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Prenatal Cocaine Exposure and Cardiometabolic Disease Risk Factors in 18- to 20-Year-Old African Americans

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Objective: The long-term effects of prenatal cocaine exposure (PCE) on physical health are largely unknown. No human studies support or refute a relationship between PCE and the long-term risk for cardiovascular and/or metabolic disease. We investigated the association of PCE on primary cardiometabolic disease risk factors in African Americans (AA) aged 18 to 20 years.

Design: Cohort, longitudinal, prospective.

Setting: Miami-Dade County, Florida, and the University of Miami Miller School of Medicine/Jackson Memorial Medical Center.

Participants: Healthy full-term inner-city AA adolescents (aged 18 to 20 years, *N*=350) previously enrolled at birth from 1990-1993.

Main Outcome Measures: Fasting serum insulin, glucose, lipids, and high-sensitivity C-reactive protein; systolic and diastolic blood pressures; and the components and prevalence of the metabolic syndrome.

Results: There were no PCE-associated differences in cardiometabolic disease risk factors including the metabolic syndrome and its individual components in AAs aged 18 to 20 years.

Conclusions: The results of our study do not support an association between PCE and increased cardiometabolic disease risk in AAs aged 18 to 20 years. Whether PCE is associated with cardiovascular or metabolic disease in adulthood would require further investigation. *Ethn Dis.* 2015;25(4):419-426; doi:10.18865/ed.25.4.419

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Introduction

The so-called "crack baby epidemic" of the late 1980s and early 1990s in the United States ushered in decades of heightened media, as well as lay and scientific interest in the outcomes of infants exposed *in utero* to cocaine. Early reports on this topic were complicated by the stigma accompanying illegal drug use, anecdotes, and small studies highlighting worse case scenarios. A generally consistent finding from follow-up studies is that prenatal cocaine exposure (PCE) is associated with decreased birthweight.[1-3] Reports of PCE being associated with abnormalities of cardiovascular structure and function, intracardiac conduction, and arrhythmias[4-9] as well as deficits in neurocognitive development are more varied in their conclusions.[10-13] Only now are studies that began decades ago able to examine the longer-term effects of PCE among 18- to 20-year-olds.

One area yet to receive attention is the effect of PCE on the development of cardiometabolic disease risk as defined by the metabolic syndrome (clustering of ≥3 of the following cardiometabolic disease risk factors: plasma glucose, abnormal waist circumference, blood pressure, triglyceride, and high density lipoprotein cholesterol [HDL] and its individual components).[14] The fetal origins hypothesis has received increasing attention over the past few decades as one explanation of how fetal exposures can have lifelong effects.[15-18] Specifically, several studies report associations between small body size at birth and during infancy and later cardiovascular disease and type 2 diabetes.[15,18] Later, this hypothesis was expanded to include several abnormal fetal perturbations, such as those

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that might be associated with the use of cocaine during pregnancy.[12] While PCE is associated with low birthweight,[3] this deficiency generally disappears in the first few years of life[19,20] and is often complicated by other environmental factors.[21]

Whether PCE is associated with future cardiometabolic disease or influences the development of underlying risk factors in healthy

> *We sought to determine the effect of PCE on anthropometric variables, cardiometabolic disease biomarkers, and the prevalence of metabolic syndrome.*

full-term African Americans (AA) is unknown.[14] Therefore, we sought to determine the effect of PCE on anthropometric variables (weight, height, body mass index, waist circumference, hip circumference, fat free mass, fat mass), cardiometabolic disease biomarkers (insulin, glucose, systolic and diastolic blood pressures, triglyceride, HDL, low density lipoprotein cholesterol [LDL], very low density lipoprotein cholesterol [VLDL], non-HDL, total cholesterol, and high sensitivity C-reactive protein [hs-CRP]) and the prevalence of metabolic syndrome in a large longitudinal study[1,14] of a well-retained birth cohort of PCE and non-PCE full-term AA infants.

METHODS

Participants

Participants for this study (*N*=350) were drawn from the Miami Prenatal Cocaine Study (MPCS), a prospective longitudinal follow-up investigation of 476 full-term infants born to AA mothers residing in the inner-city of Miami-Dade County, Florida and delivering at the University of Miami/Jackson Memorial Medical Center between 1990 and 1993. The current sample, representing 74% of the MPCS birth cohort, includes adolescents who could be located and consented to complete all of the cardiometabolic anthropometric, blood biomarker, and arterial blood pressure measurements described below at the 18- to 20-year follow-up visit. For purposes of this analysis, it is assumed that those lost to follow-up were not systematically different than study participants (ie, missing data due to lost to follow-up was at random). Because this study took place over 20 years, it would be fair to assume that those lost to follow-up were not lost in a systematic manner (ie, adequate time for many reasons for attrition across both PCE and non-PCE mothers).[22]

During the delivery hospitalization, the mothers participated in a detailed, confidential postpartum interview about their use of cocaine, alcohol, tobacco, marijuana, and other drugs before and during pregnancy. The mothers also gave consent to collect maternal and infant urine and infant meconium specimens for drug testing and maternal blood for human immunodeficiency virus (HIV) screening. Infants of HIV-positive mothers were excluded, as were infants with major congenital malformations, chromosomal aberration, or disseminated congenital infections. The MPCS study protocol is detailed elsewhere.[1,14]

Our study was approved by the Institutional Review Board of the University of Miami/Jackson Memorial Medical Center and was conducted under a federal Department of Health and Human Services Certificate of Confidentiality.

Measurements

Cardiometabolic Anthropometric Biomarkers

Weight was measured to the nearest .1 kg and standing height (cm) was measured with a Detecto Physician's electronic scale (Cardinal Scale Manufacturing Co., Webb City, MO).

Waist and hip circumferences were measured to the nearest .1 cm using a non-stretchable plastic tape measure by a standard method.[14] Waist circumference was measured over the navel at the end of gentle exhalation and hip circumference was measured at the maximum circumference over the buttocks.

Bicep, triceps, subscapular, and suprailiac skinfold thicknesses were measured to the nearest .1 mm following standard procedures.[23] These values were combined with the Durnin formula[24] to estimate percent body fat.

All anthropometric measures of each participant were collected in triplicate, and the average was used for analysis. Weight and height were converted to sex- and age-specific body mass index (BMI) z-scores according to the 2000 US Centers for Disease Control and Prevention growth charts.[25]

Cardiometabolic Blood Biomarkers

The cardiometabolic blood bio-markers for this study were measured and analyzed using standardized methods at the University of Miami Diabetes Research Institute. Fasting insulin and glucose concentrations were measured by an automated analyzer (Roche Cobas-Mira, Indianapolis, IN) using commercially available kits with standard procedures applied according to the manufacturer's instructions.[26]

Fasting lipid profiles, included total, HDL, LDL, VLDL, and non-HDL cholesterol (total cholesterol minus HDL cholesterol), were determined.[27-29] High sensitivity C-reactive protein concentrations were also measured.[30]

Arterial Blood Pressure Measurements

Systolic and diastolic arterial blood pressures were measured with an automated blood pressure monitor (Welch Allyn Model 5200-101A, Arden, NC) using either a child or adult cuff, depending on the girth of the upper arm.[31] Three diastolic and systolic blood pressure measurements were taken successively with 1 minute between each measure. The first value was dropped, and the remaining two were averaged.

Definition of Metabolic Syndrome

Metabolic syndrome was diagnosed according to the National Cholesterol Education Program's Adult Treatment Panel (ATP) III definition[32] of having ≥3 of 5 risk factors: 1) a fasting blood glucose concentration >110 mg/dL; 2) a waist circumference >102 cm for males and >88 cm for females; 3) a systolic blood pressure >130 mm Hg or a diastolic blood pressure >80

mm Hg; 4) triglyceride concentrations >150 mg/dL; and 5) a HDL cholesterol concentration <40 mg/dL in males and <50 mg/dL in females. Because subjects were adolescents, a modified ATP definition of metabolic syndrome of ≥2 risk factors was also considered.

Trained research staff at the University of Miami Clinical Research Center (UMCRC) obtained all anthropometric measures. All cardiometabolic outcome variables were collected at the UMCRC by registered nurses and phlebotomists who were trained on the standardized methodologies and procedures.

Measures of Prenatal Substance Exposure at Birth

Maternal Self-Report (SR) Cocaine Usage.

A structured postpartum interview to ascertain maternal SR cocaine use during their entire pregnancy was conducted by separate research staff distinct from the infant and child assessment examiners. Although an attempt was made to quantify the degree of use, for mothers who were nonusers, degree information was a constant (ie, 67% of the degree scores were zero). This created a mixed distribution of binary and continuous responses that prohibited any type of unified statistical analysis or that was responsive to a normalizing transformation. Consequently, for analysis purposes, SR usage was dichotomized as either positive (SR+) or negative (SR-).

Benzoylecgonine Detection of Cocaine Use.

When available, maternal and infant urine and infant meconium

specimens were collected after delivery and tested for the cocaine metabolite benzoylecgonine (BE). Each of the mother/infant dyads had at least one type of specimen available for testing; 97% had at least two; and 68% had all three. Screening for BE was performed by EMIT® (Syva DAU) at a cutoff of 150 mg/mL urine and 150 ng/g meconium, respectively. Cocaine-positive specimens were confirmed by gas chromatography/mass spectrometry.[33] As with the SR measure, the distributional discontinuity of the degree of BE metabolite dictated the use of a binary classification scheme for the presence of BE. Infants were classified as benzoylecgonine-positive (BE+) if any one of the three specimens were positive or as benzoyecgonine-negative (BE-) when all available specimens were negative.

STATISTICAL METHODS

Participants were classified into four groups on the basis of the two measures of cocaine use: SR+ or SR- and BE+ or BE-. This classification provided a factorial group arrangement (two factors each at two levels) in which the main effect of self-reported cocaine use, benzoylecgonine status, and their interaction could be examined. Three other models were also estimated: an overall four-group model (one-way layout); a double-negative (ie, negative for both self-report and benzoylecgonine) vs a positive status in either measure (a classification scheme typically used in the literature); and an extreme value (unconflicted classification) in which double negatives were compared to double positives. Since both

SR and BE classifications are subject to measurement error, the six statistical models serve to provide a sensitivity analysis on the PCE effect.[34]

Statistical effects were estimated with the generalized linear model (GZLM).[35] With the exception of metabolic syndrome, all dependent outcomes were modeled with a normal distribution and an identity link function. For metabolic syndrome, the distribution was changed to binomial (ie, proportion) and the logit link function was used to model the log odds between PCE and non-PCE mothers. To normalize their distributions, insulin, triglyceride, and hs-CRP concentrations were $\log_e$ transformed before analysis. For descriptive purposes (ie, table values) variables were re-transformed back to their original scales. All estimated effects were adjusted for age and sex either internally (ie, the methodology for the variables' calculation took age and sex into account) or externally within the GZLM statistical model (ie, age

and sex were included as covariates).

All statistical calculations were performed using SAS® (version 9.3) and SAS-JMP® (version Pro 11) statistical software (SAS® Institute, Cary, NC).

RESULTS

Mean responses across the four classifications of cocaine usage are given in Tables 1 and 2. Table 1 summarizes the effects for the anthropometric data while cardiometabolic biomarkers and prevalence of metabolic syndrome are given in Table 2. Table 3 describes and summarizes the statistical results (ie, *P* values) for the six statistical models as applied to the dependent measures listed in Tables 1 and 2.

Of the 350 participants, the overall proportion of males (*n*=159, 45%) and females (*n*=191, 55%) was relatively constant across all four classifications of cocaine usage (*P*=.224). There was no evidence of any type of SR cocaine usage effect or any indica-

tion of a SR by BE interaction on any cardiometabolic anthropometric or blood biomarkers. The only statistically detectable effect was a main effect of BE+ status on height and height z-score (see Tables 1 and 3). The BE+ vs the BE- main effect comparison yielded adjusted heights of 168.1 vs 170.4, respectively. All other *P*s associated with the main effect of BE status exceeded .10. Most of the BE height and height z-score effect was driven by the two mixed indicator groups (SR+/BE-, SR-/BE+), rather than the expected double-negative (SR-/BE-) or double-positive (SR+/BE+) groups. This was confirmed by a further analysis of the overall four-group, one-way model, which yielded *P* of .06 for height z-score and .07 for height. Post hoc analysis for the overall model, as well as for the extreme-value model, indicated no statistical difference between the SR+/BE+ and SR-/BE- groups for either height z-score or height (*P* >.48 for both comparisons). Furthermore, when

Table 1. Anthropometric values of 18- to 20-year-old African Americans with and without prenatal cocaine exposure (*N*=350)

Dependent Measure	Prenatal Cocaine Exposure			
	SR-/BE- *n* = 171	SR+/BE- *n* = 25	SR-/BE+ *n* = 59	SR+/BE+ *n* = 95
Height, mean (SD), cm	169.7 (9.7)	171.1 (8.2)	167.2 (12.3)	169.0 (9.1)
Height, mean (SD), z-score[a]	-0.03 (0.94)	0.22 (1.05)	-0.41 (1.47)	-0.11 (1.09)
Weight, mean (SD), kg	76.1 (20.5)	74.5 (20.4)	76.4 (26.2)	74.0 (23.9)
Weight, mean (SD), z-score[a]	0.65 (1.18)	0.63 (1.17)	0.56 (1.35)	0.41 (1.40)
Body mass index, mean (SD), kg/m²	26.4 (6.8)	25.5 (7.1)	27.3 (8.4)	25.7 (7.4)
Body mass index, mean (SD), z-score[a]	0.60 (1.21)	0.50 (1.14)	0.69 (1.16)	0.42 (1.38)
Waist circumference, mean (SD), cm	84.7 (17.0)	83.3 (16.9)	85.5 (17.9)	84.3 (18.1)
Hip circumference, mean (SD), cm	100.6 (14.2)	100.2 (14.6)	100.4 (13.9)	99.6 (14.9)
Waist-to-hip ratio, mean (SD)	0.83 (0.06)	0.83 (0.06)	0.85 (0.07)	0.84 (0.07)
Waist-to-height ratio, mean (SD)	0.50 (0.10)	0.49 (0.11)	0.52 (0.12)	0.50 (0.10)
Percent body fat, mean (SD)[b]	25.8 (9.8)	27.5 (10.0)	26.1 (10.4)	26.2 (10.1)

SR+/-, self-report positive/negative prenatal cocaine use; BE+/-, benzoylecgonine positive/negative prenatal presence.
Age and sex corrections are intrinsic to the calculations for z-scores and percent body fat (ie, standardized). Means are externally corrected via statistical covariance modeling for age and sex. Standard deviations are uncorrected.
a. see reference 25 for standardization methodology.
b. see reference 24 for standardization methodology.

Table 2. Cardiometabolic biomarker values in 18- to 20-year-old African Americans with and without prenatal cocaine exposure (*N*=350)

Dependent Measure	Prenatal Cocaine Exposure			
	SR-/BE- *n* = 171	SR+/BE- *n* = 25	SR-/BE+ *n* = 59	SR+/BE+ *n* = 95
Insulin, mean (SD), uIU/mL[a]	10.1 (6.3)	9.6 (6.4)	9.7 (7.3)	10.4 (6.3)
Glucose, mean (SD), mg/dL	88.9 (9.2)	89.3 (6.3)	90.6 (8.5)	90.4 (12.5)
Triglycerides, mean (SD), mg/dL[a]	58.5 (18.6)	60.3 (18.2)	60.2 (22.6)	63.0 (22.8)
HDL cholesterol, mean (SD), mg/dL	51.8 (12.8)	53.7 (14.6)	51.5 (14.1)	49.0 (11.3)
LDL cholesterol, mean (SD), mg/dL	87.0 (26.5)	88.4 (25.9)	85.1 (25.7)	84.7 (27.2)
VLDL cholesterol, mean (SD), mg/dL	12.6 (5.4)	13.7 (8.8)	13.1 (6.5)	13.6 (5.6)
Non-HDL cholesterol, mean (SD), mg/dL	99.6 (27.4)	102.2 (25.9)	98.2 (28.6)	98.3 (28.7)
Total cholesterol, mean (SD), mg/dL	151.4 (28.5)	155.9 (28.4)	149.7 (29.8)	147.4 (29.4)
Hs-CRP, mean (SD), mg/dL[a]	0.94 (1.6)	0.82 (1.8)	1.19 (2.5)	0.93 (2.2)
Systolic blood pressure, mean (SD), mm Hg	111.5 (10.3)	107.4 (8.9)	111.0 (10.1)	111.0 (10.6)
Diastolic blood pressure, mean (SD), mm Hg	69.5 (7.2)	66.1 (5.5)	69.2 (7.5)	69.4 (7.6)
Metabolic syndrome I[b], %	1.2	4.0	5.1	3.2
Metabolic syndrome II[c], %	15.8	16.0	20.3	19.0

SR+/-, self-report positive/negative prenatal cocaine use; BE+/-, benzoylecgonine positive/negative prenatal presence; HDL, high density lipoprotein; LDL, low density lipoprotein; VLDL, very low density lipoprotein except for metabolic syndrome (externally corrected for sex), means are corrected for sex and age in the statistical model. Standard deviations are uncorrected.

a. Values were log$_e$ transformed to normalize the distributions before analysis. Table values have been transformed back to the original scale. Standard deviations were estimated from the 17th and 83rd smoothed empirical likelihood quantiles of the log-normalized distribution.

b. Standard Adult Treatment Panel III definition (≥3 risk factors).

c. Modified Adult Treatment Panel III definition (≥2 risk factors).

adjusted for multiple statistical test generation (ie, Bonferroni), the height and height -z score differences were not statistically significant (*P* = .48).

Although not a primary aim of the current investigation, all models were checked for additivity (ie, interaction) across sex. There was no evidence (*P*s ≥.33) that the overall lack of an effect seen across the variables in Tables 1 and 2 would be conditional on the sex of the individual.

DISCUSSION

We found no clinically important or statistically significant relationships between PCE and the assessed primary cardiometabolic disease risk factors or metabolic syndrome in adolescents aged 18 to 20 years who were healthy full-term births. Although PCE was associated with lower birthweight, there were no differences observed in current weight. Other studies that included AAs have shown PCE to be associated with increased BMI and blood pressure at 9 years of age and with lower weight-for-height ratios at

Table 3. Results of modeling the estimated effects of prenatal cocaine exposure in 18- to 20-year-old African Americans (*N*=350)

Estimated Effect[a]	Models Compared	Range of *P* for Variables Listed in Tables 1 and 2
Overall effect (one-way layout)	SR⁻/BE⁻ = SR⁺/BE⁻ = SR⁻/BE⁺ = SR⁺/BE⁺	.06 to .97
Factorial main effect (self-reported PCE)	(SR⁻/BE⁻ + SR⁻/BE⁺) = (SR⁺BE⁺ + SR⁺/BE⁻)	.07 to .94
Factorial main effect (benzoylecgonine status)	(SR⁻/BE⁻ + SR⁺/BE⁻) = (SR⁻/BE⁺ + SR⁺/BE⁺)	.02[b] to .99
Factorial interaction (synergy, BE x SR)	(SR⁻/BE⁻ - SR⁻/BE⁺) = (SR⁺/BE⁻ - SR⁺/BE⁺)	.07 to .96
Double-negative vs any positive	(SR⁻/BE⁻) = (SR⁺/BE⁻ + SR⁻/BE⁺ + SR⁺/BE⁺)	.16 to .99
Extreme value (unconflicted)	(SR⁻/BE⁻) = (SR⁺/BE⁺)	.09 to .92

SR+/-, self-report positive/negative prenatal cocaine use; BE+/-, benzoylecgonine positive/negative prenatal presence.

a. All comparisons (including the extreme-value comparison) were conducted with full model denominator degrees of freedom (approximately 346).

b. Height (z), *P*=.02, *P*(Bonferroni) = .48; Height (cm), *P*=.02, *P*(Bonferroni) = .48 all others, *P* >.10.

10 years of age.[36] Richardson et al reported that 1st trimester cocaine use resulted in decreased weight, height, and head circumference at age 10 years.[37]

Our prevalence estimates of the metabolic syndrome in 18- to 20-year-old AAs (3.4% average across all 4 groups) are similar to national prevalence estimates in adolescents aged 12 to 18 years (mean of 2.5%).[38-41] Interestingly, these same national prevalence estimate reports also show that after controlling for socioeconomic status and lifestyle, AA children aged 8 to 18 years are less likely to have metabolic syndrome compared with their non-Hispanic White and Hispanic counterparts.[38-41] However, AA adolescents have higher rates of obesity,[42] insulin resistance,[43] and elevated blood pressure[44] and a greater likelihood of an adult diagnosis of type 2 diabetes and cardiovascular disease (CVD) versus non-Hispanic Whites.[45] While we did not have non-Hispanic White PCE/non-PCE comparison groups, it is probably unlikely that the previously reported difference in metabolic syndrome between AAs and non-Hispanic Whites can be explained by the possible PCE/non-PCE exposure. However, this does not eliminate the possibility that PCE moderates the relationship between race and metabolic syndrome.

Perhaps the most limiting factor associated with any study of the relationship between the fetal environment and disease in later life is the concept of "epigenetic drift."[46] This concept is supported by studies that document the independent effect of childhood social circumstances on adult health, as opposed to initial genetic differences. Similarly, the socio-medical community has proposed a

We found no clinically important or statistically significant relationships between PCE and the assessed primary cardiometabolic disease risk factors or metabolic syndrome in adolescents aged 18 to 20 years who were healthy full-term births.

"social programming model" or "life course approach" that combines both the biological and social determinants of health.[47] This model suggests that the relationship between fetal exposure and adult health outcomes is mediated by the social environment and such key factors as education level, income, marital status, stress, employment, living conditions, and lifestyle patterns. This would also include the concomitant use of other illicit drugs, alcohol and cigarettes. In fact, we found that prenatal alcohol, tobacco, and marijuana exposure were all positively and moderately correlated with PCE (r's =.40, .55, .45, respectively). These co-behaviors make it virtually impossible to separate the individual effects of these substances, ie, multicollinearity.[48]

Although the fetal origins hypothesis[15] may be considered an early stage influence within the social program-

ming model, we found PCE to be of no consequence in terms of its influence on metabolic syndrome or its components. The existence of epigenetic drift in conjunction with later life social programming suggests that the newborn is much more resilient and adaptive to negative maternal prenatal exposures than previously believed and that the fetal origins hypothesis may be an oversimplification.[15,49,50]

Limitations and Strengths of the Study

The MPCS sample was restricted to healthy full-term AA infants living in the low-income areas of an inner-city. Excluding infants born prematurely or with serious medical difficulties was intentional in order to reduce confounding, but may have inadvertently excluded more heavily cocaine-exposed children from the sample. Although omitting co-morbidities may decrease generalizability, there should be a corresponding higher internal validity resulting from reduced experimental error.

Another limitation of the study is the reliability of self-reported cocaine use during pregnancy, a time when women may feel particularly vulnerable to admitting use. However, adding biomarkers as an indicator of PCE and considering several different models of PCE should have substantially increased the reliability of the exposure category assignment. Other methodological limitations intrinsic to investigating prenatal drug exposures include the observational nature of the study, which subsequently makes it difficult to separate the unique influence of PCE from the myriad of other behavioral/environmental fac-

tors positively correlated with cocaine use (eg, alcohol, cigarettes, marijuana).

A study matched comparison group of Caucasians would be required to model and subsequently formulate conclusions regarding the differential race effects of PCE. Since this study consists only of 18- to 20-year-old AAs, caution must be taken when generalizing the results to Caucasians or extrapolating to adulthood.

Finally, statistical power needs to be considered in the face of negative results. With approximately 346 error degrees of freedom available for all statistical tests, and considering only a slight variance reduction from covariates, the current study has 80% power when only 2% of the total variance is explained. This high degree of statistical precision makes it unlikely that the lack of statistically significant findings were a result of a small sample size.

Conclusions

In our study, PCE showed no direct adverse association with risk factors for cardiovascular and/or metabolic disease among AAs aged 18 to 20 years who were healthy full-term births. However, whether PCE is associated with cardiovascular or metabolic disease in adulthood will require further investigation. Similarly, whether PCE is associated with cardiovascular or metabolic disease among AAs born prematurely would require further study.

Author Contributions
Research concept and design: Messiah, Lipshultz, Miller, Bandstra. Acquisition of data: Messiah, Vidot, Accornero, Lipshultz, Xue, Bandstra. Data analysis and interpretation: Messiah, Ludwig, Vidot, Xue, Bandstra. Manuscript draft: Messiah, Ludwig, Vidot, Accornero, Miller, Xue, Bandstra. Statistical expertise: Messiah, Ludwig, Vidot, Xue. Acquisition of funding: Messiah, Ludwig, Accornero, Miller, Bandstra. Administrative: Messiah, Ludwig, Vidot, Accornero, Xue, Bandstra. Supervision: Messiah, Ludwig, Lipshultz, Miller, Bandstra.

References
1. Bandstra ES, Morrow CE, Anthony JC, et al. Intrauterine growth of full-term infants: impact of prenatal cocaine exposure. *Pediatrics*. 2001;108(6):1309-1319. http://dx.doi.org/10.1542/peds.108.6.1309. PMID:11731653.
2. Lambert BL, Bauer CR. Developmental and behavioral consequences of prenatal cocaine exposure: a review. *J Perinatol*. 2012;32(11):819-828. http://dx.doi.org/10.1038/jp.2012.90. PMID:22791278.
3. 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(4):340.e1-340.e12. http://dx.doi.org/10.1016/j.ajog.2010.11.013. PMID:21257143.
4. Plessinger MA, Woods JR Jr. Cocaine in pregnancy. Recent data on maternal and fetal risks. *Obstet Gynecol Clin North Am*. 1998;25(1):99-118. http://dx.doi.org/10.1016/S0889-8545(05)70360-0. PMID:9547762.
5. Frassica JJ, Orav EJ, Walsh EP, Lipshultz SE. Arrhythmias in children prenatally exposed to cocaine. *Arch Pediatr Adolesc Med*. 1994;148(11):1163-1169. http://dx.doi.org/10.1001/archpedi.1994.02170110049008. PMID:7921117.
6. Lipshultz SE, Frassica JJ, Orav EJ. Cardiovascular abnormalities in infants prenatally exposed to cocaine. *J Pediatr*. 1991;118(1):44-51. http://dx.doi.org/10.1016/S0022-3476(05)81842-6. PMID:1986097.
7. Mone SM, Gillman MW, Miller TL, Herman EH, Lipshultz SE. Effects of environmental exposures on the cardiovascular system: prenatal period through adolescence. *Pediatrics*. 2004;113(4)(suppl):1058-1069. PMID:15060200.
8. Swanson JM, Entringer S, Buss C, Wadhwa PD. Developmental origins of health and disease: environmental exposures. *Semin Reprod Med*. 2009;27(5):391-402. http://dx.doi.org/10.1055/s-0029-1237427. PMID:19711249.
9. Behnke M, Eyler FD, Garvan CW, Wobie K. The search for congenital malformations in newborns with fetal cocaine exposure. *Pediatrics*. 2001;107(5):E74. http://dx.doi.org/10.1542/peds.107.5.e74. PMID:11331724.
10. Bandstra ES, Morrow CE, Mansoor E, Accornero VH. Prenatal drug exposure: infant and toddler outcomes. *J Addict Dis*. 2010;29(2):245-258. http://dx.doi.org/10.1080/10550881003684871. PMID:20407980.
11. 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. http://dx.doi.org/10.1542/peds.2009-0637. PMID:20142293.
12. Buckingham-Howes S, Berger SS, Scaletti LA, Black MM. Systematic review of prenatal cocaine exposure and adolescent development. *Pediatrics*. 2013;131(6):e1917-36. http://dx.doi.org/10.1542/peds.2012-0945.
13. What are the effects of maternal cocaine use? In Cocaine. National Institute on Drug Abuse website. http://www.drugabuse.gov/publications/research-reports/cocaine/what-are-effects-maternal-cocaine-use. Updated September 2010. Accessed July 27, 2014.
14. Messiah SE, Lipshultz SE, Miller TL, Accornero VH, Bandstra ES. Assessing latent effects of prenatal cocaine exposure on growth and risk of cardiometabolic disease in late adolescence: design and methods. *Int J Pediatr*. 2012;2012:467918. http://dx.doi.org/10.1155/2012/467918.
15. Barker DJP, Eriksson JG, Forsén T, Osmond C. Fetal origins of adult disease: strength of effects and biological basis. *Int J Epidemiol*. 2002;31(6):1235-1239. http://dx.doi.org/10.1093/ije/31.6.1235. PMID:12540728.
16. Barker DJ. Fetal origins of cardiovascular disease. *Ann Med*. 1999;31(suppl 1):3-6. PMID:10342493.
17. Barker DJ. Fetal origins of coronary heart disease. *BMJ*. 1995;311(6998):171-174. http://dx.doi.org/10.1136/bmj.311.6998.171. PMID:7613432.
18. Barker DJ. The origins of the developmental origins theory. *J Intern Med*. 2007;261(5):412-417. http://dx.doi.org/10.1111/j.1365-2796.2007.01809.x. PMID:17444880.
19. Hurt H, Brodsky NL, Betancourt L, Braitman LE, Malmud E, Giannetta J. Cocaine-exposed children: follow-up through 30 months. *J*

Dev Behav Pediatr. 1995;16(1):29-35. http://dx.doi.org/10.1097/00004703-199502000-00005. PMID:7730454.

20. Arendt RE, Short EJ, Singer LT, et al. Children prenatally exposed to cocaine: developmental outcomes and environmental risks at seven years of age. *J Dev Behav Pediatr*. 2004;25(2):83-90. http://dx.doi.org/10.1097/00004703-200404000-00002. PMID:15083129.

21. Wilcox AJ. On the importance--and the unimportance--of birthweight. *Int J Epidemiol*. 2001;30(6):1233-1241. http://dx.doi.org/10.1093/ije/30.6.1233. PMID:11821313.

22. Kristman VL, Manno M, Côté P. Methods to account for attrition in longitudinal data: do they work? A simulation study. *Eur J Epidemiol*. 2005;20(8):657-662. http://dx.doi.org/10.1007/s10654-005-7919-7. PMID:16151878.

23. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Anthropometric Procedural Manual. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. 2002

24. Durnin JV, Womersley J. Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72 years. *Br J Nutr*. 1974;32(1):77-97. http://dx.doi.org/10.1079/BJN19740060. PMID:4843734.

25. Kuczmarski RJ, Ogden CL, Guo SS, et al; National Center for Health Statistics. 2000 CDC Growth Charts for the United States: methods and development. *Vital Health Stat 11*. 2002;(246):1-190. PMID:12043359.

26. Public Health Service, Centers for Disease Control and Prevention. A proposed method for determining glucose using hexokinase and glucose-6-phosphate dehydrogenase. Centers for Disease Control and Prevention, 1-1-1976.

27. Rana JS, Boekholdt SM, Kastelein JJ, Shah PK. The role of non-HDL cholesterol in risk stratification for coronary artery disease. *Curr Atheroscler Rep*. 2012;14(2):130-134. http://dx.doi.org/10.1007/s11883-011-0224-x. PMID:22203405.

28. Allain CC, Poon LS, Chan CS, Richmond W, Fu PC. Enzymatic determination of total serum cholesterol. *Clin Chem*. 1974;20(4):470-475. PMID:4818200.

29. Cole TG, Klotzsch SG. McNamara JR. Measurement of triglyceride concentration. *Handbook of Lipoprotein Testing*. 2000;16:207.

30. Khuseyinova N, Imhof A, Trischler G, et al. Determination of C-reactive protein: comparison of three high-sensitivity immunoassays. *Clin Chem*. 2003;49(10):1691-1695. http://dx.doi.org/10.1373/49.10.1691. PMID:14500603.

31. Urbina E, Alpert B, Flynn J, et al; American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee. Ambulatory blood pressure monitoring in children and adolescents: recommendations for standard assessment: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee of the council on cardiovascular disease in the young and the council for high blood pressure research. *Hypertension*. 2008;52(3):433-451. http://dx.doi.org/10.1161/HYPERTENSIONAHA.108.190329. PMID:18678786.

32. National Institutes of Health. The Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Bethesda, MD: National Institutes of Health; NIH Publication 1-3670;2001.

33. Mulé SJ, Casella GA. Confirmation and quantitation of cocaine, benzoylecgonine, ecgonine methyl ester in human urine by GC/MS. *J Anal Toxicol*. 1988;12(3):153-155. http://dx.doi.org/10.1093/jat/12.3.153. PMID:3386211.

34. Saltelli A, Chan K, Scott M, eds. *Sensitivity Analysis. Wiley Series in Probability and Statistics*. New York: John Wiley and Sons; 2000.

35. Nelder JA, Wedderburn RWM. Generalized linear models. *J R Stat Soc*. 1972;135(3), Series A (General):370-84.

36. Shankaran S, Bann CM, Bauer CR, et al. Prenatal cocaine exposure and BMI and blood pressure at 9 years of age. *J Hypertens*. 2010;28(6):1166-1175. PMID:20486281.

37. Richardson GA, Goldschmidt L, Larkby C. Effects of prenatal cocaine exposure on growth: a longitudinal analysis. *Pediatrics*. 2007;120(4):e1017-e1027. http://dx.doi.org/10.1542/peds.2006-3482. PMID:17893189.

38. de Ferranti SD, Gauvreau K, Ludwig DS, Neufeld EJ, Newburger JW, Rifai N. Prevalence of the metabolic syndrome in American adolescents: findings from the Third National Health and Nutrition Examination Survey. *Circulation*. 2004;110(16):2494-2497. http://dx.doi.org/10.1161/01.CIR.0000145117.40114.C7. PMID:15477412.

39. Cook S, Weitzman M, Auinger P, Nguyen M, Dietz WH. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National Health and Nutrition Examination Survey, 1988-1994. *Arch Pediatr Adolesc Med*. 2003;157(8):821-827. http://dx.doi.org/10.1001/archpedi.157.8.821. PMID:12912790.

40. Messiah SE, Arheart KL, Luke B, Lipshultz SE, Miller TL. Relationship between body mass index and metabolic syndrome risk factors among US 8- to 14-year-olds, 1999 to 2002. *J Pediatr*. 2008;153(2):215-221. http://dx.doi.org/10.1016/j.jpeds.2008.03.002. PMID:18534237.

41. Messiah SE, Arheart KL, Lopez-Mitnik G, Lipshultz SE, Miller TL. Ethnic group differences in cardiometabolic disease risk factors independent of body mass index among American youth. *Obesity (Silver Spring)*. 2013;21(3):424-428. http://dx.doi.org/10.1002/oby.20343. PMID:23456910.

42. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. *JAMA*. 2014;311(8):806-814. http://dx.doi.org/10.1001/jama.2014.732. PMID:24570244.

43. Chen W, Bao W, Begum S, Elkasabany A, Srinivasan SR, Berenson GS. Age-related patterns of the clustering of cardiovascular risk variables of syndrome X from childhood to young adulthood in a population made up of black and white subjects: the Bogalusa Heart Study. *Diabetes*. 2000;49(6):1042-1048. http://dx.doi.org/10.2337/diabetes.49.6.1042. PMID:10866058.

44. Din-Dzietham R, Liu Y, Bielo MV, Shamsa F. High blood pressure trends in children and adolescents in national surveys, 1963 to 2002. *Circulation*. 2007;116(13):1488-1496. http://dx.doi.org/10.1161/CIRCULATIONAHA.106.683243. PMID:17846287.

45. Crawford AG, Cote C, Couto J, et al. Prevalence of obesity, type II diabetes mellitus, hyperlipidemia, and hypertension in the United States: findings from the GE Centricity Electronic Medical Record database. *Popul Health Manag*. 2010;13(3):151-161. http://dx.doi.org/10.1089/pop.2009.0039. PMID:20521902.

46. Heyn H, Li N, Ferreira HJ, et al. Distinct DNA methylomes of newborns and centenarians. *Proc Natl Acad Sci USA*. 2012;109(26):10522-10527. http://dx.doi.org/10.1073/pnas.1120658109. PMID:22689993.

47. Järvelin MR. Fetal and infant markers of adult heart diseases. *Heart*. 2000;84(2):219-226. http://dx.doi.org/10.1136/heart.84.2.219. PMID:10908268.

48. Zidek JV, Wong H, Le ND, Burnett R. Causality, measurement error and multicollinearity in epidemiology. *Environmetrics*. 1996;7:441-451

49. Editorial The Lancet. An overstretched hypothesis? *Lancet*. 2001;357(9254):405. http://dx.doi.org/10.1016/S0140-6736(00)04027-7. PMID:11273052.

50. Schempf AH, Strobino DM. Illicit drug use and adverse birth outcomes: is it drugs or context? *J Urban Health*. 2008;85(6):858-873. http://dx.doi.org/10.1007/s11524-008-9315-6. PMID:18791865.