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Prenatal Cocaine Exposure Alters Cortisol Stress Reactivity in 11 Year Old Children

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Abstract

Objective—Determine the association between prenatal cocaine exposure and postnatal environmental adversity on salivary cortisol stress reactivity in school aged children.

Study design—Subjects included 743 11 year old children (n=320 cocaine exposed; 423 comparison) followed since birth in a longitudinal prospective multisite study. Saliva samples were collected to measure cortisol at baseline and after a standardized procedure to induce psychological stress. Children were divided into those who showed an increase in cortisol from baseline to post stress and those who showed a decrease or blunted cortisol response. Covariates measured included site, birthweight, maternal pre and postnatal use of alcohol, tobacco or marijuana, social class, changes in caretakers, maternal depression and psychological symptoms, domestic and community violence, child abuse and quality of the home.

Results—With adjustment for confounding variables, cortisol reactivity to stress was more likely to be blunted in children with prenatal cocaine exposure. Cocaine exposed children exposed to domestic violence showed the strongest effects.

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Conclusion—The combination of prenatal cocaine exposure and an adverse postnatal environment could down regulate the hypothalamic-pituitary-adrenal axis (HPA) resulting in the blunted cortisol response to stress possibly increasing risk for later psychopathology and adult disease.

Keywords

prenatal cocaine exposure; cortisol reactivity; environmental adversity

Alterations in the reactivity of the HPA axis affecting cortisol levels have been related to an array of adverse outcomes ranging from medical disease to psychotic disease.[1-4] In populations of at risk children, cortisol stress reactivity has been associated with low socioeconomic status, (SES) [5-7] maternal depression, [8, 9] maltreatment and abuse [10-13] and exposure to community violence. [14] However, there are only four reports of cortisol reactivity in children with prenatal cocaine exposure. These studies have all been conducted with infants and the findings have been inconsistent.[15-18] In two studies, preterm cocaine exposed neonates showed depressed cortisol responses following a standard physical exam and following a heel prick [15] and higher urinary cortisol levels compared with neonates who were not exposed to cocaine. [17] In 13-month-old infants tested before and after blood draw, prenatal cocaine exposure was associated with lower prestress cortisol. [16] Seven month old cocaine exposed infants showed increased cortisol reactivity to a behavioral procedure designed to elicit arousal.[18] Cortisol reactivity in this study was also affected by instability of the infant's caregiver. Thus, among infants with higher caregiver instability those with prenatal substance exposure had higher cortisol reactivity than unexposed infants and infants with low caregiving instability. These findings suggest that postnatal environmental stress can add to the effects of prenatal cocaine exposure on cortisol reactivity.[18]

We report a study of the effects of prenatal cocaine exposure on cortisol stress reactivity in school age children. Given that cocaine exposed children grow up in adverse environments including factors such as poverty, maltreatment, violence, parental psychopathology and substance use, [19, 20] we wanted to evaluate the possible association of prenatal cocaine exposure with cortisol reactivity in 11 year old children, and to determine if these hypothesized associations are magnified by postnatal environmental adversity. This report is from the Maternal Lifestyle Study (MLS) multi-site longitudinal cohort study on the evaluation of the long-term outcomes of children exposed to cocaine in-utero. The four data collection sites are Brown University, Providence, RI; University of Miami, Miami, FL; University of Tennessee at Memphis, Memphis, TN and Wayne State University, Detroit, MI.

METHODS

Enrollment and exclusion criteria for the MLS have been described in detail.[21, 22] The study had approval from the Institutional Review Board at each site. Each site also had a certificate of confidentiality from the National Institute on Drug Abuse. Informed consent was obtained from all participants. Infants in the longitudinal study were selected to be in the exposed group (maternal report of cocaine or opiate use during pregnancy or gas chromatography-mass spectrometry confirmation of presumptive positive meconium screens for cocaine or opiate metabolites) or the comparison group (maternal denial of cocaine or opiate use during the pregnancy and a negative enzyme multiplied immunoassay meconium screen for cocaine and opiate metabolites). Exposed and comparison infants were group matched on race, sex, and gestational age. 1388 mother-infant dyads (658 in the exposed

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group and 730 in the comparison group) were enrolled in the longitudinal study at the first (1-month, age corrected for prematurity) visit.

At the one month visit, each mother was interviewed for a detailed inventory of her legal and illegal drug use during pregnancy. Prenatal cocaine use was categorized into high, some, and no use. High cocaine use referred to ≥ 3 times/week use in the first trimester. Any other use was referred to as some cocaine use. Prenatal tobacco use was categorized into high (≥ 10 cigarettes/day), some (<10 cigarettes/day) and no use. Prenatal alcohol use was categorized into high (≥ 0.5 oz absolute alcohol/day), some (< 0.5 oz/ day), and no use. Prenatal marijuana was categorized into high (≥ 0.5 joints/day), some (< 0.5 joint/day), and no use. For tobacco, alcohol and marijuana the per day values were calculated for the entire pregnancy. These cutoffs have been used in our previous work. [21, 23] Postnatal substance use of cocaine (number days/week), cigarettes (number/day), alcohol (number drinks/day), and marijuana (number joints/day) was based on caretaker interview visits from 4 months to 11 years averaged across visits for each substance. The number of changes in primary caretaker was computed from 1 month to 11 years. Socioeconomic status (SES) was measured with the Hollingshead Index of Social Position [24, 25] based on education and occupation averaged over annual visits. Child abuse was ascertained by caregiver report and defined as “Yes” if a Child Protective Services case opened for evidence of physical and/or sexual abuse at any age from 1 month to 11 years. Domestic violence was defined as “Yes” if any physical or sexual abuse was reported by caregiver at any annual visit. Community violence was based on the averaged scores of 2 questionnaires; child-report Things I’ve Seen and Heard at age 8 [26] and caregiver-report Survey of Exposure to Community Violence at age 9. [27] Caretaker psychological distress was the averaged number of psychological symptoms above clinical cutoff on the Brief Symptom Inventory (BSI) [28] at 4 and 30 months, 4 ½, 9 and 11-year visits. Depression was the averaged scores on caregiver report Beck Depression Inventory (BDI) at 4 and 30 month, 4 ½, 7, 9, and 11-year visits. The quality of the home environment was based on averaged scores of Home Observation Measurement of the Environment (HOME Scale)[29] at home visits at 10 month, 5 ½ and 9 year visits.

Cortisol stress reactivity was measured based on an expanded version of the Trier Social Stress Test [30] administered at age 11. The Trier task is a standardized protocol for the induction of moderate psychosocial stress in laboratory settings and has been widely used in children and adults as well as in clinical populations.[31, 32] The Trier is a motivated performance task consisting of a preparation period (5 minutes) followed by a test period in which the subject has to deliver a free speech (5 minutes) and perform mental arithmetic (5 minutes) in front of an audience. With this, the total exposure time adds up to 15 minutes. We added a mirror tracing task [33, 34] to provide a challenging nonverbal performance task. In this 5 minute task, the child used a mirror that reversed directionality as they traced the figure of a six-sided star. The apparatus beeped for each error and the child was instructed to begin again.

Four saliva samples were collected. The prebaseline sample was collected 20 minutes before the start of the Trier task. The prebaseline task was a computerized task of executive function that was familiar to the children. The baseline sample was collected just before the start of the Trier test. The baseline task (between the first two samples) was an interview conducted by a research assistant on topics that were innocuous and familiar to the child from previous visits (e.g., Extracurricular Activities). The first reactivity sample was collected at the end of the mirror tracing task (20 minutes from the onset of the Trier) and the second reactivity sample was collected 20 minutes after the end of the mirror tracing task. During this period, we conducted a debriefing interview with the child, where the research assistants explained the purpose of the tasks and reassured the child that they

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performed well. Previous research is inconsistent as to whether cortisol levels peaked at 20 minutes post stress onset then recover to baseline levels at 40 minutes or are maintained at the same level 20 to 40 minutes post stress onset. [35, 36] Thus we collected cortisol samples at both 20 and 40 minute post stress.

To collect the samples, the child deposited saliva through a straw directly into a 2 mL vial for each of the four specimens. Ideally, the samples were ≥1.0 mL, but 0.5 mL was accepted if collection time was over 3 minutes. The vials were all pre-labeled with study site, ID and sample type with unique barcodes (provided by Salimetrics, LLC, State College, PA). Samples were immediately placed in a −20° C freezer until shipped on dry ice to Salimetrics Laboratory for assay. All samples were assayed in duplicate for salivary cortisol using a highly sensitivity cortisol enzyme immunoassay kit. Each test uses 25 ul of saliva, has a limit of sensitivity of .007 ug/dl, a range of sensitivity from .007 to 1.8 ug/dl. Mean intra-assay and inter-assay coefficients of variations were less than 5% and 10% and averaged duplicate scores were used in all statistical analysis. 97% of participants provided the baseline sample between 11:00 am and 5:00 pm to address the diurnal cycle of cortisol that flattens between late morning and early evening.[37] The earliest baseline sample was 10:37 am and the last was 5:10 pm. We also collected information on steroid medications, [38] time of last meal or beverage including dairy or caffeine [39] and vigorous physical exercise. [40]

Statistical Analysis

The raw cortisol values (μg/dL) were positively skewed and normalized using a log transformation. Cortisol reactivity was calculated as the difference between the cortisol level at baseline and the first reactivity or poststress sample. Outliers above or below 3 SD in all four samples and the difference score were winsorized by replacing the value with the value at 3 SD (<1.5% of cortisol values affected). Children were then grouped into those who showed an increase in cortisol greater than zero (N=422, 57%) from baseline to post stress and those who showed a decrease or blunted cortisol response less than zero (N=321, 43%) from baseline to post stress.

Analysis of variance (ANOVA) was used to compare maternal and child characteristics and mean cortisol values between exposed and comparison groups. Chi-square was also used to compare maternal and child demographic characteristics and the number of children who showed increases or decreases in cortisol response from baseline to post stress. Logistic regression models were fit to relate prenatal cocaine exposure (yes/no) and level of prenatal cocaine exposure (high, some or none), [21, 41] to cortisol reactivity (increases or decreases) while controlling for covariates. Covariates were based on conceptual and statistical criteria. A priori covariates were site, prenatal exposure, including level of exposure (high, some or none), [21, 41] to prenatal cocaine exposure and the outcome variable tobacco, alcohol, marijuana; sex; SES and birth weight. Other covariates were included if associated with both at p <= .10. These candidate covariates were, number of caretaker changes; average BDI, BSI; postnatal caretaker use of cocaine, tobacco, alcohol, marijuana; domestic violence; community violence; child abuse; and HOME score. Final, reduced models were generated through stepwise backward removal of covariates that contributed to the model at p >.10. Interactions between prenatal cocaine exposure and covariates were tested and removed if p > .10. Analysis of variance, Chi-square and Pearson correlation coefficients were also used to address potential methodological issues that could affect the results including time of day, steroid medication and eating or drinking beverages within an hour of the baseline sample.

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RESULTS

Of the 1388 children enrolled at the one month visit, 115 were excluded because they were exposed to opiates, 388 did not participate in the 11 year visit. Of the 885 attending the 11-year visit, 115 did not participate in the cortisol reactivity task due to chronic disability (57) child or parent unable or refusal (14) or technical problems or resource limitations (44). Of the 770 who participated in the cortisol reactivity task; 22 had an incomplete procedure or saliva collection, 2 cases was excluded due to interference (per Salimetrics) and 3 excluded because the quantity of saliva was insufficient. The final sample was 743 subjects. The level of prenatal cocaine use was measured by self-report of the biological mother at the 1 month visit. Of the 743 subjects, 57 were in out of home placement at the one-month visit and 47 mothers denied use but were included in the exposed group due to positive meconium results. Thus, analysis of level of cocaine use was conducted on 639 subjects.

For the 743 subjects in the study (Table I), more mothers in the exposed group were older, single, low SES, on Medicaid, less well educated and used alcohol, tobacco and marijuana, than in the comparison group. The child's birth weight and birth length were lower in the exposed group. Comparisons of the 743 children included with 530 children not included in this study (Table II) show that the included group were more likely to be Black and single parents with higher birth weight and greater birth length in their infants.

There were no statistically significant differences between the exposed and comparison groups on the mean cortisol values (Table III) for the pre-baseline (P=0.330), baseline (P=0.924) or two post stress samples (P=0.404 and P=0.203, respectively). The mean difference between the first reactivity and baseline cortisol the second reactivity and baseline cortisol levels levels was lower in the exposed group than in the comparison group (P=0.036). The mean difference between was not statistically different (P=0.096). The number of children who showed a decreased or blunted cortisol response to stress was greater in the cocaine exposed than in the comparison group (N=157, 49.1% vs. N=164, 38.8%, Chi Square =7.864, P=.005). After controlling for covariates, there was a cocaine by domestic violence interaction (P=0.009) (Figure). Cocaine exposed children who experienced domestic violence were more likely to show the blunted cortisol response than children in the comparison group who experienced domestic violence (Chi Square = 11.74, P=.001). There was also an effect of level of cocaine exposure (Chi Square = 7.558, P=0.023). The number of children who showed a decreased or blunted cortisol response was greater in the heavy (N= 37, 52.9%) and some (N=73, 48.0%) exposed group than in the group with no cocaine exposure (N= 161, 38.6%). After controlling for covariates, children with heavy cocaine exposure were more likely to show the blunted cortisol response than children in the no cocaine exposure group (AOR = 1.95, CI = 1.09-3.50).

Analysis of potential methodological issues showed no association between the time of baseline saliva collection and exposure status (mean time: exposed 12 hr. 50 min., comparison 13 hr. 00 min., P=0.165) or with the group of children who showed the increased (mean time: 12 hr. 58 min.) or blunted (mean time: 12 hr. 53 min.) cortisol response (P=0.514). There was an association between baseline cortisol level and time of day ($r = -0.10$, P=0.033). Sixteen children had taken a steroid medication within 12 hours of baseline sample and six within 4 hours of the baseline sample. There was no association of steroid medication with cortisol levels at baseline (12 hours p=0.195, 4 hours p=0.855) or reactivity (12 hours P=0.317, 4 hours P=0.833) or between those with increased versus blunted cortisol response (12 hours P=0.964, 4 hours p=0.736). No one reported eating or drinking beverages within an hour of the baseline sample or vigorous exercise within 1.75 hours of the baseline sample.

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DISCUSSION

We report cortisol stress reactivity in school aged children with prenatal cocaine exposure. We found that cortisol reactivity to stress was more likely to be blunted in children with prenatal cocaine exposure. These effects were also related to domestic violence but they were independent of other covariates including prenatal and postnatal drug exposures. Thus, more children with prenatal cocaine exposure and exposure to domestic violence showed the blunted cortisol response than children with prenatal cocaine exposure or exposure to to show the blunted cortisol response than children domestic violence alone. We also found that children with heavy prenatal cocaine exposure were more likely with no cocaine exposure. These effects were independent of covariates including domestic violence suggesting that there is no association between cortisol reactivity and domestic violence in children with heavy cocaine exposure.

The association between stress and activation of the HPA axis, ultimately resulting in an increased secretion of cortisol from the adrenal glands has been well documented since the work of Selye. [42] However, a growing literature suggests that the adrenal is hypoactive in some stress-related states, resulting in suppression of the HPA axis. [43-45] Examples of such hypocortisolism include low cortisol levels, flat daytime (e.g. morning to evening) production patterns and a blunted cortisol response to stress.[37, 43] Hypocortisolism is related to prenatal stress and early adversity in animal models. The exposure of infant rats to stress, such as daily handling, results in decreased basal corticosterone levels, reduced adrenocortical responses to acute stressors and enhanced suppression of stress-induced HPA activation by dexamethasone in adult life. [46] Administration of ACTH to pregnant rats results in decreased basal corticosterone levels, reduced adrenocortical reactivity and decreased adrenal volumes in the offspring.[13, 47, 48]

In human studies, hypocortisolism has been reported in adults with post-traumatic stress disorder,[49] patients suffering from bodily disorders, such as burnout with physical complaints, chronic fatigue syndrome, fibromyalgia, chronic pelvic pain and asthma among others, [50-54] in very low-income women with high levels of depressive symptoms[55] and in healthy individuals who lived under conditions of ongoing stress. [56-59] In children, hypocortisolism has been reported in at risk populations of children,[37] including children with chronic stress,[43, 44, 60] children reared in institutions,[61] or in foster care, [62, 63] boys with attention problems, [64] clinically depressed maltreated school aged children,[65, 66] boys of low income depressed mothers,[67] post-traumatic stress disorder,[68] boys with antisocial behavior [69-75] and autism.[76] Blunting specifically has been found in children with psychosocial dwarfism,[77] atopic dermatitis,[35] Oppositional Defiant Disorder (ODD),[78] juvenile delinquents with ODD and Conduct Disorder (CD),[79] early onset or adolescent onset CD,[80] sexually abused girls,[81] and maltreated children.[12]

Hypocortisolism is one form of neurobiological dysregulation of the HPA axis and there are a number of potential mechanisms involved including reduced biosynthesis at various levels of the HPA axis, hypersecretion of CRH in the hypothalamus, increased and enhanced sensitivity to the negative feedback of developmental perspective it has been suggested that early experience can affect adult health in at least two glucocorticoids, and morphological changes such as structural changes of the adrenal gland.[13] From a ways, by the biological embedding of insults during sensitive developmental periods and by accumulating damage over time due to chronic stress.[82] It is likely that the combination of biological embedding and cumulative stress resulted in the hypocortisolism that we observed.

We speculate that the biological embedding in our study is due to the insult of prenatal cocaine exposure that could have affected the intrauterine neuroendocrine environment. As a

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toxin, the teratogenic effects of cocaine have been described along two major pathways but there may be a third pathophysiology in which cocaine affects the HPA system. The first pathway is the direct effects of cocaine on neurotransmitter turnover in the brain and peripheral nervous system sites. Preclinical studies suggest effects of prenatal cocaine exposure on the developing monoaminergic system, resulting in both structural and functional changes to circuitry subserving functions such as arousal, regulation and reactivity.[83, 84] The second pathway is through vasoconstrictive effects on arteries in the uterus resulting in increased plasma catecholamine concentrations and marked secondary effects such as fetal hypoxemia and possibly ischemic injury.[85] Elsewhere, we[86] have suggested a third neuroendocrine pathophysiology. In this model, cocaine acts as an intrauterine stressor altering the expression of key placental genes, specifically the norepinephrine transporter (NET) and 11ß-HSD-2 which protect the fetus from excess catecholamines and glucocorticoids. 11ß-HSD-2 in particular converts maternal cortisol to inert cortisone protecting the developing fetus from exposure to maternal cortisol.[87] Epigenetic mechanisms such as DNA methylation downregulate 11ß-HSD-2, increasing fetal exposure to cortisol and shifting the set points for HPA axis responses to the extrauterine environment.[86] Prenatal stressors other than cocaine including other substances such as tobacco or other types of insults such as low birthweight could have similar affects. This could result in dysregulation, e.g., hyperactivity of the HPA axis, which becomes hypoactive with cumulative exposure to postnatal stress.

Hypocortisolism is one pattern that can result from the long-term effect of the physiologic response to stress. This has been referred to as “allostatic load” or the wear and tear of the body produced by the repeated activation of the HPA axis and related biological stress systems.[88, 89] This prolonged activation of the neuroendocrine stress axes has been related to physical disease and behavioral disorders.[90] The children in our study are growing up in largely impoverished, high risk environments and the children with blunted cortisol response. As mentioned earlier, hypocortisolism has been related to chronic stress in prenatal cocaine exposure who were also exposed to domestic violence were the most likely to show the children.[43, 44, 60] Other studies have documented the associations between adverse environments and cortisol reactivity, [5-10, 12, 13] including violence [14] and violence has also been associated with the effects of prenatal cocaine exposure on child outcome.[19] Our findings also relate to those of Eiden et al [18] who found that cortisol reactivity in cocaine exposed infants was moderated by caregiving instability suggesting that postnatal environmental factors can exacerbate the effects of prenatal cocaine exposure supporting a dual hazard vulnerability model.[18] We suggest that the cumulative exposure to stress experienced by the children in our study could have resulted in allostatic load leading to downregulation of the HPA axis and the hypocortisolemic blunted cortisol response.

Parental substance use and family violence are major risk factors included under the description of toxic stress developed by the National Scientific Council on the Developing Child[91] that refers to chronic activation of the HPA and related stress response systems resulting in stress related disorders. The notion of toxic stress is also important because of our finding related to heavy cocaine exposure. At this more “toxic” dose, there was no effect of domestic violence on cortisol reactivity which could suggest that at high levels of prenatal cocaine exposure the physiological pathways that were altered *in utero* may have been affected by the overall chronic adversity endemic in the sample as a whole.

One limitation of this study is that genetic factors were not measured. Also, cortisol was measured from saliva rather than blood. However, the correlation between salivary and plasma cortisol in serum or plasma is very high (r>.90)[92, 93] and saliva sampling has the advantage of being a non-invasive technique. On the other hand blood sampling would have

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enabled us to also sample ACTH which is “higher up” on the HPA axis and is the principle tropic hormone for cortisol. The design of our study could be considered both a weakness and strength. The limitation is that there is no group without prenatal drug exposure or adversity in the postnatal caregiving environment. Therefore it is impressive that effects such as those reported here can be detected between two groups of essentially high risk children. The fact that these differences can be detected suggests that these are robust effects. It may be useful to include other physiological measures that are part of the activation of the HPA axis response to stress, such as blood pressure or heart rate. Of the methodological factors we examined, only time of day was associated with baseline cortisol level. However, time of day was not associated with cocaine exposure group or cortisol reactivity. Therefore, it is unlikely that our results were affected by time of day. We also ruled out potential effects of steroid medication, food or beverage consumption or exercise. Of course, it is possible that there are factors that we did not measure that could have affected our findings. A final limitation is sample size. Only approximately half of the subjects from the original sample were included. However, there were no clinically significant differences between those included and those not included (Table II). The cell size was also small (n=37) for children with heavy prenatal exposure.

Most of the literature on the effects of prenatal cocaine exposure is focused on behavioral outcomes. In other populations activity of the HPA system, specifically hypocortisolism, is related to psychopathology [94, 95] and adult disease.[4, 60, 89] Although the children in our study are certainly at risk for poor developmental outcome, [23, 41, 96] these findings suggest that they may also be at greater risk for adult disease. Prenatal cocaine exposure, including effects on the neuroendocrine system, could contribute to allostatic load which could result in cocaine not only affecting behavior but also the development of stress related medical problems. It is important that these children continue to be followed to determine the possible long term effects of prenatal cocaine exposure on the later development of behavioral disorders and adult disease.

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Abbreviations

ACTH	Adrenocorticotropic Hormone
ANOVA	Analysis of Variance
BDI	Beck Depression Inventory
BSI	Brief Symptom Inventory
CD	Conduct Disorder
CRH	Corticotropin-releasing hormone
HOME Scale	Home Observation Measurement of the Environment
HPA	Hypothalamic-Pituitary-Adrenal Axis
MLS	Maternal Lifestyle Study
NET	Norepinephrine Transporter
ODD	Oppositional Defiant Disorder
SES	Socioeconomic status

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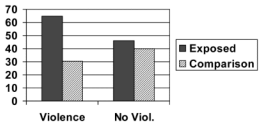

Figure 1.

Number of children with the blunted cortisol response to stress in the Cocaine and Comparison groups with and without exposure to domestic violence (unadjusted). Cocaine exposed children who experienced domestic violence were more likely to show the blunted cortisol response than children in the comparison group who experienced domestic violence (P=.001, adjusted).

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TABLE 1

Maternal and child characteristics of the exposed subjects and the comparison cohort. Values are expressed as percent or mean (SD) where indicated.

Variables	Exposed N=320	Comparison N= 423	P value
Race: Black	267 (83.4)	342 (80.9)	0.364
Maternal Age: Mean (SD)	30.4 (4.7)	26.8 (5.7)	<0.001
Marital status: Single	293 (91.6)	329 (77.8)	<0.001
Low SES (Hollingshead level 5)	90 (29.6)	85 (20.2)	0.004
Medicaid	282 (88.1)	325 (76.8)	<0.001
Education < 12years	159 (49.7)	134 (31.7)	<0.001
Prenatal alcohol use	241 (75.3)	225 (53.2)	<0.001
Prenatal tobacco use	262 (81.9)	119 (28.1)	<0.001
Prenatal marijuana use	127 (39.7)	40 (9.5)	<0.001
Child's Sex: male	168 (52.5)	215 (50.8)	0.652
Child's Gestational Age, wk, Mean(SD)	36.1 (4.0)	36.3 (4.1)	0.284
Child's Birth Weight, g, Mean(SD)	2560 (740)	2683 (865)	0.008
Child's Head Circumference, cm, Mean(SD)	32.0 (2.8)	32.2 (3.1)	0.100
Child's Birth Length, cm, Mean(SD)	46.4 (4.7)	47.0 (5.2)	0.024

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Table 2

Comparison of dyads who were included and those with not included in the study. Results expressed as number (%) or where indicated mean (SD).

Variables	Not included N=530	Included N= 743	P value
Race: Black	396 (74.7)	609 (82.0)	0.002
Maternal Age: Mean (SD)	27.8 (5.9)	28.3 (5.6)	0.122
Marital status: Single	403 (76.3)	622 (83.7)	0.001
Low SES (Hollingshead level 5)	114 (22.6)	175 (24.2)	0.528
Medicaid	431 (81.3)	607 (81.7)	0.865
Education < 12years	207 (39.1)	293 (39.4)	0.913
Prenatal alcohol use	305 (57.6)	466 (62.7)	0.063
Prenatal tobacco use	280 (52.8)	381 (51.3)	0.585
Prenatal marijuana use	129 (24.3)	167 (22.5)	0.438
Child's Sex: male	290 (54.7)	383 (51.6)	0.264
Child's Gestational Age, wk, Mean (SD)	36.1 (4.1)	36.3 (4.0)	0.284
Child's Birth Weight, g, Mean (SD)	2628 (816)	2632 (817)	0.008
Child's Head Circumference, cm, Mean (SD)	32.1 (3.1)	32.1 (3.0)	0.100
Child's Birth Length, cm, Mean (SD)	46.7 (5.1)	46.8 (4.9)	0.024

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Table 3

Cortisol values by exposure status (unadjusted).

	Exposed N=320	Comparison N= 423	P value
Prebaseline	0.155 (0.089)	0.149 (0.082)	0.330
Baseline	0.145 (0.83)	0.146 (0.090)	0.924
Reactivity-1	0.153 (0.089)	0.160 (0.099)	0.404
Reactivity-2	0.149 (0.092)	0.159 (0.100)	0.203
Reactivity	0.007 (0.049)	.015 (0.61)	0.036

Note: All cortisol levels above are measured in μg/dL. The analyzed data have been log transformed.