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## Long-Term Impact of Maternal Substance Use during Pregnancy and Extrauterine Environmental Adversity: Stress Hormone Levels of Preadolescent Children

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### Abstract

Prenatal cocaine exposure (PCE) is associated with blunted stress responsivity within the extrauterine environment. This study investigated the association between PCE and diurnal salivary cortisol levels in preadolescent children characterized by high biological and/or social risk ( $N = 725$ ). Saliva samples were collected at their home. Analyses revealed no group differences in basal evening or morning cortisol levels; however, children with higher degrees of PCE exhibited blunted overnight increases in cortisol, controlling for additional risk factors. Race and caregiver depression were also associated with diurnal cortisol patterns. While repeated PCE may contribute to alterations in the normal or expected stress response later in life, sociodemographic and environmental factors are likewise important in understanding hormone physiology, especially as more time elapses from the PCE. Anticipating the potential long-term medical, developmental, or behavioral effects of an altered ability to mount a normal protective cortisol stress response is essential in optimizing the outcomes of children with PCE.

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## Introduction

The hypothalamic-pituitary-adrenal (HPA) axis of the neuroendocrine system maintains physiologic homeostasis by regulating the body's response to internal and external stressors. Following a threatening exposure, cortisol, a stress hormone secreted by the adrenal gland, is released, resulting in immediate elevations of heart rate and blood pressure (i.e., the “fight or flight” response). As the perceived threat dissipates, elevated hormone levels and physiological parameters gradually return to baseline. Under normal, nonstressful conditions, cortisol is released in a diurnal pattern with the highest concentrations present in the morning in preparation for daily activities (1). Levels rapidly decline toward midday, dropping more gradually into the evening. Repetitive stress exposures over time may permanently disrupt this typical pattern, leading to prolonged elevations in cortisol levels and eventual system desensitization and down-regulation (2). The individual may then display decreased morning cortisol levels that remain low throughout the day. This lowered responsivity has been associated with alterations in attention regulation, motivation, immune system functioning, sleep cycle, and onset of stress-related diseases (3).

Atypical cortisol patterns have been reported in children living in high-stress environments (1, 4-9). Acute (or periodic) stress exposures may result in increased cortisol levels while chronic (or pervasive) stress exposures may result in decreased levels (10). For instance, children in foster care who experienced severe, chronic physical neglect have exhibited lowered morning cortisol levels as opposed to children experiencing severe, intermittent emotional maltreatment who had the highest levels (5). These findings support evidence that chronic stress may affect system down-regulation and blunted cortisol production (2, 10, 11). Flattened diurnal cortisol patterns have also been observed in children who continued to live with birth parents following Child Protective Services involvement. However, children who were removed from similar chronic threatening situations and placed in foster care exhibited more normal cortisol patterns (8). Other variables associated with alterations in child cortisol patterns include premature birth, secondhand smoke, low socioeconomic status (SES), caregiver depression, and domestic violence (1, 4, 7, 9, 12, 13). Documenting the details of a child's environment is essential to better understand factors that may alter the integrity of their stress physiology.

Prolonged stress exposure in utero may also disrupt the usual pattern of cortisol secretion later in life. Evidence suggests that maternal cocaine use during pregnancy may permanently affect developing fetal systems that control arousal regulation and stress response, altering the threshold response of the HPA axis to extrauterine stressors (14). Specific human brain regions, such as the hippocampus and amygdala, which primarily regulate other systems (e.g., emotional functioning) are also affected by stress hormones (15). Understanding mechanisms that alter stress reactions in children may provide insights into potential dysfunctions in other developmental realms.

Limited and somewhat contradictory data have been published regarding the association between prenatal cocaine exposure (PCE) and cortisol physiology. One study reported elevated cortisol levels in preterm neonates with PCE (12), while another reported lowered basal cortisol levels in exposed infants (gestational age 32 weeks) (16). Another study reported no group differences in basal cortisol levels; however, exposed infants demonstrated suppressed cortisol reactivity (the difference between basal cortisol and peak levels) following an induced stress event (17). Blunted reactivity has also been observed in preadolescent children with PCE with the greatest effects seen in exposed children whose caregivers had experienced domestic violence (13). In contrast, an infant study reported greater cortisol reactivity, especially among exposed boys (18). Differences in child age or level of PCE may contribute somewhat to inconsistencies in study findings. In addition,

these studies reflect the cortisol levels of children in a clinic setting (an atypical environment that may induce additional stress). To our knowledge, no published reports have examined the diurnal cortisol variation in older children with PCE or have examined cortisol levels of exposed children within the more naturalistic home setting.

Multiple comorbid risk factors besides PCE may alter the stress response system of infants and older children. Women who use cocaine during pregnancy typically use greater amounts of legal and illegal substances and are more likely to raise their children in compromised environments (19). The objective of the current study was to examine the basal cortisol levels of 11-year-old children at high social and/or biological risk within the home setting. This report examines both the association between levels of PCE and basal cortisol levels and the change in these levels between evening and morning, controlling for various biological, social, and environmental characteristics of this high-risk sample.

## Methods

### Participants

Children were enrolled at birth in the Maternal Lifestyle Study (MLS), a prospective, longitudinal investigation of the effects of prenatal cocaine and/or opiate exposure on acute and long-term child outcomes. Four institutions participated: Brown University, the University of Miami, the University of Tennessee-Memphis, and Wayne State University. Institutional review board approval occurred at each site and informed maternal consent was obtained. Exposure status was determined by maternal admission of drug use and/or a positive enzyme multiplied immunoassay technique (EMIT) screening for drug metabolites in meconium confirmed with gas chromatography/mass spectroscopy (GC/MS) (20). Nonexposure was determined by denial of cocaine/opiate use during pregnancy and a negative meconium toxicology screen. Detailed information regarding screening and participant enrollment has been previously reported (21). A total of 1388 dyads (658 cocaine/opiate exposed and 730 nonexposed) attended the first clinic visit at 1 month of age, which defined enrollment into the follow-up component. There were 18 visits scheduled between the 1-month and 11-year visits.

Of these 1388 children, 1023 attended the 11-year clinic visit. Children who attended the visit were less likely to have prenatal opiate exposure or to be white compared to children who did not attend the visit ( $p$ 's < .001). Groups were comparable on PCE level, prenatal tobacco, alcohol, or marijuana exposure, maternal education, race, small for gestational age (SGA), low birth weight (LBW), and preterm birth. Of the 1023 children who attended the 11-year clinic visit, 725 were included in the current sample (see Figure 1). Similar contrasts revealed that children included in the current sample were less likely to be white and to be born preterm compared to excluded children ( $p$ 's < .05). Groups were otherwise comparable.

### Measures

**Child birth outcomes, gender, and maternal demographics**—Preterm birth (<37 weeks gestation), SGA (<10th percentile), LBW (<2500 grams), child gender, maternal education (<high school (HS), HS diploma, >HS), and maternal race (black, white, other) were included as control variables.

**Prenatal drug exposure**—At the 1-month visit, detailed information regarding drug use was collected through maternal interview. Level of PCE was categorized as high (≥ 3 times/week during the first trimester), some (any other use during pregnancy), or none. Other drug exposures were entered as control variables. Prenatal alcohol (average ounces of absolute alcohol consumed p/day), tobacco (average number of cigarettes smoked p/day), marijuana

(average number of joints smoked p/day) were calculated for the entire pregnancy consistent with our previous work (13, 22). Binge drinking (≥ 5 drinks at one time) and opiate use during pregnancy were recorded dichotomously (yes/no).

**Salivary Cortisol**—Saliva is a reliable and accessible source of cortisol levels in both children and adults (23). Families were provided with instructions and materials to collect children's saliva at home. One evening and one morning sample were collected in individual test tubes using a small straw until the amount met or exceeded the line indicated on the tube. On the night prior to their clinic appointment, evening samples were collected around bedtime at least one hour after eating or drinking and before brushing their teeth. Morning samples were collected the following day right after waking and before eating or brushing their teeth. Drinking water was acceptable at least 15 minutes prior to saliva collection. Documentation of collection times was required and both saliva samples were expected to be capped and kept in their freezer at home until their clinic appointment. Returned samples were placed in a -20°C freezer until they were shipped in dry ice to Salimetrics Laboratory (Salimetrics, LLC) for analysis.

**Caregiving Environment**—Potential risk factors related to the child's caregiving environment were investigated. SES was based on the Hollingshead Index of Social Position score (Hollingshead, 1975; unpublished report) at the 11-year visit. Higher scores indicated higher SES. The total number of caretaker changes and foster care placement (yes/no) was based on information gathered at any visit. As reported at the 11-year visit, caretaker abuse (yes/no) was determined by caregiver-report of experiencing physical or sexual violence and child abuse (yes/no) was based on any report of abuse or neglect since their last clinic visit (usually 12 months prior). Community violence exposure was based on caregiver-report on the 12-item Survey of Exposure to Community Violence interview (24) at the 9-year visit. Higher scores indicated more exposure. Caregiver depression was assessed using the Beck Depression Inventory (BDI) (25) at the 11-year visit. Caregivers with scores ≥ 16 were classified as being depressed within the past 7 days. Caregiver postnatal alcohol, tobacco, and marijuana intake and binge drinking were assessed using the same quantification definitions as for prenatal exposures and refer to occurrence since their last clinic visit as reported during the 11-year visit.

The aforementioned environmental variables were used to assess recent environmental stress. To assess the potential differential effects of cumulative stress exposure, a modified set of environmental covariates were created for use in a logistic regression model. SES was redefined as the mean SES score recorded across the 1-month to 11-year visits. Caregiver abuse and child abuse were determined by caregiver-report (yes/no) at any visit. Chronic caregiver depression referred to the total number of times the caregiver scored ≥ 16 on the BDI at the 4-month, 30-month, and 4-, 7-, 9-, and 11-year visits. Caregiver postnatal substance use variables were redefined based upon self-report data at any visit. The remaining covariate definitions were unchanged for this cumulative stress model.

## Analyses

Differences between PCE groups (high, some, and none) were assessed on all covariates using chi-square tests for categorical variables and analyses of variance (ANOVAs) for continuous variables. Evening and morning cortisol values were compared by PCE level using linear regression. Distributions of raw cortisol values were highly positively skewed; therefore, square root transformations were applied to achieve more normal distributions. We also tested whether change in diurnal cortisol values between evening and morning measurements varied by PCE (i.e., time x exposure interactions) using generalized estimating equations (GEE) models to account for repeated measurements. Follow-up

analyses were conducted for linear regression and GEE models controlling for site, other prenatal drug exposures, birth outcomes, gender, maternal demographics, and caretaking environment.

Finally, we assessed whether children had typical versus atypical patterns of change in diurnal cortisol levels. Patterns were defined as atypical if their increase in cortisol levels between evening and morning measurements fell at or below the 25th percentile (i.e., increased 0.091  $\mu\text{g}/\text{dL}$  or less). A logistic regression model was conducted to examine the relationship between PCE and atypical cortisol patterns, controlling for site, other prenatal drug exposures, birth outcomes, gender, maternal demographics, and caretaking environment. An additional logistic regression was then conducted for the cumulative environmental stress model which examined the association between PCE and atypical cortisol patterns, controlling for site, other prenatal drug exposures, birth outcomes, gender, maternal demographics, and the modified set of environmental covariates (i.e., variables based on longitudinal data).

A majority of the sample (84%) completed saliva sampling as instructed collecting the evening sample first and the morning sample second. The remaining children collected their samples in the opposite order. Overnight change in cortisol levels was calculated the same (morning-evening) regardless of the order of sample collection. Excluding these children did not affect results; therefore, all 725 children were included in analyses.

## Results

Anthropometric, sociodemographic, and environmental characteristics of the analytic sample are presented in Table 1. PCE groups (high, some, and none) were comparable on gender, LBW, preterm birth, prenatal opiate exposure, caregiver abuse, child abuse, caregiver depression, and caregiver postnatal marijuana intake. Group differences occurred on the remaining variables. PCE was associated with an increased likelihood of prenatal exposure to alcohol, binge drinking, tobacco, or marijuana. Children with any cocaine exposure had mothers with less education, had caregivers with higher SES, experienced more caretaker changes, were more likely to have been placed in foster care, and were exposed to more community violence in contrast to children with no PCE. Children with high PCE (vs. nonexposed) were more likely to be born SGA. Lastly, children with some PCE (vs. nonexposed) were more likely to be black and to have caregivers who reported recent alcohol consumption, binge drinking, and greater tobacco use. Lastly, supplemental, exploratory analyses revealed that exposed children were less likely to live with a biological parent(s) than nonexposed children (65% vs. 94%) at the 11-year visit. Similarly, exposed children were more likely to have an adoptive parent as their primary caregiver than nonexposed children (11% vs. 1%;  $p$ 's < .001).

Mean time for evening samples was 8:46 p.m. ( $SD = 3:42$ ) and 7:57 a.m. ( $SD = 1:27$ ) for morning samples. No differences were found among exposure groups for basal evening or morning cortisol levels (see Table 2). Results generally remained the same when controlling for site, birth outcomes, gender, maternal demographics, other prenatal drug exposures, and caretaking environment. However, children of black mothers had lower morning cortisol levels compared to children of white mothers ( $b = -6.50$ ,  $p = .026$ ). Results of unadjusted GEE analyses are reported in Table 2 and Figure 2. These analyses revealed that children with none and some PCE had similar patterns of overnight increase; however, children with high PCE had smaller increases in cortisol from the evening to morning measurements than those with some or no PCE. In adjusted analyses controlling for similar covariates, children with high PCE continued to demonstrate smaller increases in cortisol compared to children

with no PCE ( $p = .046$ ). There was no longer a difference between the high and some PCE groups. =

When examining typical versus atypical patterns of change, children with high PCE (vs. nonexposed children) were more likely to demonstrate an atypical change (increase the 25th percentile) in cortisol levels from evening to morning (Table 2). This difference remained after controlling for site, birth outcomes, gender, maternal demographics, other prenatal drug exposures, and caretaking environment (see Table 3). Children with high PCE had more than twice the odds of demonstrating an atypical pattern of change in diurnal cortisol. Race and caregiver depression were also predictive of cortisol patterns. Children with black mothers were more than twice as likely to demonstrate a blunted increase in cortisol levels compared to children with white mothers. Children with caregivers reporting *recent* depression (vs. children with non-depressed caregivers) were approximately one-third as likely to demonstrate this atypical pattern of change.

For the cumulative environmental stress model (controlling for site, birth outcomes, gender, maternal demographics, other prenatal drug exposures, and longitudinal environmental variables), results of a logistic regression generally remained the same. High PCE (Odds ratio (OR), 2.06; 95% confidence interval (CI), 1.07-4.00) and race (OR, 2.45; 95% CI, 1.13-5.30) were associated with atypical diurnal cortisol patterns ( $p < .05$ ). Caregiver depression *over time*, however, was not associated with cortisol patterns ( $p = .614$ ). As in the previous model, no other covariates predicted atypical cortisol patterns.

Supplemental analyses were conducted to examine issues related to collinearity and the potential effect of differences in sample collection time across children on diurnal cortisol patterns. With regard to collinearity, associations among the original predictor variables were examined. As expected, prenatal alcohol, binge drinking, tobacco, marijuana exposure were strongly associated with PCE. There was also a strong association between PCE and number of caretaker changes. It is essential to control for other prenatal drug exposures to isolate the effect of PCE on diurnal cortisol patterns from the potential effect of other substances; thus, these variables remained in our model. However, a logistic regression was re-run excluding caretaker changes to avoid potential overlap with PCE. Results were consistent with a slightly larger effect for high PCE (OR, 2.29; 95% CI, 1.17-4.50;  $p = .016$ ). A median split was then used to classify children as having early or late collection times for the evening and morning measurements. Results of a logistic regression model (controlling for timing of sample collections) were consistent. Children with high PCE (vs. nonexposed) were more likely to have atypical diurnal cortisol patterns (OR, 2.28; 95% CI, 1.12-4.66;  $p = .023$ ). There were no differences for children with some versus no PCE.

## Discussion

Early stressful experiences have been associated with altered development and subsequent dysfunction of the HPA system, specifically in regard to cortisol secretion. In this study, preadolescent children with higher levels of PCE showed a blunted increase in cortisol levels between evening and morning measurements, especially compared to nonexposed children. Extensive maternal use of cocaine during pregnancy may constitute a pervasive stress resulting in increased maternal and fetal cortisol secretion and prolonged exposure to elevated cortisol levels (14). Chronic over-stimulation of the HPA axis during this critical developmental period may lead to later dysfunction of the normal stress response, resulting in physiologic down-regulation of systems that are normally responsive to cortisol. Blunted periodicity could place the body at chronic disadvantage in mounting the normal protective response to day-to-day stresses or to an acute, perhaps, life-threatening event.

Physiologic down-regulation of the neuroendocrine system during early development may have important health implications later in life. Abnormalities in arousal regulation and stress responsivity have been associated with cognitive, behavioral, and socioemotional dysfunction, as well as increased risk for stress-related diseases (e.g., chronic fatigue syndrome, and fibromyalgia) (1, 2, 4, 11, 26, 27). Recent evidence also suggests that several adult diseases, such as cardiovascular and psychiatric diseases, may be etiologically linked to developmental and biological disturbances during early childhood (28). Chronic adverse exposures during sensitive developmental periods may result in significant biologic disruptions that contribute to permanent damage over time. Blunted cortisol reactivity was recently observed in preadolescent children with PCE within a clinic setting (13). Similar to current study findings, this blunted response was associated with higher levels of PCE as well as extrauterine stressors supporting evidence that intrauterine and extrauterine stressors may disrupt the neuroendocrine system. Lester et al. also found that exposure to domestic violence mediated the effect of PCE on cortisol reactivity. Domestic violence was used as a control variable in the current study but mediating analyses were not conducted.

In addition to PCE, race and recent caregiver depression were associated with patterns of overnight change in diurnal cortisol levels. Specifically, children with black mothers were more likely to have low cortisol levels in the evening that remained low in the morning, rather than following the more typical pattern of increase. Few studies have reported racial/ethnic disparities in diurnal cortisol values. Flattened diurnal cortisol patterns have been observed in black and Hispanic adolescents in contrast to white peers, regardless of socioenvironmental factors (29). Similar patterns have also been observed in adults (30). Additional research is necessary to determine what specific characteristics of minority populations may help explain this racial disparity in hormonal response. For instance, race-based discrimination has been associated with increased stress in blacks, subsequently increasing risk for involvement in socially deviant behaviors (e.g., substance use) (31). Other factors such as a higher incidence of adverse health conditions (e.g., hypertension, heart disease) among blacks may also help explain variance in stress hormone levels (32).

In contrast, children with caregivers experiencing recent depression were less likely to demonstrate this atypical cortisol pattern compared to children of non-depressed caregivers. Timing and duration of a child's exposure to caregiver depression may differentially affect cortisol levels. Elevated cortisol levels have been reported in school-aged children exposed to maternal depression during early childhood and in children of recently depressed mothers (9). However, chronic maternal depression has been associated with lower basal cortisol levels in children (33). In this study, recent caregiver depression may have had less of a negative impact on child cortisol patterns because the definition of the exposure was limited to the past week. When assessing reports of caregiver depression occurring over the 11-year period, no group differences were found. Recent caregiver depression in this study may represent a transient rather than a chronic stressor. Given that a hypocortisolism is typically associated with chronic stress exposure, it is not surprising that this specific aspect of the child's environment did not have the same blunting effect on their cortisol secretion as did more chronic variables (PCE and race).

While other anthropometric and environmental variables (e.g., prematurity, foster care, secondhand smoke, SES, and domestic violence) have been associated with variations in child cortisol levels, no such associations were found in the current study between similar variables and diurnal cortisol patterns. This may be partly due to the fact that our sample as a whole was characterized by increased sociodemographic, environmental, and/or biological risk, regardless of PCE. Nonetheless, controlling for these various risk factors is essential in isolating factors that have a stronger impact on the integrity of at-risk children's stress response physiology.

Limitations to the current study must be acknowledged. First, the elevated risk for this cohort (e.g., low SES, predominantly ethnic minority participants, licit prenatal drug exposure) limits the generalizability of results to other high-risk populations. Second, we attempted to statistically control for potential confounders that may have coexisted (e.g., prenatal licit and illicit drug exposure) or arisen over time (e.g., exposure to violence, caregiver depression); however, it was not possible to identify all potential stressors within this sample. The presence of multiple risk factors also limits our ability to determine causality between PCE and later cortisol patterns. In addition, factors such as child caffeine intake may influence cortisol levels. Such data was not available in this study. Lastly, cortisol levels are known to vary between individuals as well as within individuals (e.g., across different days or times of day). Availability of cortisol samples for more than two time-points and across multiple days would have likely enhanced our assessment of diurnal cortisol rhythm. Unfortunately, such methodology was not feasible in this study.

There are also important strengths of this study. To our knowledge, this is the first report of diurnal cortisol patterns in older children with PCE. In addition, reliability and generalizability of study findings were enhanced given that PCE was confirmed through positive EMIT screening and GC/MS confirmation of drug metabolites in meconium, as opposed to a classification based purely on self-report or urine determination of only recent drug metabolites, in a large, multi-site sample. Finally, this study contributes to the growing body of evidence supporting the potential long-term impact of PCE on child health outcomes.

Limited information is available regarding the potential long-term impact of PCE on alterations in cortisol physiology. The current findings suggest that higher levels of PCE may have a long-term effect on a child's neuroendocrine physiology, even after controlling for other acute or pervasive stressors. Being able to anticipate the potential long-term medical, developmental, or behavioral dysfunctions related to altered cortisol physiology is important in optimizing outcomes for children with PCE. Given the potential impact specific stressors may have on children's stress regulation abilities, health professionals (e.g., pediatricians, social workers, counselors) may need to intervene to help reduce the stress load of children with PCE (e.g., referrals for appropriate social services, avoid multiple caretaker changes, address caregiver psychopathology). Ongoing research is needed to understand the long-term consequences that prenatal substance exposure may have on physiology and health into adolescence and adulthood.

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## Abbreviations

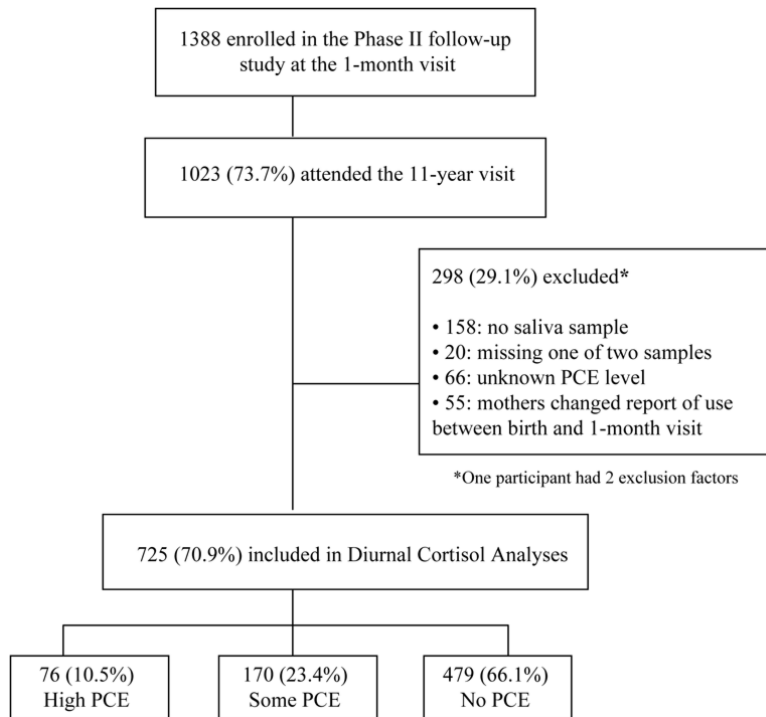
<b>HPA</b>	Hypothalamic-pituitary-adrenal
<b>HS</b>	high school
<b>PCE</b>	prenatal cocaine exposure
<b>SES</b>	socioeconomic status
<b>SGA</b>	small for gestational age

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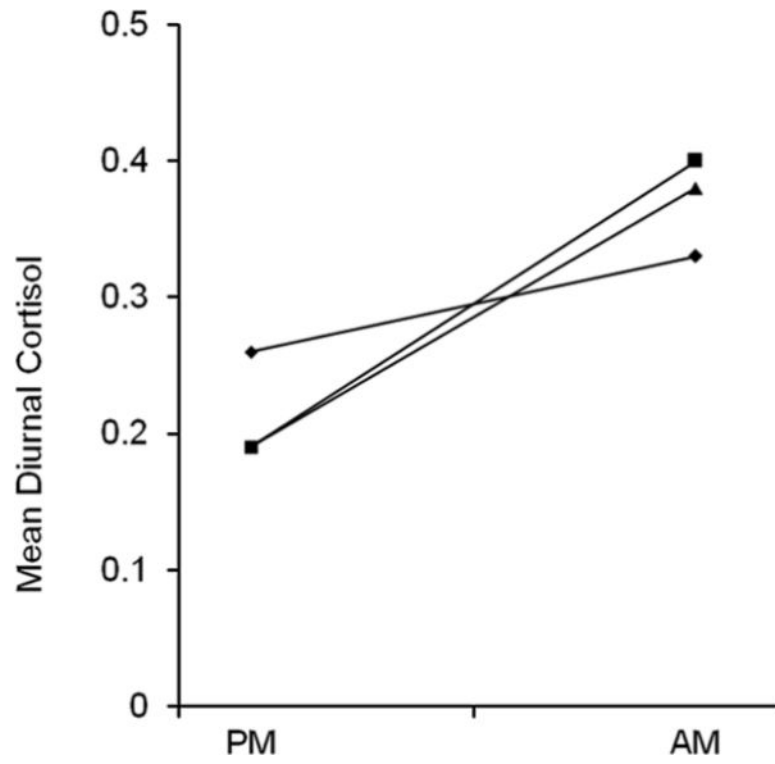
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**Figure 1.**  
Delineation of Study Sample



**Figure 2.** Mean Evening and Morning Diurnal Cortisol Values by Level of PCE. ◆: high PCE; ■: some PCE; ▲: no PCE.

**Table 1**  
Sociodemographic, Anthropometric, and Environmental Characteristics of Study Sample

Characteristic	All (N = 725)	High PCE (n = 76)	Some PCE (n = 170)	No PCE (n = 479)	H vs. N p	S vs. N p	H vs. S p
Male, n (%)	373 (51)	41 (54)	87 (51)	245 (51)	.65	.995	.688
Maternal education, n (%)							
> HS	163 (22)	17 (22)	29 (17)	117 (24)	.002	.001	.309
HS	299 (41)	21 (28)	63 (37)	215 (45)			
< HS	262 (36)	38 (50)	78 (46)	146 (30)			
Race, n (%)							
Black	599 (83)	63 (83)	152 (89)	384 (80)	.813	.024	.346
White	83 (11)	8 (11)	12 (7)	63 (13)			
Other	43 (6)	5 (7)	6 (4)	32 (7)			
SES, mean (SD)	3.48 (0.99)	3.65 (0.86)	3.70 (0.97)	3.38 (1.00)	.025	< .001	.741
SGA, n (%)	166 (23)	24 (32)	42 (25)	100 (21)	.037	.283	.272
LBW, n (%)	293 (40)	33 (43)	71 (42)	189 (39)	.512	.598	.808
Preterm birth, n (%)	288 (40)	26 (34)	71 (42)	191 (40)	.34	.601	.234
Prenatal alcohol use, mean (SD)	0.33 (0.98)	0.89 (1.81)	0.69 (1.27)	0.11 (0.48)	< .001	< .001	.117
Prenatal binge drinking, n (%)	129 (18)	24 (32)	66 (39)	39 (8)	< .001	< .001	.276
Prenatal tobacco use, mean (SD)	6.12 (9.65)	11.42 (11.01)	10.86 (10.78)	3.60 (7.88)	< .001	< .001	.655
Prenatal marijuana use, mean (SD)	0.08 (0.30)	0.19 (0.45)	0.12 (0.40)	0.04 (0.21)	< .001	.002	.112
Prenatal opiate exposure, n (%)	49 (7)	8 (11)	11 (6)	30 (6)	.172	.924	.271
Foster care, n (%)	76 (10)	22 (29)	34 (20)	20 (4)	< .001	< .001	.122
Caretaker changes, mean (SD)	0.75 (1.34)	1.89 (2.08)	1.25 (1.41)	0.38 (0.96)	< .001	< .001	< .001
Caretaker abuse, n (%)	17 (2)	2 (3)	6 (4)	9 (2)	.622	.206	.738
Child abuse, n (%)	9 (1)	2 (3)	3 (2)	4 (1)	.155	.311	.650
Community violence, mean (SD)	3.98 (3.97)	4.74 (4.12)	5.20 (4.16)	3.44 (3.77)	.009	< .001	.417
Caregiver depression, n (%)	64 (9)	6 (8)	15 (9)	43 (9)	.886	.99	.892
Caregiver alcohol use, mean (SD)	0.24 (0.72)	0.25 (0.69)	0.43 (1.04)	0.17 (0.56)	.401	< .001	.081
Caregiver binge drinking, n (%)	100 (14)	7 (9)	38 (22)	55 (11)	.629	< .001	.016
Caregiver tobacco use, mean (SD)	5.59 (9.08)	6.39 (8.66)	7.96 (9.98)	4.64 (8.65)	.125	< .001	.22
Caregiver marijuana use, mean (SD)	0.05 (0.28)	0.05 (0.25)	0.05 (0.17)	0.05 (0.31)	.932	.986	.948

Note. H = high, S = some, and N = none. Statistical comparisons are based on chi-square tests for categorical variables and ANOVAs for continuous variables.

**Table 2**

Diurnal Cortisol Values by Level of PCE

Measurement	All		PCE		H vs. N		S vs. N		H vs. S	
	Mean (SD)	N	High	Some	None	P	P	P	P	
Diurnal Cortisol values (µg/dL), mean (SD)										
Evening	0.20 (0.52)		0.26 (0.59)	0.19 (0.56)	0.19 (0.49)	.180	.791			.170
Morning	0.38 (0.33)		0.33 (0.21)	0.40 (0.45)	0.38 (0.29)	.093	.969			.127
Morning-Evening	0.18 (0.49)		0.07 (0.59)	0.20 (0.45)	0.20 (0.48)	.036	.816			.043
Atypical pattern of change, n (%)	181 (25)		26 (34)	46 (27)	109 (23)	.032	.259			.255

Note. H = high, S = some, and N = none. Statistical comparisons are based on unadjusted linear regression models for diurnal cortisol values, an unadjusted GEE regression model for change in cortisol values over time, and an unadjusted logistic regression model for atypical pattern of change (i.e., increase in diurnal cortisol levels at or below the 25th percentile). Although data transformations were applied in analyses, original units are presented here for easier interpretability.

**Table 3**

Logistic Regression Model of Atypical Pattern of Change in Diurnal Cortisol from Evening to Morning

Variable	Adjusted OR	95% CI	<i>p</i>
Site			
A	0.47	0.22, 1.00	0.051
B	0.66	0.30, 1.44	0.295
C	0.42	0.18, 1.00	0.050
Male	1.14	0.77, 1.67	0.511
Maternal education level			
HS	1.03	0.59, 1.79	0.925
< HS	1.32	0.80, 2.20	0.279
Race			
Black	2.91	1.32, 6.44	0.008
Other	1.10	0.36, 3.36	0.873
SES	1.04	0.84, 1.28	0.745
SGA	1.18	0.71, 1.96	0.524
LBW	0.57	0.32, 1.02	0.057
Preterm birth	1.62	0.93, 2.82	0.091
Prenatal cocaine exposure			
High	2.23	1.11, 4.47	0.025
Some	1.51	0.89, 2.56	0.129
Prenatal alcohol use	0.77	0.55, 1.06	0.112
Prenatal binge drinking	1.44	0.77, 2.69	0.249
Prenatal tobacco use	0.99	0.97, 1.02	0.648
Prenatal marijuana use	0.90	0.45, 1.82	0.779
Prenatal opiate exposure	1.95	0.95, 3.98	0.068
Caretaker changes	1.03	0.88, 1.20	0.749
Foster care placement	0.79	0.37, 1.67	0.538
Caregiver depression	0.38	0.17, 0.89	0.025
Caretaker abuse	2.06	0.68, 6.21	0.200
Child abuse	0.98	0.17, 5.81	0.982
Community violence exposure	0.97	0.92, 1.03	0.321
Caregiver alcohol use	1.03	0.72, 1.47	0.865
Caregiver binge drinking	0.84	0.42, 1.71	0.639
Caregiver tobacco use	1.00	0.97, 1.02	0.782
Caregiver marijuana use	0.62	0.20, 1.94	0.409

*Note.* Atypical change is defined as those in the 25th percentile for least increase in diurnal cortisol levels ( $\mu\text{g/dL}$ ) from evening to morning measurements. Reference categories are site D, female, more than high school, white, average for gestational age, normal birth weight, term, no PCE, no binge drinking, no foster care, and no abuse.