship quality associated with lower adolescent reported anxiety immediately after stressor.	Child abuse; domestic violence; community violence	Report of abuse or neglect since last visit; Report of physical or sexual violence since last visit; Survey of Exposure to Community Violence	PCE > NCE to experience community violence.
Chaplin et al 2010 ³⁴	Caregiver-child relationship quality	Parenting Stress Index, parent-child relationship subscale	Caregiver-child relationship quality did not moderate relationship between PCE and any outcomes. Poorer relationship quality associated with lower adolescent reported anxiety immediately after stressor.	NA/NR	NA/NR	NA/NR
Lester et al 2010 ⁴⁴	Quality of home environment; caregiver stability; postnatal caregiver drug use; caregiver changes; caregiver psychological distress; caregiver depression	HOME; number of caretaker changes; From 1 mo to 11 y: changes in primary caretaker; caregiver report of postnatal drug use; Brief Symptom Inventory; Beck Depression Inventory	No report of findings based on these measures.	Child abuse; domestic violence; community violence	From 1 mo to 11 y: • Child Protective Services case opened; • Domestic violence (caregiver report); • Things I've Seen and Heard; • Survey of Exposure to Community Violence	PCE > NCE to have blunted cortisol in context of domestic violence.

>, more likely than; <, less likely than; =, no significant differences, Rivkin et al 2008, Avants et al 2007, Hurt et al 2008, Liu et al 2011, Rao et al 2007, Bridgett et al 2011, Landi et al 2012 did not include violence exposure or caregiving environment variables. PCE, prenatal cocaine exposure; NCE, non prenatal cocaine exposure; Add Health, National Longitudinal Study of Adolescent Health; ADHD, attention-deficit/hyperactivity disorder; CD, conduct disorder; HOME, Home Observation Measurement of the Environment; NA/NR, not analyzed/not reported; ODD, oppositional defiant disorder; PTSD, posttraumatic stress disorder.

executive functioning.⁴⁸ A third found no relations with working memory or inhibitory control, but the PCE group improved at a slower rate and had marginally lower scores than the NCE group on incidental memory tasks.³⁶ Another study found that the PCE group demonstrated poorer performance on 2 memory tasks compared with the NCE group.²⁴ A final study found that PCE group boys improved more slowly in inhibitory control than nonexposed boys and all girls.³⁵

One study reported greater enrollment in an Individualized Education Plan (IEP) among the PCE group.⁴⁵ Oppositional defiant disorder (ODD) moderated the association, with the PCE/ODD group more likely to have an IEP than youth with only 1 condition (ODD or PCE).⁴⁵

Covariates

Six of the 8 studies examined prenatal tobacco, alcohol, and marijuana exposure^{35–37,45,48,49}; 1 included prenatal tobacco and alcohol only.²⁴ Five measured exposures as any versus none (Table 5).^{24,35–37,45} One study reported negative associations with prenatal marijuana and alcohol exposure and positive associations with prenatal tobacco exposure and executive functioning.⁴⁸ Another study reported that youth with prenatal marijuana exposure were less likely to have an IEP.⁴⁵ Five studies examined the caregiving environment, including the quality of the home, caregiver stability, postnatal/current caregiver drug use, and caregiver depression/psychopathology (Table 6).^{24,36,37,45,49} Two studies found that caregiver depression was not associated with language development³⁶ or neurocognitive function,³⁷ and 1 found that environmental stimulation was associated with neurocognitive function.³⁷ Three studies examined violence exposure,^{24,45,48} and 2 did not examine the caregiving environment or violence ex-

posure.^{35,45} Associations were direct and did not interact with PCE.

Effect Sizes and Clinical Importance

Of the 6 cognition/school studies with significant effects, 1 reported small effects,⁴⁵ 4 reported small-moderate effects,^{24,35,36,43} and 1 reported large effects.⁴⁹

Memory scores on the Children's Memory Scales were near the 25th percentile for both exposure groups.²⁴ Language scores were deficient to low-WNL for both groups on the Peabody Picture Vocabulary Test,^{36,37} Clinical Evaluation of Language Fundamentals,^{43,49} and Test for Reception of Grammar.³⁷ Mental processing scores were low-WNL to WNL on the Delis-Kaplan Executive Function System.⁴⁸

Many studies ($n = 17$) reported IQ scores. PCE group means were WNL in 1 study,⁴² low-WNL in 8,^{24,32,35,39–41,45,47} deficient in 4,^{36–38,49} and either WNL or low-WNL depending on high/low exposure in 2.^{12,48} NCE group means were WNL in 2 studies,^{32,42} low-WNL in 10,^{12,24,35,38–41,45,47,48} and deficient in 3.^{36,37,49} Two studies reported deficient IQ scores, without differentiating exposure groups.^{18,21}

Neuroimaging

Eight studies investigated adolescent brain morphology and functioning using neuroimaging (Table 3).^{24,33,38–42,47} All had small sample sizes ($N = 34–56$), used few covariates other than other prenatal drug exposures, and had different neuroimaging methods (3 used similar methods).

One study found the PCE group had smaller left, right, and total caudate volumes than the NCE group.³³ Another found lower cerebral blood flow intensities in the posterior and inferior brain regions in the PCE group. After adjusting for global cerebral blood flow, cerebral blood flow intensities in anterior and superior brain regions were higher in the PCE group with no

differences in total gray or white matter volume or total cerebrospinal fluid volume.⁴¹ A third study found no group differences in subregions of the corpus callosum on measures of mean diffusivity or fractional anisotropy.⁴² One study found that differences in cortical gray matter, parenchymal volume, and head circumference were not significant after adjustment.⁴⁷

Five neuroimaging studies examined how brain function relates to behavior (Table 3). One found no differences on working memory.³⁸ Another found prefrontal cortex activity suppression in the PCE group, associated with negative emotion.⁴⁰ A third study found associations between PCE and alterations in the excitatory/inhibitory balancing mechanism.³⁹ In a fourth study, lower fractional anisotropy was not related to sensation seeking in youth with PCE.⁴² Finally, 1 study found that the PCE group had larger hippocampi than the NCE group, with associations between larger hippocampi and poorer performance on memory tasks.²⁴

Covariates

Of the 8 studies, 4 included prenatal tobacco, alcohol, and marijuana exposure;^{39–41,47} 2 did not;^{33,38} 1 included only tobacco exposure;⁴² and 1 included tobacco and alcohol exposure (Table 5).²⁴ One study reported an inverse relation between number of prenatal exposures and head circumference.⁴⁷ Two studies found that youth with PCE had more caregiver changes and violence exposure (Table 6).^{39,40} A third study reported that PCE group effects were often diminished after adjusting for the caregiving environment and violence exposure.²⁴

Effect Sizes

Of the 8 studies, 1 reported small-medium effects,²⁴ 1 reported small-large effects,⁴¹ and 2 reported moderate-large effects.^{39,40}

Physiologic Responses

Three studies examined physiologic response variability (Table 4).^{25,34,44} One found higher cortisol levels before and after stress exposure in the PCE group; PCE group boys had lower diastolic blood pressure than NCE boys, with no difference in girls, suggesting a lower level of cardiovascular arousal.³⁴ There were no exposure or gender differences in heart rate or systolic blood pressure.³⁴ Another study found the PCE group was more likely than the NCE group to have a blunted cortisol response to stress.⁴⁴ The final study found no group differences in basal or morning cortisol, but the high PCE group demonstrated a blunted cortisol increase from evening to morning and greater likelihood of atypical changes compared with the low PCE and NCE groups.²⁵

Covariates

All studies examined prenatal tobacco, alcohol, and marijuana exposure and the caregiving environment (Table 5).^{25,34,44} One examined the quality of the home, postnatal/current caregiver drug use, caregiver stability, caregiver depression/psychopathology;⁴⁴ 1 included caregiver-child relationship quality;³⁴ and the final study included caregiver stability, caregiver depression, postnatal/current caregiver drug use, domestic violence, child abuse, and community violence.²⁵ One study found that caregiver depression was associated with an atypical diurnal cortisol pattern,²⁵ and caregiver-child relationship quality did not moderate relationship between PCE and cortisol response.³⁴ Another study found that the PCE group was more likely than the nonexposed group to demonstrate a blunted cortisol response that was amplified with exposure to domestic violence (Table 6).⁴⁴

Effect Sizes

The effect sizes were small-moderate in the 2 studies that included them.^{25,34}

DISCUSSION

The 27 studies reviewed represent the initial wave of investigations of PCE among adolescents. Previous reviews reported persistent associations with PCE in infancy, childhood, and early adolescence, including small but significant differences in neurobehavioral functioning,⁹ attention and emotional expressivity,¹⁰ and speech and language development.¹¹ This review does not support previous concerns that cognitive and behavior problems might be more prominent during adolescence in response to increased cognitive and social demands.⁹ Although 70% of the studies (19 of 27) reported significant findings favoring nonexposed youth, effects were small to medium, and scores were WNL, with uncertain clinical importance. Thus, the associations between PCE and multiple areas of development persist through adolescence but do not increase.

Definition of PCE

Although some studies attempted to quantify PCE, most dichotomized it into any versus no exposure. Definitions of heavy exposure varied across studies, potentially contributing to discrepant findings; however, significant findings appeared to be evenly distributed between dichotomous and dosage definitions. Conclusions regarding the long-term effects of PCE would be strengthened by differential dose relationships.

Covariates

Covariates varied in number and type, potentially contributing to discrepant findings. Most studies measured prenatal marijuana, tobacco, and/or al-

cohol exposure, often using direct methods (urine and/or meconium, plus caregiver report). Although measurement strategies differed, prenatal exposures were often associated with negative adolescent outcomes. As with cocaine, clarity in examining dose relationships may increase validity. Eight studies included both cocaine and heroin exposure. However, analyses were rarely adjusted, thus interfering with attribution.

The environmental aspects of PCE have been well recognized.¹³ Many studies included measures of caregiver stability, postnatal/current caregiver drug use, home quality, and caregiver depression/psychopathology, along with violence exposure. With the exception of the neuroimaging studies, many used the same or comparable measures, often finding that caregiving environment and/or violence were directly related to adolescent functioning, regardless of PCE status.

Covariates were frequently included in analyses in an attempt to isolate the effects of PCE, and analyses often examined the direct effects of PCE. Recent developmental theories recommend focusing on individual differences in response to environmental stressors and opportunities.⁵⁰ Thus, models that examine the mechanisms linking PCE and the caregiving environment may yield a more comprehensive understanding of PCE and adolescent functioning.

Behavioral Problems

Behavioral problems were the largest area of research with 11 studies. Although almost two-thirds (7/11) found associations between PCE and behavior problems, across multiple sources (adolescent-, caregiver-, teacher-report, and laboratory paradigms [Table 1]) effect sizes were small with differences WNL, raising concerns about their clinical importance. Two studies that did

not find a link with PCE examined illegal behaviors (eg, property damage, violence), based on youth report.^{19,46} Two studies conducted with youth aged 14 to 16 found a link with adolescent use of psychoactive substances.^{12,18} Findings suggest the need for additional investigation between PCE and nonillegal behaviors and among older adolescents on their vulnerability to substance use.

Cognition/School

Although 74% (6/8) of cognition/school studies had significant findings, results lacked specificity, because most areas (language, memory, neurocognitive functioning, executive control, and inhibitory control) were investigated by only 1 or 2 studies. The most consistent findings were among language and memory tasks.^{24,35,36,43,49} Cognition/school performance warrants additional investigation with models that incorporate indirect effects and environmental conditions, as well as attention to the clinical importance of the findings. Several studies reported means with either the PCE group or both groups low-WNL. Almost all reported low-WNL or deficient IQ scores for both exposure groups, suggesting the negative effects of poverty.

Neuroimaging

Most of the 8 studies examining brain morphology using neuroimaging found significant differences; however, morphologic differences rarely translated to behavioral differences. Thus, the significance of the morphologic differences is unknown.

Effect sizes tended to be medium to large, and neuroimaging studies had small sample sizes, often with limited covariate control, little standardization in methods, and infrequent replication. Neuroimaging is an emerging area in the investigation of PCE and next steps include (1) using larger sample sizes, (2) other prenatal drug

exposures, (3) direct and indirect relations with environmental conditions, (4) relations with behavioral functioning, and (5) replication.

Physiologic Responses

The relationship between PCE and the neuroendocrine system is an emerging topic of theoretical interest.^{25,34,44,51} Although the 3 studies that examined associations between PCE and the HPA system through the cortisol response had inconsistent findings, the HPA axis was altered, suggesting additional research studies to understand how PCE relates to cortisol reactivity and developmental variability.

Methodologic Considerations

Several methodologic considerations limit interpretations. First, the 27 studies relied on 9 cohorts, potentially limiting generalizability. However, the studies were distributed evenly across the 4 outcomes of interest, indicating that data from multiple cohorts informed the conclusions. Second, authors reported statistical significance but little information on clinical importance. Including the percentage of children with clinically relevant findings would increase our understanding of the implications of PCE. Third, although there are examples of research in the 4 areas we identified (behavior, cognitive performance, neuroimaging, and physiologic response), there has been limited standardization regarding methods or measures, making it difficult to interpret discordant finding. Fourth, there is a risk of publication bias against null findings and selective reporting. Finally, because PCE includes both substance exposure and environmental exposure to a drug-using lifestyle, comparison groups are difficult to define. Although analytical models may adjust for environmental differences, investigations of mechanisms and synergistic effects are often overlooked. For example, responsive caregiving and

low stress may alter brain structure⁵² and functioning,⁵³ thereby potentially protecting children from the negative consequences of PCE.

Summary

Compared with previous reviews, PCE continues to be associated with elevated behavioral problems, particularly externalizing problems.^{13,14} A promising area of behavioral research is adolescent drug use, particularly as youth age and are exposed to drug-using opportunities. Although the language vulnerability reported in previous reviews has continued into adolescence,^{11,14} effect sizes are small, raising concerns about their clinical importance. Executive functioning and neurocognition, identified in previous work as vulnerable areas for children with PCE,^{9,14} had few associations in adolescence; however, findings were mixed.

On the basis of this review, we identified 6 areas for future research. First, in addition to examining the direct effects of PCE and adjusting for potential confounders, investigators could use recent developmental theories⁵⁰ to examine the indirect effects of PCE on adolescent functioning. Second, most PCE/NCE differences are small and of unknown clinical importance. Understanding the clinical implications of differences (eg, the need for special educational services) and their response to intervention would be helpful. Third, although parent-child relationships related to PCE were an important area of research during early childhood, there has been little research on parent-child relationships during school-age and adolescence, including their potential ability to mitigate the negative effects of PCE on child and adolescent functioning.¹⁴ Fourth, only 3 studies considered adolescent internalizing problems. Because internalizing problems can be a precursor to subsequent mental health problems,

additional attention is warranted.²⁰ Fifth, little is known about the effects of the timing and dose of PCE. Although several investigators attempted to differentiate between heavy and light prenatal exposure, definitions differed, and there were few findings. Future research is needed to identify precise measures of the timing and dose of PCE. Finally, longitudinal investigations of patterns of strengths and weaknesses among children, adolescents, and adults with PCE would aid in our understanding of resilience and developmental consistency.

In conclusion, the field of PCE has advanced significantly since the misleading “crack baby” scare of the 1980s. Investigators have recognized (1) that the physiologic disruptions associated with PCE do not necessarily lead to behavioral or cognitive deficits, (2) that the

impact of PCE should be considered in the context of other prenatal and environmental exposures, and (3) that understanding life span development may depend on the relationships that physiologic responses and brain morphology/functioning play in response to stressful events, such as PCE, along with environmental and caregiving threats and opportunities.

Children in longitudinal research cohorts have reached adolescence, enabling us to examine long-term associations with PCE. As in earlier reviews, findings are often mixed, with evidence of small, but significant associations with development. However, there has not been a strong emergence of clinically relevant findings during adolescence, perhaps because development is influenced by multiple biological and environmental factors. What is evident

are the pervasive effects of poverty on both PCE and nonexposed youth.⁵ Many adolescents, regardless of their prenatal exposures, obtained scores on standardized measures at the low end of the normal range, possibly increasing their risk for future challenges across the life span. A better understanding of the mechanisms linking early stressors, including both poverty and PCE, with subsequent functioning will benefit the field of PCE and enhance our understanding of the determinants of adolescent development.

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REFERENCES

1. Substance Abuse and Mental Health Services Administration. *Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings* (NSDUH Series H-41, HHS Publication No. [SMA] 11-4658). Rockville, MD: Substance Abuse and Mental Health Services Administration; 2011
2. Zuckerman B. Drug exposed infants: Understanding the medical risk. *Drug Exposed Infants*. 1991;1(1):26–35
3. The National Center on Addiction and Substance Abuse at Columbia University. *Family Matters: Substance Abuse and the American Family*. New York, NY: Columbia University; 2005
4. Hans SL. Studies of prenatal exposure to drugs: focusing on parental care of children. *Neurotoxicol Teratol*. 2002;24(3):329–337
5. Farah MJ, Shera DM, Savage JH, et al. Childhood poverty: specific associations with neurocognitive development. *Brain Res*. 2006;1110(1):166–174
6. Gouin K, Murphy K, Shah PS; Knowledge Synthesis Group on Determinants of Low Birth Weight and Preterm Births. Effects of cocaine use during pregnancy on low birthweight and preterm birth: systematic review and metaanalyses. *Am J Obstet Gynecol*. 2011;204:340.e1–340.12
7. Nordstrom-Klee B, Delaney-Black V, Covington C, Ager J, Sokol R. Growth from birth onwards of children prenatally exposed to drugs: a literature review. *Neurotoxicol Teratol*. 2002;24(4):481–488
8. Held JR, Riggs ML, Dorman C. The effect of prenatal cocaine exposure on neurobehavioral outcome: a meta-analysis. *Neurotoxicol Teratol*. 1999;21(6):619–625
9. Bandstra ES, Morrow CE, Mansoor E, Accornero VH. Prenatal drug exposure: infant and toddler outcomes. *J Addict Dis*. 2010;29(2):245–258
10. Frank DA, Augustyn M, Knight WG, Pell T, Zuckerman B. Growth, development, and behavior in early childhood following prenatal cocaine exposure: a systematic review. *JAMA*. 2001;285(12):1613–1625
11. Cone-Wesson B. Prenatal alcohol and cocaine exposure: influences on cognition, speech, language, and hearing. *J Commun Disord*. 2005;38(4):279–302
12. Frank DA, Rose-Jacobs R, Crooks D, et al. Adolescent initiation of licit and illicit substance use: impact of intrauterine exposures and post-natal exposure to violence. *Neurotoxicol Teratol*. 2011;33(1):100–109
13. Ackerman JP, Riggins T, Black MM. A review of the effects of prenatal cocaine exposure among school-aged children. *Pediatrics*. 2010;125(3):554–565
14. Lester BM, Lagasse LL. Children of addicted women. *J Addict Dis*. 2010;29(2):259–276
15. Reyna VF, Chapman SB, Dougherty MR, Confrey J, eds. *The Adolescent Brain: Learning, Reasoning, and Decision Making*. Washington, DC: American Psychological Association; 2011
16. Steinberg L. Risk taking in adolescence: new perspectives from brain and behavioral science. *Curr Dir Psychol Sci*. 2007;16(2):55–59
17. Sisk CL, Zehr JL. Pubertal hormones organize the adolescent brain and behavior. *Front Neuroendocrinol*. 2005;26(3-4):163–174
18. Delaney-Black V, Chiodo LM, Hannigan JH, et al. Prenatal and postnatal cocaine exposure predict teen cocaine use. *Neurotoxicol Teratol*. 2011;33(1):110–119
19. Lagasse LL, Hammond J, Liu J, et al. Violence and delinquency, early onset drug use, and psychopathology in drug-exposed youth at 11 years. *Ann N Y Acad Sci*. 2006;1094:313–318
20. Whitaker TM, Bada HS, Bann CM, et al. Serial pediatric symptom checklist screening in children with prenatal drug exposure. *J Dev Behav Pediatr*. 2011;32(3):206–215

21. Greenwald MK, Chiodo LM, Hannigan JH, Sokol RJ, Janisse J, Delaney-Black V. Teens with heavy prenatal cocaine exposure respond to experimental social provocation with escape not aggression. *Neurotoxicol Teratol.* 2011;33(2):198–204
22. Bada HS, Bann CM, Bauer CR, et al. Pre-adolescent behavior problems after prenatal cocaine exposure: relationship between teacher and caretaker ratings (Maternal Lifestyle Study). *Neurotoxicol Teratol.* 2011; 33(1):78–87
23. Buckingham-Howes S, Oberlander SE, Kim EM, Black MM. Prenatal drug exposure and peer victimization in early adolescence: testing childhood anxiety/depression and aggression as possible mediators. *J Dev Behav Pediatr.* 2012;33(5):416–422
24. Riggins T, Cacic K, Buckingham-Howes S, Scaletti LA, Salmeron BJ, Black MM. Memory ability and hippocampal volume in adolescents with prenatal drug exposure. *Neurotoxicol Teratol.* 2012;34(4):434–441
25. Bauer CR, Lambert BL, Bann CM, et al. Long-term impact of maternal substance use during pregnancy and extrauterine environmental adversity: stress hormone levels of preadolescent children. *Pediatr Res.* 2011;70(2):213–219
26. Leri F, Bruneau J, Stewart J. Understanding polydrug use: review of heroin and cocaine co-use. *Addiction.* 2003;98(1):7–22
27. Substance Abuse and Mental Health Services Administration. *The DASIS Report: Polydrug Admissions, 2002*. Arlington, VA: Office of Applied Studies, Substance Abuse and Mental Health Services; 2005
28. Breaugh JA. Effect size estimation: factors to consider and mistakes to avoid. *J Manage.* 2003;29(1):79–97
29. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Hillsdale, NJ: Erlbaum; 1988
30. Chinn S. A simple method for converting an odds ratio to effect size for use in meta-analysis. *Stat Med.* 2000;19(22):3127–3131
31. Cohen J. A power primer. *Psychol Bull.* 1992;112(1):155–159
32. Warner TD, Behnke M, Eyler FD, Szabo NJ. Early adolescent cocaine use as determined by hair analysis in a prenatal cocaine exposure cohort. *Neurotoxicol Teratol.* 2011;33(1):88–99
33. Avants BB, Hurt H, Giannetta JM, et al. Effects of heavy in utero cocaine exposure on adolescent caudate morphology. *Pediatr Neurol.* 2007;37(4):275–279
34. Chaplin TM, Freiburger MB, Mayes LC, Sinha R. Prenatal cocaine exposure, gender, and adolescent stress response: a prospective longitudinal study. *Neurotoxicol Teratol.* 2010;32(6):595–604
35. Bridgett DJ, Mayes LC. Development of inhibitory control among prenatally cocaine exposed and non-cocaine exposed youths from late childhood to early adolescence: the effects of gender and risk and subsequent aggressive behavior. *Neurotoxicol Teratol.* 2011;33(1):47–60
36. Betancourt LM, Yang W, Brodsky NL, et al. Adolescents with and without gestational cocaine exposure: longitudinal analysis of inhibitory control, memory and receptive language. *Neurotoxicol Teratol.* 2011;33(1): 36–46
37. Hurt H, Betancourt LM, Malmud EK, et al. Children with and without gestational cocaine exposure: a neurocognitive systems analysis. *Neurotoxicol Teratol.* 2009;31(6): 334–341
38. Hurt H, Giannetta JM, Korczykowski M, et al. Functional magnetic resonance imaging and working memory in adolescents with gestational cocaine exposure. *J Pediatr.* 2008;152(3):371–377
39. Li Z, Santhanam P, Coles CD, et al. Increased “default mode” activity in adolescents prenatally exposed to cocaine. *Hum Brain Mapp.* 2011;32(5):759–770
40. Li Z, Coles CD, Lynch ME, et al. Prenatal cocaine exposure alters emotional arousal regulation and its effects on working memory. *Neurotoxicol Teratol.* 2009;31(6): 342–348
41. Rao H, Wang J, Giannetta J, et al. Altered resting cerebral blood flow in adolescents with in utero cocaine exposure revealed by perfusion functional MRI. *Pediatrics.* 2007; 120(5). Available at: www.pediatrics.org/cgi/content/full/120/5/e1245
42. Liu J, Cohen RA, Gongvatana A, Sheinkopf SJ, Lester BM. Impact of prenatal exposure to cocaine and tobacco on diffusion tensor imaging and sensation seeking in adolescents. *J Pediatr.* 2011;159(5):771–775
43. Landi N, Crowley MJ, Wu J, Bailey CA, Mayes LC. Deviant ERP response to spoken non-words among adolescents exposed to cocaine in utero. *Brain Lang.* 2012;120(3): 209–216
44. Lester BM, Lagasse LL, Shankaran S, et al. Prenatal cocaine exposure related to cortisol stress reactivity in 11-year-old children. *J Pediatr.* 2010;157(2):288–295, e1
45. Levine TP, Lester B, Lagasse L, et al. Psychopathology and special education enrollment in children with prenatal cocaine exposure. *J Dev Behav Pediatr.* 2012;33(5):377–386
46. Gerteis J, Chartrand M, Martin B, et al. Are there effects of intrauterine cocaine exposure on delinquency during early adolescence? A preliminary report. *J Dev Behav Pediatr.* 2011;32(5):393–401
47. Rivkin MJ, Davis PE, Lemaster JL, et al. Volumetric MRI study of brain in children with intrauterine exposure to cocaine, alcohol, tobacco, and marijuana. *Pediatrics.* 2008;121(4):741–750
48. Rose-Jacobs R, Soenksen S, Appugliese DP, et al. Early adolescent executive functioning, intrauterine exposures and own drug use. *Neurotoxicol Teratol.* 2011;33(3):379–392
49. Bandstra ES, Morrow CE, Accornero VH, Mansoor E, Xue L, Anthony JC. Estimated effects of in utero cocaine exposure on language development through early adolescence. *Neurotoxicol Teratol.* 2011;33(1): 25–35
50. Ellis BJ, Boyce WT, Belsky J, Bakermans-Kranenburg MJ, van Ijzendoorn MH. Differential susceptibility to the environment: an evolutionary—neurodevelopmental theory. *Dev Psychopathol.* 2011;23(1):7–28
51. Lester BM, Padbury JF. Third pathophysiology of prenatal cocaine exposure. *Dev Neurosci.* 2009;31(1-2):23–35
52. Luby JL, Barch DM, Belden A, et al. Maternal support in early childhood predicts larger hippocampal volumes at school age. *Proc Natl Acad Sci USA.* 2012;109(8): 2854–2859
53. Shonkoff JP, Garner AS; Committee on Psychosocial Aspects of Child and Family Health; Committee on Early Childhood, Adoption, and Dependent Care; Section on Developmental and Behavioral Pediatrics. The lifelong effects of early childhood adversity and toxic stress. *Pediatrics.* 2012; 129(1). Available at: www.pediatrics.org/cgi/content/full/129/1/e232