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Dysmorphic and anthropometric outcomes in 6-year-old prenatally cocaine-exposed children

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Abstract

Dysmorphologic and anthropometric assessments were performed on 154 6-year-old children prenatally exposed to cocaine (PCE) and 131 high-risk controls (NCE) of similar race and social class. Adjusted mean height *z* scores demonstrated a dose–response with metahydroxybenzoylecgonine above a threshold of 100 ng/g of meconium and greater cocaine exposure predicted lower weight for height *z* score. Higher average alcohol exposure throughout pregnancy and 3rd trimester predicted lower head circumference and weight *z* scores, respectively. Severity of marijuana use also predicted lower height for age but greater weight for height. There was not an increased rate of minor anomalies among the PCE cohort, nor was a consistent phenotype identified. After controlling for covariates, higher average prenatal cigarette exposure predicted higher incidence of cranial facial abnormalities. First trimester alcohol exposure predicted greater rates of ear abnormalities and third trimester marijuana exposure predicted greater rates of chest and head shape abnormalities. These finding indicate that prenatal cocaine exposure has a negative effect on specific growth outcomes including standardized height and weight for height, but not a systematic pattern of structural abnormalities.

Keywords: Dysmorphology; Prenatal cocaine-exposure; Anthropometric; Height; Cocaine metabolite; Meconium

1. Introduction

Prenatal cocaine exposure (PCE) has been associated with a variety of adverse peri- and neonatal effects [32]. Included among these are prematurity, low birth weight, microcephaly, and newborn neurobehavioral abnormalities [35,37]. Vasoconstrictive effects of cocaine on the placenta [39] have raised additional concerns including increased dysmorphologic abnormalities and birth defects among exposed children. It is believed that disruptions in fetal blood flow could result in various structural abnormalities during gestation [17,32], depending on the severity and timing of cocaine exposure. However, the association between prenatal cocaine exposure and dysmorphologic abnormalities has been reported sporadically through case studies and research reports, and has not been replicated in well controlled studies at ages beyond birth. For example, Bingol et al. [7] reported an increased rate of major anomalies (exencephaly, encephalocoele) among PCE newborns compared to controls (non-drug exposed and those exposed to other drugs). They noted no difference in the occurrence of minor anomalies, such as hypertelorism, epicanthal folds, and micrognathia. In another study Hoyme et al. [18] reported on a small cohort of cocaine-exposed newborns with limb reduction defects and/or intestinal atresias, and suggested that in utero cocaine exposure may be causally related to these vascular anomalies. However, a large-scale prospective study that controlled for a large number of covariates does not support these findings. Behnke et al. [6], using 16 anthropometric measurements and a checklist of 180 physical features, in 154 prenatally cocaine-exposed infants

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and 154 non-using controls, did not identify an increased number or consistent pattern of abnormalities.

Related to fetal growth however, there are consistent findings indicating that after consideration of a large number of covariates, prenatal cocaine exposure has specific effects on infant birth parameters including head circumference, weight and length [4,5,9,11,12,31,37,41]. Growth deficits are believed to result from poor maternal nutrition, restricted placental blood flow or some other unknown mechanism. But not all studies have found a specific cocaine effect for fetal growth. Jacobson et al. [19] and Miller et al. [25] found that after control for other substances there were not weight or length differences specifically related to prenatal cocaine exposure. In later childhood (>1 year) research on cocaine effects on growth outcome is limited, and the results are contradictory. Jacobson et al. [20] reported an independent effect of prenatal cocaine exposure on weight, but not height at 13 months. Richardson [29] found an effect of prenatal cocaine exposure on head circumference, but not weight and height at 3 years of age after control for demographic and other substance exposure. In another study by Richardson et al. [30] no effect of prenatal cocaine exposure on height, weight, or head circumference was found at 6 years of age. In the only report on growth parameters at 7 years of age, after control for other exposures and demographic variables, Covington [11] found that cocaine-exposed children were up to 1 in. shorter and twice as likely to fall below the 10th percentile in height compared to controls. This relationship was mediated by maternal age, with children born to women over 30, 2 in. shorter and four times more likely to have clinical height deficits.

The possible association of PCE with a recognizable pattern of physical findings was suggested by Fries et al. [13] and Robin and Zackai [33]. Each described similar facial and other physical findings in PCE infants that could be distinguished from those associated with prenatal exposure to alcohol or other drugs. These findings included a large anterior fontanel, prominent glabella, periorbital and eyelid edema, low nasal bridge with transverse crease, short nose with lateral buildup, and hypoplastic toenails. The authors concluded that PCE may cause a distinct phenotype. However, this assertion was challenged by a subsequent study. Little et al. [24] examined 25 prenatally cocaine-exposed newborns and 25 controls blinded to their cocaine status. They did not identify a higher rate of major or minor anomalies among the PCE children. However, they did find growth retardation and microcephaly among the PCE newborns. While this study examined both dysmorphia and growth retardation, it was limited in several ways. The study included a relatively small cohort, and was restricted to newborns. Some subtle findings may be difficult to identify in infants, or may be apparent only in older children. In an effort to explore the relationship between in-utero cocaine exposure and physical anomalies, we performed anthropometric and dysmorphologic examinations on a large sample of prenatally cocaine-exposed 6-year-old children and a high-risk control group. In addition to having a large sample size, determination of cocaine status was made through infant meconium analyses at birth, insuring correct subject grouping. It was hypothesized that children exposed to cocaine would exhibit a higher rate of dysmorphic features and maintain growth deficits identified at infant birth compared to a control group similar in race, social class and high-risk status at birth.

2. Methods

2.1. Participants

Between September 1994 and June of 1996, 415 infants (218 prenatally cocaine-exposed (PCE) and 197 non-cocaine-exposed (NCE)) were recruited from a large urban teaching hospital to participate in a longitudinal follow-up study evaluating the developmental effects of prenatal cocaine exposure from birth through 6 years of age [36]. Women determined to be at risk for prenatal substance abuse due to previous involvement with the Department of Human Services, lack of prenatal care, behavior suggesting intoxication, or self admitted drug use, were given urine drug toxicology screenings (99%). The Syva Emit method (Syva Company, Palo Alto, CA) was used for urine analyses. Positive analyses were followed up with gas chromatography. A nurse recruiter approached women screened for substance abuse. Of the women and infants identified (647), 54 were excluded (20 PCE; 34 NCE) for the following reasons: no meconium sample (15), Down Syndrome (2), maternal psychiatric history (16), primary heroin use (2), HIV positive (5), maternal low IQ (1), fetal alcohol syndrome (1), maternal age <19 years (2), infant medical illness or congenital malformation (3) maternal chronic illness (4) and other (3). One hundred and fifty five women refused to participate (49 positive, 106 negative) and 23 (9 PCE, 14 NCE) failed to come to the enrollment visit. Four hundred and fifteen women and their infants enrolled in the study. Upon agreement to participate in the study, women signed a consent form approved by the hospital's institutional review board.

For study participants, an additional biologic marker of cocaine/polydrug use, infant meconium, was collected for analyses of cocaine and its metabolites (benzoylecgonine (BZE), meta-hydroxybenzoylecgonine (m-OH-bze). Cocaethylene, a metabolite present when cocaine and alcohol are used in combination, as well as other drugs of abuse including cannabinoids (THC), opiates, phencyclidine, amphetamines, and benzodiazepines [22,28] were also assessed. Meconium sampling was completed by collecting successive diapers from the same newborn and scraping the meconium from the diaper with a wooden spatula. The sample was stirred for 5 min to insure homogeneity and kept refrigerated until analysis. Assays were completed using Abbott Diagnostic polarization immunoassay reagents (FPIA) (United States Drug Testing Laboratories, Des Plaines, IL). Cutoff levels for cocaine and metabolites were 25 ng/g. Confirmatory assays were performed on positive screening assays using gas chromatography-mass spectrometry (GC/MS) operated in electron impact, selected ion monitoring mode. Cocaine exposure status was identified by a positive response on any of the following measures: infant meconium or urine, maternal urine, or report to hospital or

research staff. For 11 (6%) control subjects, meconium was unavailable, but all other screenings and follow-up indicated no evidence of infant exposure. Cocaine-exposed infants were further subdivided into heavier and lighter cocaine exposure. Heavier cocaine exposure was defined as cocaine exposure above the 70th percentile for concentrations of cocaine metabolites in meconium, and/or above the 70th percentile for self-report. The lighter exposure group was at the 70th percentile or below for all measures. Exposure to nicotine, alcohol, and marijuana was also identified through a combination of self-report and meconium metabolites for nicotine and marijuana, and used for phenotype correlations. Assurance of confidentiality was afforded to all participants through a Writ of Confidentiality (DA-98-91) issued by the National Institutes on Drug Abuse for the purposes of protecting the principal investigator from releasing drug use history data, even under court order or subpoena.

Approximately 6 years after infant birth, 404 subjects were available for participation in this dysmorphology study (11 subjects had died since infant birth). Thirty-four of the available subjects were unable to be contacted (lack of working phone, changed address, missing) and 17 had dropped out of the study. Three hundred and fifty three caregivers were approached by research staff and asked to participate in the dysmorphology and anthropometric examination. Of those contacted, 285 gave written consent approved by the institutional review board and were given the dysmorphology exam. The final sample represents 70% of the original living cohort and 76% of those seen at the 6-year cognitive assessment. Sixty-eight of approached subjects were not able to schedule an appointment when the geneticist was available.

2.2. Procedure

Infant birth and maternal medical and demographic data including maternal race, age, parity, number of prenatal care visits, education level, type of medical insurance, socioeconomic status [16], infant gestational age, birth weight, length, head circumference, and Apgar scores were computed from hospital records. As soon as possible after infant birth (median = 3.43 weeks; interquartile range; 2.29–6.43 weeks) a research assistant assessed infants and caregivers. Biologic mothers were interviewed regarding prenatal drug use using the Maternal Post-Partum Interview [36–38] adapted for this study. Fetal drug exposure was quantified by asking mothers to recall frequency and amount of drug use for the month prior to and for each trimester of pregnancy. Number of tobacco cigarettes and marijuana joints smoked, and the number of drinks containing alcohol (each drink equivalent to .5 oz of absolute alcohol) was computed. The majority of women used crack cocaine (91.2%). Therefore the number of approximately $20 rocks and the dollar amount of other forms of cocaine (intranasal, injections) consumed were noted. A standardized "unit" was developed based on a rock/other form equivalent. For each drug, frequency of use was recorded on a scale ranging from 0 (not at all) to 7 (daily use). An average dose per week was computed by multiplying the amount of reported drug use per occasion by the number of days per week for the month prior to pregnancy and each +trimester. This score was then averaged to obtain a total average amount of exposure over the pregnancy for each drug.

Anthropometric and dysmorphologic examinations and neuromotor strength screenings were completed by a board certified clinical geneticist (NHR), blind to subject group at a mean assessment age of 6.65 ± .4 years. The age range of subjects assessed was from 5.4 to 8 years. Anthropometric measurements included head circumference, height, weight, inter-pupil distance, inner and outer canthal distance, ear length, chest circumference, inter-nipple distance, palm and total hand length, total foot length, arm span and lower segment (top of pubic symphysis to the floor). Each measurement was done twice, and the average taken for final analysis. Measurement percentiles were computed using published gender matched growth curves for each measurement [14] and were also converted to *z* scores. At birth and 6.5 years height, weight and head circumference only were available for the whole sample, not just those receiving the dysmorphology exam. Therefore, all analyses concerning height, weight and head circumference have an *n* of 415 at birth and 365 at 6 years.

The dysmorphologic examination followed a standardized checklist[1] that was developed for this study. The presence or absence of 271 common dysmorphic characteristics including maxillary hypoplasia, frontal bossing, low set ears, hypertelorism, and mandibular hypoplasia were evaluated and summarized into 53 main body areas. Body areas such as facies, head shape, hair texture, hair distribution, eyes, lips, mouth, and palate were then coded as abnormal or normal based on all individual observations. Body areas were grouped into major regions that consisted of craniofacial, limb or extremities, and other abnormalities (neck, chest, abdomen, genitor-urinary, spine and skin) and coded as abnormal if any one of the body areas included in that region was abnormal. A lip-philtrum guide developed by the University of Washington FAS diagnostic and Prevention Network [3] was used to assess philtrum smoothness and upper lip thinness. A score of 5 represents the smooth philtrum and thin upper lip seen in fetal alcohol syndrome. A score of 1 represents a normal score with a very deep philtrum and full upper lip. A neuromotor exam included an assessment of cranial nerve function, motor strength, muscle mass and cerebellar function. The total examination was completed in approximately 45 min. All subjects were given $45 compensation for participation in the study.

2.3. Statistical analyses

Prior to analyses, continuous variables were examined for distributional characteristics using stem-and-leaf and quantile-quantile plots for deviations from normality. Variables that were positively skewed, including drug self-report measures

[1] Checklist is available upon request.

and meconium quantification variables, were normalized by log $(x+1)$ transformation prior to analyses. Means and standard deviations are reported in terms of the original distribution. Groups were compared on demographic variables, drug use severity measures, infant birth and maternal characteristics and anthropometric and dysmorphic outcomes using t tests for continuous data and Pearson χ^2 or Fisher's exact tests for categorical variables. ANOVA models were used for comparison of continuous data by three groups (none, lighter, or heavier fetal cocaine exposure). Summary dysmorphology variables (craniofacial, limb, and other findings) and subgroups that were different by cocaine status at $p<.20$ were further evaluated for a cocaine effect using logistic regression models. Potential covariates including race, maternal age, parity, and prenatal drug exposure including alcohol, marijuana and tobacco by trimester and averaged over pregnancy were correlated with outcome variables using Spearman and Pearson's correlations and were evaluated in regression models if correlated at $p<.20$. Variables remained in the model if they predicted the outcome at $p<.10$ or less. Six-year height, weight, head circumference and weight for height data were converted to z scores [8]. Cocaine effects were evaluated using linear regression models controlling for previously mentioned covariates plus potential environmental factors including HOME scores, maternal IQ, psychological symptoms, and caregiver status (relative versus foster/adoptive care) assessed at the regular 6-year assessment visit by interview or self report. Generalized additive models (GAM) [15] were used to identify the functional form (dose–response) of the relationship between cocaine severity and anthropometric outcome after adjusting for potential cofounders. The GAM models were fit with a non-parametric loess function of log (cocaine severity) to describe the functional form. Based on the results from a plot of the predicted log (cocaine severity) versus growth (e.g., height-for-age z score), a threshold dose–response was identified and a piecewise linear model was then fit to allow for the threshold effect.

3. Results

NCE subjects that did not receive the dysmorphology exam ($n=63$) were more likely to have fewer siblings ($p=.03$), to have been exposed to alcohol ($p=.008$) and more average tobacco per day prenatally ($p=.03$) then non-cocaine-exposed children who were seen for a dysmorphology exam. NCE subjects who did not receive the dysmorphology exam were also less likely to have been African-American ($p=.008$) than NCE receiving the exam. Among the PCE group, those not seen for a dysmorphology exam ($n=56$) were more likely to have been exposed prenatally to tobacco ($p=.02$), and have larger head circumferences at birth ($p=.008$) than those who had exams. They were also less likely to be African-American ($p=.01$). There were no differences in the amount of prenatal cocaine exposure for children who had dysmophology exams versus those who did not. All other demographic and drug use variables were not different by group.

3.1. Demographic and substance exposure characteristics

Maternal demographic and fetal substance exposure characteristics are presented in Table 1. Mothers of both groups were primarily African-American and of low socio-economic status. Cocaine-using women were older at the time of infant birth, had more children, and were less likely to have had prenatal care or be employed. Maternal head circumference and height were not different by group. Cocaine-using women also reported using more average cigarettes per day, and alcohol and marijuana per week during all trimesters of their pregnancy than non-cocaine-using women (Table 2). After adjustment for prematurity, the PCE group was significantly lower in weight, length, and head circumference than the NCE group at birth (see Table 3). While the groups were not different for gestational age, the percentage of children born less than 2500 g and the percentage small for gestational age was greater for the PCE group.

Table 1
Maternal characteristics at birth by cocaine status

Maternal characteristics	Cocaine ($n=154$)		Non-cocaine ($n=131$)		t	p-value
	Mean	SD	Mean	SD		
Years of education	11.68	1.7	11.93	1.5	1.33	0.19
Age (years)	29.82	5.1	25.69	4.9	−7.00	<0.0001
Parity	3.38	1.8	2.86	1.9	−2.41	0.02
Gravida	4.94	2.3	3.89	2.2	−3.96	<0.0001
Number of prenatal visits	5.36	4.4	8.77	4.8	6.24	<0.0001
Head circumference (cm)	55.70	2.4	56.15	2.3	1.41	0.16
Height (cm)	162.52	7.8	163.52	7.0	1.00	0.32
	n	%	N	%	χ^2	p-value
Race (African-American)[a]	131	85.1	111	84.7	0.0061	0.94
No prenatal care[a]	26	16.9	11	8.4	4.51	0.03
Maternal employment[a]	9	5.9	27	20.8	14.03	0.0002
Married [a]	15	9.7	23	17.6	3.74	0.05
Low socioeconomic status [b]	151	98.7	127	97.0	1.04	0.31

[a] Indicates yes/no variables.
[b] Low socio economic status determined using the Hollingshead scale.

Table 2
Maternal drug use characteristics

Maternal drug use	Cocaine ($n=154$)		Non-cocaine ($n=131$)		t	p-value
	Mean	SD	Mean	SD		
Cigarette/day						
Month prior	12.9	13.0	4.8	9.6	−8.51	<0.0001
1st trimester	11.9	12.7	3.3	7.5	−9.79	<0.0001
2nd trimester	10.2	11.9	2.5	6.4	−9.84	<0.0001
3rd trimester	8.6	11.1	2.2	4.7	−8.70	<0.0001
Average	10.9	11.4	3.2	5.6	−9.61	<0.0001
Alcohol drinks/week[a]						
Month prior	12.5	23.7	2.1	6.3	−7.45	<0.0001
1st trimester	11.9	25.1	1.3	3.7	−7.82	<0.0001
2nd trimester	7.9	20.4	0.6	3.3	−7.50	<0.0001
3rd trimester	5.7	17.1	1.5	9.2	−6.03	<0.0001
Average	9.5	17.9	1.4	4.9	−9.27	<0.0001
Marijuana joints/week[a]						
Month prior	1.6	3.8	1.1	7.3	−3.69	0.0003
1st trimester	1.5	4.2	0.7	4.2	−3.33	0.0010
2nd trimester	1.5	4.6	0.3	2.0	−3.89	0.0001
3rd trimester	1.1	4.1	0.1	0.9	−3.26	0.0013
Average	1.4	3.6	0.5	3.4	−4.20	<0.0001
Average cocaine units/week	21.3	36.2				
Average cocaine metabolites in meconium (ng/g)						
Cocaine	172.3	489.9				
Cocaethylene	14.9	57.4				
Benzolylecgonine	520.4	1365.6				
M-OH-benzoylecgonine	297.3	1352.2				
	n	%	n	%	χ^2	p-value
Alcohol use[b]	125.0	81.2	76.0	59.8	21.06	<0.0001
Marijuana use[b]	74.0	50.0	17.0	13.4	41.38	<0.0001
Tobacco use[b]	126.0	85.1	48.0	37.8	65.91	<0.0001
Amphetamine use[b]	3.0	2.0	1.0	0.8	0.73	0.39
Barbiturate use[b]	1.0	0.7	1.0	0.8	0.01	0.91
Benzodiazepine use[b]	15.0	13.0	0.0	0.0	13.89	0.0002
Heroin use[b]	3.0	2.0	0.0	0.0	2.60	0.11
PCP use[b]	8	5.4	0.0	0.0	7.01	0.01

[a] Number of drinks, joints per day x number of days/week.
[b] Indicates yes/no variable.

Table 3
Infant birth characteristics by cocaine status

Infant birth characteristics	Cocaine ($n=154$)		Non-cocaine ($n=131$)		t	p-value
	Mean	SD	Mean	SD		
Gestational age (weeks)	37.8	2.9	38.3	3.0	1.35	0.18
Birth weight (g)[a]	2710	678.0	3086	704.0	5.58	<0.0001
Birth length (cm)[a]	47.2	4.2	49.0	3.9	3.76	0.0002
Head circumference (cm)[a]	32.3	2.3	33.4	2.5	4.21	<0.0001
Apgar (1 min)	8.0	1.4	7.9	1.6	−0.12	0.91
Apgar (5 min)	8.8	0.7	8.7	0.8	−0.24	0.81
Hobel neonatal risk score	8.1	17.9	6.7	18.1	−0.66	0.51
	n	%	n	%	χ^2	p−value
Gender (male)	72	46.8	63	48.1	0.05	0.82
African-American	130	84.4	110	84.0	0.01	0.92
Prematurity (<37 weeks gestational age)	44	28.6	27	20.6	2.40	0.12
Low birth weight (<2500 g)	53	34.4	29	22.1	5.21	0.02
Very low birth weight (<1500 g)	10	6.5	6	4.6	0.49	0.48
Small for gestational age	19	12.5	3	2.3	10.12	0.0015

p's adjusted for prematurity.
[a] Entire sample used for measurement [cocaine ($n=218$), non-cocaine ($n=197$)].

Table 4
Six-year anthropometric data

Measure*	Cocaine ($n=154$)		Non-cocaine ($n=131$)		t	p-value
	Mean	SD	Mean	SD		
Age at measurement (years)	6.5	0.4	6.5	0.4	−0.08	0.93
Weight (kg)[a]	22.8	4.7	23.6	5.2	1.65	0.10
Height (cm)[a]	116.6	5.4	117.3	5.2	1.40	0.16
Head circumference (cm)[a]	51.5	1.5	51.7	1.8	0.99	0.32
Weight-for-age[a,b]	0.4	1.1	0.6	1.1	1.53	0.13
Height-for-age[a,b]	0.1	1.0	0.2	1.0	0.80	0.43
Head circumference-for-age[a,b]	1.6	1.0	1.7	1.2	0.86	0.39
Weight-for-height[a,b]	0.36	1.1	0.5	1.0	0.68	0.50
Lower segment	59.9	3.7	60.1	3.7	0.49	0.63
Upper segment	58.7	2.6	58.4	3.0	−0.67	0.50
Chest circumference	58.7	5.3	59.1	6.2	0.64	0.53
Inter nipple distance	12.6	1.5	12.6	1.5	0.04	0.96
Palpebral fissure length right	2.6	0.2	2.7	0.3	1.98	0.05
Palpebral fissure length left	2.6	0.2	2.7	0.3	1.33	0.19
Inter pupil distance	5.5	0.3	5.5	0.3	0.06	0.95
Inner canthal distance	2.9	0.3	2.9	0.3	−0.92	0.36
Outer canthal distance	7.9	0.4	7.9	0.4	0.72	0.47
Ear length right	5.5	0.4	5.5	0.4	1.47	0.14
Ear length left	5.5	0.4	5.5	0.4	1.71	0.09
Arm span	121.6	6.5	122.2	6.8	0.79	0.43
Height-span	−3.0	3.2	−3.7	3.3	−1.88	0.06
Total right	13.7	0.8	13.8	0.8	0.78	0.44
Total hand left	13.7	0.8	13.8	0.8	1.07	0.28
Total palm right	7.8	0.5	7.9	0.5	1.52	0.13
Total palm left	7.8	0.5	7.9	0.5	1.88	0.06
Total foot right	19.4	1.3	19.5	1.4	0.36	0.72
Total foot left	19.2	1.3	19.3	1.4	0.52	0.60
	n	%	n	%	χ^2	p-value
%Weight-for-age[a,c]	15.0	8.1	11.0	6.2	0.51	0.48
%Height-for-age[a,c]	14.0	7.5	10.0	5.6	0.56	0.45
%Head circumference-for-age[a,c]	1.0	0.6	0.0	0.0	0.96	0.33
%Weight-for-height[a,c]	9	7.4	8	7.2	0.005	0.96

*All measurements are in centimeters unless otherwise noted.
[a] Entire sample used for measurement [cocaine ($n=186$), non-cocaine ($n=179$)].
[b] z-score measures.
[c] Percent less than the 10th percentile.

3.2. Anthropometric characteristics

Results for all anthropometric measurements by cocaine status are reported in Table 4. Right palpebral fissure length was significantly longer for the PCE group than the NCE group (see Table 4). There were non-significant trends for the PCE group to have lower 6-year weight, longer left ear length, lower height span and shorter total left palm length. When height, weight, and head circumference percentiles were dichotomized ($\leq$10th percentile and >10th percentile) no significant group differences were found. Controlling for demographics and other prenatal drug exposures, there were specific cocaine effects for left total palm length only (see Table 5). African-American race predicted larger palpebral fissure length. Greater number of cigarettes per week during the second trimester predicted smaller right palpebral fissure length. Greater average exposure to alcohol during gestation predicted smaller right ear length. Non African-American race predicted smaller height span. Higher average tobacco exposure during the third trimester predicted larger height span. African-American race predicted higher left total palm length. When evaluated by none, lighter, and heavier cocaine exposure, only right palpebral fissure had a trend for group differences (none=2.67±.02, lighter=2.64±.03, heavier=2.59±.03; ($F=2.91$; $p=.06$). Follow-up tests indicated a significant difference for heavily exposed children to have a smaller

Table 5
Association of anthropometric measures with prenatal drug use

Outcomes and covariates	Estimate (β)	SE	p-value
Right palpebral fissure length			
Race (African-American)	0.08	0.04	0.04
Log of number of cigarettes/week 2nd trimester	−0.03	0.01	0.02
Right ear length			
Log of average alcohol dose/wk	−0.05	0.02	0.005
Height-span			
Race (African-American)	−1.67	0.55	0.003
Log of number of cigarettes/week 3rd trimester	0.31	0.16	0.05
Left total palm			
Race (African-American)	0.39	0.07	<0.0001
Cocaine (yes versus no)	−0.10	0.05	0.05

Table 6
Association of weight, height, and head circumference *z*-scores, at 6 years, with prenatal drug use

Outcomes and covariates[a]	Estimate (β)	SE	*p*-value
Height for age *z*-score			
Parity	−0.08	0.03	0.02
Number of prenatal visits	0.02	0.01	0.08
Race	0.40	0.15	0.006
Log of average alcohol dose/week	−0.06	0.05	0.24
Log of average marijuana dose/week	−0.18	0.09	0.05
Log of nanograms/gram of M-OH-Benzoylecgonine (Slope 1)	0.07	0.04	0.08
Log of nanograms/gram of M-OH-Benzoylecgonine (Slope 2)	−0.23	0.14	0.05
Weight for age *z*-score			
Parity	−0.06	0.03	0.05
Number of prenatal visits	0.02	0.01	0.10
Race	0.38	0.15	0.01
Log of alcohol dose/week 3rd trimester	−0.13	0.06	0.03
Head circumference for age *z*-score			
Parity	−0.04	0.03	0.18
Log of average alcohol dose/week	−0.12	0.05	0.03
Weight for height *z*-score			
Number of prenatal visits	0.02	0.01	0.19
Log of average marijuana dose/week	0.31	0.09	0.0006
Log of average cocaine units/week	−0.09	0.04	0.05

[a] Entire sample used for measurement [cocaine ($n=186$), non-cocaine ($n=179$)].

palpebral fissure length than non-exposed infants ($t=5.57$; $p=.02$).

Statistical modeling identified a threshold effect at log(m-OH-bze) of 4.61 (corresponding to a m-OH-bze level of approximately 100 ng/g) with height *z* score. The mean, standard deviation and median for m-OH-bze are 297±1352 and 0, respectively. The regression coefficients from the two-slope regression model, incorporating this threshold effect and controlling for confounding effect, are reported in Table 6. The first slope assesses the relationship between log(m-OH-bze) and height *z* score before the bend (log(m-OH-bze)<4.61), while the second slope describes the relationship after the bend. There is some evidence of a relationship between log(m-OH-bze) and height for log(m-OH-bze)<4.61 (slope=0.07, $p=0.08$). However, at levels of log(m-OH-bze)>4.61, there was a significant linear relationship with height (slope=−0.23, $p=0.05$). Other significant predictors of lower 6-year height *z* score were non African-American race, higher average prenatal marijuana exposure ($p=.02$), and more siblings at birth.

Weight for height *z* score was predicted by level of prenatal cocaine exposure indicating that for a given height, higher average prenatal cocaine exposure was related to lower weight. Log of average marijuana dose per week was also a significant predictor of weight for height *z* score. For a given height,

Table 7
Presence of dysmorphic features by cocaine status[a]

Abnormality	Cocaine ($n=154$)		Non-cocaine ($n=131$)		t/χ^2	*p*-value
	N	%	*N*	%		
Craniofacial	140	90.9	116	88.6	0.43	0.51
Mouth	84	54.6	75	57.3	0.21	0.65
Ear	111	72.1	85	64.9	1.71	0.19
Eye	114	74.0	91	69.5	0.73	0.39
Facies	52	33.8	41	31.3	0.20	0.66
Head shape	19	12.4	8	6.2	3.20	0.07
Nose	120	78.4	101	77.1	0.07	0.79
Lips (mean, SD)[b]	2.14	1.1	2.13	1.1	−0.07	0.94
Philtrum (mean, SD)[b]	2.43	1.2	2.40	1.2	−0.25	0.80
Limb	108	70.1	100	76.3	1.38	0.24
Hands	63	40.9	57	43.5	0.20	0.66
Skin	94	61.0	87	66.4	0.88	0.35
Arms*	2	1.3	2	1.6	0.03	1.00
Legs*	0	0.0	1	0.8	1.20	0.46
Feet	66	43.1	59	45.7	0.19	0.66
Other findings	137	89.0	118	90.1	0.09	0.76
Hair	9	5.8	11	8.4	0.71	0.40
Chest	34	22.1	19	14.5	2.68	0.10
Neurologic*	4	2.6	0	0.0	0.82	0.13
Forehead	73	47.4	54	41.2	1.09	0.30
Neck*	6	3.9	1	0.8	2.87	0.13
Abdomen	7	4.6	4	3.1	0.45	0.51
Genito-urinary	8	5.4	6	4.7	0.07	0.80
Spine	9	5.9	6	4.6	0.22	0.64
Joints	15	9.7	14	11.1	0.14	0.71
Motor*	4	2.6	0	0.0	3.37	0.13
Total anomalies/subject (mean, SD)[b]	14.97	5.7	14.55	5.7	−0.62	0.54

*Fisher's Exact test used due to small sample size.
[a] Indicates number and percent with abnormal features (coded as yes/no).
[b] Expressed as mean and standard deviation.

Table 8
Association of dysmorphology measures with prenatal drug use

Outcomes and covariates	OR	95% CI	*p*-value
Craniofacial			
Log of average cigarettes/day	1.41	1.00–1.97	0.05
Limb			
Log of number of cigarettes/3rd trimester	0.81	0.66–1.01	0.06
Ear			
Race (African-American)	0.33	0.13–0.83	0.02
Log of average cigarettes/day	1.10	0.87–1.39	0.41
Log of alcohol dose/week 1st trimester	1.31	1.03–1.68	0.03
Chest			
Race (African-American)	0.41	0.19–0.87	0.02
Log of marijuana dose/week 3rd trimester	1.88	1.16–3.05	0.01
Head shape			
Log of marijuana dose/week 3rd trimester	1.91	1.16–3.15	0.01

higher average prenatal marijuana exposure was related to heavier weight. Head circumference was not different by cocaine status. Only greater average prenatal alcohol exposure predicted lower head circumference *z* score. Of note is that the only case of microcephaly at 6 years was in a heavily cocaine-exposed child. Non African-American race, having more children, and higher third trimester prenatal alcohol exposure were significant predictors of lower weight *z* score.

3.3. Dysmorphology outcomes

Higher rate of dysmorphic abnormalities, summarized into major categories, craniofacial, limb/extremities, other findings and total anomalies/subject were not seen more commonly among the PCE cohort than NCE (see Table 7). Furthermore, the mean number of total anomalies in each group was almost identical: 15.0 (±5.7) for PCE, 14.6 (±5.7) for NCE. Neurologic and motor strength abnormalities were found to occur exclusively among PCE children (4 versus 0). While both groups had a relatively high rate of minor findings, there was no consistent pattern. When dysmorphic features were further evaluated by none, lighter, and heavier prenatal cocaine exposure, there were no statistically significant group differences. Once other potential confounding factors and other prenatal drug exposure were controlled, there were no specific effects of prenatal cocaine exposure on rates of dysmorphic features (see Table 8). Higher average prenatal tobacco exposure significantly increased the likelihood of craniofacial abnormalities and there was a non-significant trend for average 3rd trimester tobacco exposure to predict limb abnormalities. Higher average exposure to alcohol during the first trimester of pregnancy, and non African-American race predicted higher rates of ear abnormalities. Abnormal chest and head shape were predicted by higher average exposure to marijuana during the third trimester. Chest abnormalities were also predicted by non African-American race.

4. Discussion

Consistent with our hypothesis that prenatal cocaine exposure would have an effect on long-term growth, heavier prenatal exposure to cocaine negatively affected height and height for weight *z* scores at age 6. We did not however find an effect of cocaine exposure on continued growth deficits in head circumference or weight *z* scores. In this same sample at birth, we found specific negative effects of cocaine on weight and on head circumference [37] but not length. The current longitudinal data indicates that growth suppression in prenatally cocaine-exposed children persists to school age for weight for height and height *z* scores but not head circumference after control for other drug exposures and environmental factors. Research on prenatal malnutrition indicates that growth of brain structures, and therefore head size, recover after nutritional rehabilitation [23], providing an explanation for why head circumference in this cohort may have been affected by cocaine at birth but not at 6 years. While lower growth parameters have been found consistently for prenatally cocaine-exposed children when evaluating outcomes at birth [4,5,9,12,31,36], findings for long-term growth outcomes to age 7 are inconclusive [11,30].

A threshold effect for the cocaine metabolite (m-OH-bze) found in infant meconium at birth predicted shorter height *z* score, emphasizing the importance of evaluating threshold effects in addition to grouping subjects by exposure status and evaluating linear relationships based on the amount of prenatal exposure. A study by Covington et al. [11], also found specific effects of cocaine on length at 7 years, lending support for our current findings. They did not however evaluate threshold effects of cocaine or height for weight *z* scores and therefore, a direct comparison cannot be made. The detrimental effects of the specific cocaine metabolite, m-OHbze, on height *z* scores at 6 years is of special interest as significant correlations with outcomes across several domains including infant growth and cognitive development have also been found in this sample [35–37].

The relationship between cocaine metabolites found in infant meconium and the amount of actual drug consumed is poorly understood and complicated by several factors. For example, maternal factors such as placental status, maternal age, and nutrition can influence the amount of metabolite that actually reaches the fetus regardless of the amount ingested, making estimations of corresponding street usage difficult. From a previous study of this cohort [3] relatively high (.45–.57) correlations between the amount of cocaine reportedly ingested and the concentration of cocaine metabolites in meconium were found. While we were not able to estimate how much street usage of cocaine 100 ng/g translates to within our sample, 25% of cocaine-exposed children with meconium samples had a m-OH-bze level above the threshold.

Unlike the threshold effect of m-OH-bze found for height *z* score, a linear inverse relation was found for average prenatal cocaine exposure and height for weight *z* score. In this sample lower weight for height *z* score increased with greater amounts of cocaine exposure while height suppression occurred only after a threshold level of exposure (approximately 100 ng/g m-OH-bze). The differential effects of cocaine on growth

outcomes may be due to the early effects of cocaine on brain growth and organization, which then may govern later growth trajectories through alterations of the endocrine system. Another explanation is that body weight, which was suppressed for a given height in this sample, is known to drive height attainment. Without adequate weight, height suppression may follow. However the mechanisms by which growth suppression continues in prenatally cocaine-exposed children in both weight for height and height beyond infancy are unclear and warrant further investigation.

Prenatal alcohol exposure independently predicted lower weight and head circumference *z* scores at 6 years after control for other prenatal drug exposures and environmental conditions. This is not surprising as lack of weight gain over time and small head size are well documented and part of the recommended diagnostic criteria for fetal alcohol syndrome and alcohol-related effects [40]. There were also significant marijuana effects for growth found at 6 years. Heavier prenatal marijuana exposure was associated with lower height *z* score but higher weight for height *z* score. While few long-term studies of growth outcomes of prenatally marijuana-exposed children exist, data collected at birth indicate a significantly lower birth length [41].

Higher rates of dysmorphic findings among this cohort of 6-year-old PCE children compared to age-matched NCE controls were not identified. The number of anomalies was not greater among PCE children, nor was there a specific pattern of anomalies noted. These findings support those of Little et al. [24] and Behnke et al. [6], and suggest that PCE is not associated with a specific dysmorphic syndrome, or if it is, it occurs at a very low rate. This study is the only one known to date to evaluate prenatally cocaine-exposed children at 6 years of age, when dysmorphic features may be more evident than at birth, and to control other potential confounders and substance exposures. These data substantially add to the body of research related to prenatal cocaine exposure and dysmorphic features. While not significantly different, neurologic and motor strength abnormalities occurred exclusively among those with prenatal cocaine exposure. An early, more detailed, neurobehavioral study of this cohort at 1 month of age found higher rates of any neurobehavioral abnormality among prenatally cocaine-exposed infants [37] compared to a polydrug-exposed control group. Indications of neurologic abnormalities at both birth and 6 years suggest that a more detailed assessment should be considered to evaluate the stability and functional implications of these findings.

Specific effects of prenatal alcohol exposure were found for greater rates of ear length and other abnormalities. These results are not surprising in light of the well-documented teratogenic effects of prenatal alcohol exposure on facial features [21,26,34]. Prenatal marijuana and tobacco exposure were also related to higher rates of physical abnormalities, findings also supported by previous research [1,10,27].

This study did not address the question of whether prenatal cocaine exposure was associated with an increased rate of major structural birth defects, such as limb reductions. Newborns with such a birth defect or fetal alcohol syndrome diagnosable at birth would not have been enrolled in this study.

There are many strengths of this study that set it apart from previous research. It is the first study to assess both anthropometric and dysmorphic features in 6-year-old, prenatally cocaine-exposed children. The cohort is large and has an adequate comparison group of high-risk polydrug-exposed children and is one of few studies that adequately controlled for demographic covariates and other prenatal substance exposure. Further, the cohort was determined at infant birth to be cocaine or non-cocaine-exposed by a combination of biologic and self report measures considered state of the art for correct subject grouping [2]. Dysmorphologic exams were completed by the same clinical, board certified, geneticist blinded to subject grouping, ensuring that results were not biased in any way. To insure the most accurate anthropometric measurements, each were taken twice, and the average measurement used for final analysis.

The exclusion of children with birth defects prior to subject recruitment, including suspected or diagnosed fetal alcohol syndrome, limits the generalizability of study results. Comparison of those seen for dysmorphologic exams versus those not seen indicates that the non-cocaine-exposed group not seen for exams, were more likely to have been exposed to tobacco and alcohol, raising the possibility of having found fewer dysmorphic and anthropometric effects than would be expected. In the study sample, however, both the cocaine and non-cocaine-exposed groups had high levels of substance exposure, and therefore it may have been difficult to detect differences based on cocaine status alone. In addition, prenatally cocaine-exposed children who did not have dysmorphologic exams had larger head circumferences at birth. Therefore, the group seen for exams may have been biased toward more growth retardation at birth. That seems unlikely however, since group differences by cocaine status for head circumference at 6 years of age were not found, even after control for possible confounders. Another limitation of the study is that women were asked to report retrospectively on the amount and frequency of cocaine use during pregnancy. This limitation was minimized however, by the use of infant meconium to classify cocaine-using subjects into none, lighter or heavier prenatal exposure.

The large number of study outcomes, as well as multiple ways of measuring cocaine exposure, add concern for chance findings. However, most variables were combined into summary scores for abnormalities in body regions, reducing the number of variables evaluated. Even given the large number of dysmorphic variables evaluated, no major effects of cocaine were found. Therefore, the concerns of chance findings are minimal. And while several methods of measuring cocaine exposure were used (non-exposed versus exposed; none, light and heavy; units per week and meconium threshold analyses), this is an important analytic method in teratologic research. Failure to look at dose–response, or threshold effects, may have resulted in Type II error, or a failure to find an effect of cocaine when one was actually present.

While there were persistent dose effects of prenatal cocaine exposure on height *z* score and weight for height *z* score, no specific phenotype or increased rate of dysmorphic abnormalities among 6-year-old children prenatally cocaine-exposed children were found. Prenatal exposure to other substances including tobacco, marijuana, and alcohol continue to be associated with significant dysmorphic and persistent growth effects at 6 years of age. Therefore, prenatal substance exposure should be rigorously screened for during prenatal and early pediatric visits. Further, information on growth suppression due to prenatal cocaine and other drug exposure can be used to educate pregnant women about the potential harm to their fetuses, and encourage reduction of substance use prenatally.

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