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Salivary Cortisol and Cognitive Development in Infants From Low-Income Communities

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Abstract

Early stress exposure is proposed to have significant lasting effects on cognitive development. The glucocorticoid hormone cortisol, a product of the hypothalamic-pituitary-adrenal (HPA) axis, is a particular focus of research, however, the majority of past research has been based on studies of older children and adults. Evidence linking cortisol levels in infancy with cognitive development is lacking. In a large cohort sample of infants (N = 1,091) oversampled for psychosocial risk, we tested whether basal cortisol levels and cortisol reactivity to emotional stressors administered at 7 and 15 months of age were associated with cognitive development measured at 15 months. Cognitive development was measured using the Mental Development Index of the Bayley Scales of Infant Development. Multiple regression analyses indicated that basal cortisol levels at 15 months, and to a lesser extent at 7 months, were inversely associated with infant cognitive development after adjusting for psychosocial and obstetric risk. The findings provide some of the first evidence that HPA axis activity in infancy is associated with early cognitive development.

Keywords

cortisol; HPA axis; cognitive development; infancy; stress; allostatic load

Introduction

There is now an extensive human literature linking early stress exposure with neurocognitive development in the child and adult [1,2]. The hypothalamic-pituitary-adrenal (HPA) axis is the stress response system that has received the most attention in this area, and the glucocorticoid hormone cortisol, a downstream product of the HPA axis, is a particular focus. This is because glucocorticoid receptors are widely distributed in the brain and concentrated in key regions for cognitive functions (e.g., hippocampus). Several studies have

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shown that the endogenous release of glucocorticoids affects memory and executive aspects of human cognition [3] however key developmental questions remain. The effects of stress on neurodevelopment are thought to be evident in the first years of life [4,5] and it follows that HPA activity may also be associated with cognitive development during this time. This has not yet been confirmed, as research concerning HPA activity and cognition has been based primarily on studies of older children and adults.

The focus on cortisol as a potential influence on cognitive development derives from several lines of evidence. Experiments with adults and non-human animals have shown declines in memory associated with endogenous glucocorticoid release [6,7] and with exogenous administration of cortisol [8]. Observational studies suggest that early life stress is associated with cognitive deficits [9] and elevated cortisol levels in children [10,11]. Furthermore, there is evidence of lower cognitive performance among young children who sustain elevated cortisol levels [12]. Studies in infancy have also shown that prenatal maternal stress and fetal glucocorticoid exposure are associated with infant cortisol regulation [13,14] and reduced cognitive development [15–17].

There are significant conceptual and practical questions for research on stress, HPA activity, and cognitive development during infancy. This is because of rapid developmental changes in cortisol production patterns, including an age-related decline in cortisol reactivity to stress and a lack of stability during this time [18,19]. In addition, both basal (resting) levels of cortisol [10–12] and cortisol reactivity to an acute stressor [20,21] are common measures of HPA axis functioning. Although elevated cortisol levels are often characterized as impairing cognitive functions, there may be conditions in which low cortisol levels are associated with poor outcomes. This may be observed in instances of chronic maltreatment or neglect by caregivers [22] and in clinical cases of prematurity and low birth weight [23]. In terms of reactivity to stress, prior research indicates that moderate physiological reactivity is positively associated with early executive function and self-regulation ability in young children [24] and with increased synaptic potentiation in the prefrontal cortex and hippocampus [3,25]. It may be that blunted reactivity and regulation of cortisol in response to stress is especially relevant to the relation between psychosocial stress and early cognitive development in infancy.

The purpose of this study was to examine associations between cortisol and cognitive development in infants. Measures of basal salivary cortisol levels as well as cortisol reactivity and regulation during stress were obtained at 7 and 15 months of age and were used to predict cognitive development at 15 months. Given that infants in the current study represent a non-clinical sample whose stress exposure is within the normative range, we hypothesized that infants displaying lower basal cortisol levels at 7- and 15-months of age would evidence higher cognitive development at 15 months relative to infants sustaining higher basal cortisol levels. Furthermore, given the positive association between moderate physiological stress reactivity and children's cognition, we hypothesized that infants displaying increased reactivity to a stressor followed by down regulation (i.e. recovery) of this stress response would evidence higher cognitive development relative to infants displaying blunted reactivity and recovery from a stressor.

Method

Participants

The Family Life Project (FLP) was designed to study a representative sample of rural families in two regions of the United States with high child poverty rates [26]. Three counties in eastern North Carolina (NC) and three counties in central Pennsylvania (PA) were selected to represent the Rural South and Appalachian regions, respectively. The FLP adopted a developmental epidemiological design in which sampling procedures were employed to recruit a representative sample of 1,292 children whose families resided in one of the six counties at the time of the child's birth. Low-income families were oversampled in both states and African American families were oversampled in NC (African American families were not oversampled in PA because the communities there were at least 95% non-African American). A comprehensive description of the sampling plan and recruitment procedures are provided by Vernon-Feagans, Cox and The Family Life Project Key Investigators [27].

The data used in this analysis come from 1,091 infants who were seen at two study visits occurring at approximately 7 months of age (M = 7.67, SD = 1.42, range 5.02 – 13.71 months) and 15 months of age (M = 15.68, SD = 1.29, range 13.98 – 22.32 months; 548 boys, 543 girls). 57% of infants in the analysis sample were Caucasian and approximately 60% of families resided in NC. The average income-to-needs ratio (INR) of families was 1.95 at the 7-month visit and 1.90 at 15 months; 67% of families had an average household income below 200% of the federal poverty line (i.e., INR < 2.0) at both assessments. 50% of mothers had a high school education or less; 16% of mothers had completed at least four years of post-secondary education.

Procedures and Measures

Data collection took place at home visits when children were 7 and 15 months of age. Two home visitors were present at each visit. Visits lasted approximately 2–3 hours in duration. During the visits, mothers completed questionnaires concerning family demographics and psychosocial variables. Near the conclusion of each home visit, at which time the data collectors had been in the home for at least 1 hour, children were presented with emotion challenge tasks. At the 7-month visit, this included a mask presentation, followed by a barrier challenge and an arm restraint challenge task. At 15 months, the barrier challenge task was replaced with a toy removal challenge, which was followed by the mask presentation challenge [28]. To assess basal levels of cortisol as well as cortisol response to and recovery from the emotion challenge tasks, three saliva samples were collected. The first sample was collected prior to the administration of the emotion challenge tasks. The second sample was collected at 20 minutes post peak emotional arousal to the challenge tasks. The third sample was collected at 40 minutes post peak emotional arousal to the challenge tasks. Peak arousal was determined by the data collectors using clear guidelines established in the experimental protocol. Peak arousal for the great majority of infants occurred at the conclusion of the emotion challenge tasks at both time points. Children who became highly aroused during the course of task administration as indicated by 20 seconds of hard crying and who were determined to be too aroused for further task administration were considered

to have reached peak arousal. Unstimulated whole saliva was collected using either cotton or hydrocellulose absorbent material and expressing sample into 2-ml cryogenic storage vials using needleless syringe (cotton) or by centrifugation (hydrocellulose). Two prior studies indicated no differences in cortisol concentrations associated with the two collection techniques [29,30]. At the 15-month visit, a research assistant administered the Bayley Scales of Infant Development [31].

Prior research indicates that low birth weight [32], birth complications associated with neonatal intensive care unit (NICU) stay [33], maternal cigarette smoking during pregnancy [34], family socioeconomic status [9], duration of breastfeeding [35], and maternal psychosocial stress [36] are associated with cognitive development. To address these potential confounds in our analyses, we examined a number of obstetric and current psychosocial risk factors known to be associated with cognitive development. We also included a measure of children's temperament given prior research indicating relations between perinatal stress exposure and children's exploration, affect, and goal-directedness during cognitive tests [37] and given findings suggesting that temperamental characteristics, including children's activity levels, are significant factors contributing to infants' and toddlers' performance in cognitive tests including the Bayley Scales of Infant Development [38]. We also included a number of other child covariates including family's state of residence, child ethnicity, birth order, sex, and age at testing.

Child cognitive development—The child's cognitive development was assessed using the Mental Development Index (MDI) of the Bayley Scales of Infant Development (BSID-II) [31], the leading cognitive measure for infants.

Salivary cortisol—After saliva collection (see procedures, above), samples were immediately placed on ice, then stored frozen at −20°C and subsequently stored at −80°C until they were assayed for salivary cortisol using a highly sensitive enzyme immunoassay (Salimetrics, Carlsbad, CA); samples were assayed in duplicate. Inter and intra-assay coefficients of variation were less than 15 and 10%.

Socio-demographic, geographic, and child covariates—Socio-demographic covariates included a) Income-to-need ratio, which was based on maternal-reported income from all sources and any income from other household members; this figure was divided by the federal poverty threshold for 2004 adjusted for number of persons in the home. A family income-to-need ratio of 1.00 or below indicates family income at or below the poverty level, adjusted for family size. b) Maternal education was based on the total number of completed years of schooling. The family's state-of-residence was coded 1 for NC and 0 for PA. Child covariates included a) ethnicity coded 1 for Caucasian and 0 for non-Caucasian b) sex coded 1 for female and 0 for male c) age at testing, in months.

Maternal mental health symptoms—Maternal mental health was based on the short form of the Brief Symptom Inventory (BSI) [39] administered at the 7- and 15-month study visits. The 18 items of the BSI are evaluated on a 0–4 point Likert-type scale with higher values indicating higher levels of reported symptoms. Summing across all items provided a Global Severity Index (GSI), which was used as a global score of reported maternal

psychopathological symptomatology. Internal consistency was reasonable for 7- and 15-month scores of total symptoms (alphas were .88 and .92 for 7- and 15-month visits, respectively). 7- and 15-month GSI scores were averaged to generate a composite score of maternal symptomatology.

Child temperament—Temperament was assessed using an adaptation of the Infant Behavior Record (IBR) [40], completed independently by both home visitors after the 15-month visit and applied to behavior globally across the entire home visit [41]. The IBR scales included Sociability, Positive Affect, Attention, Activity Level, Reactivity, and Irritability. The mean of the home visitors' ratings were used. Alphas for the multi-item scales (Sociability, Positive Affect, and Attention) were .64, .65, and .82, respectively. A Principal Component Analysis (PCA) extracted two factors. The first factor, which we labeled *affect/attention*, included the irritability, positive affect, attention, and sociability scales (factor loadings on the rotated factor solution were −.91, .85, .81, .37, respectively). The second factor, which we labeled *activity/social responsiveness*, included the reactivity, activity level, and sociability scales (factor loadings of the rotated factor solution were .90, .78, .70, respectively). The sociability scale loaded onto both factors, however its contribution to the first factor, affect/attention, was small (loading was .37). The composite factors, affect/attention and activity/social responsiveness, were included as covariates predicting infant cognitive development.

Obstetric and early postnatal covariates—Obstetric and early postnatal factors included a) birth weight (grams) as well as a categorical low birth weight variable where 1 was coded as < 2500g and 0 coded as ≥ 2500g b) birth order coded 1 for first-born c) maternal smoking during pregnancy coded 1 if the biological mother reported smoking cigarettes every day for at least three months during her pregnancy d) duration of breastfeeding (total number of months by the 15-month assessment) and e) maternal report of whether the infant spent time in the NICU after birth coded 1 for yes and 0 for no.

Missing Data

Data were collected on 1,169 of the 1,292 originally recruited families when the child was approximately 15 months of age. Of the 1,169 infants seen at 15-months, 1,091 had complete data on the Mental Development Index (MDI) of the Bayley Scales of Infant Development. Families missing MDI data (n = 78) were excluded from the analysis sample. Of the remaining 1,091 families, 10% or fewer were missing data for any analysis variable other than cortisol. Children missing cortisol at 7 or 15 months tended to be older and to have lower family income. To avoid bias in the parameter estimates associated with missing data, full information maximum likelihood (FIML) [42] was used as a missing data treatment in all analyses. FIML uses all of the information in the independent variables to estimate the covariance matrix, allowing us to include all infants that had complete MDI data, regardless of their amount of missingness on the independent variables.

Statistical analyses

The cortisol distributions were subjected to natural log (ln) transformation to correct for positive skew. Outliers greater than +/− 3 *SD* after transformation were treated as missing (at

7 months: n = 11, 13, and 14 for baseline, 20-minute, and 40-minute samples, respectively; at 15 months: n = 16, 8, and 10 for baseline, 20-minute, and 40-minute samples, respectively). Time of day of saliva collection was inversely associated with cortisol at each time point (rs ranged from −.18 to −.31, $p < .001$), which indicates that saliva samples collected later in the day had lower cortisol concentrations, on average, than saliva samples collected earlier in the day. Thus, consistent with much prior literature showing the diurnal pattern of cortisol, it was important that we control for time of day in all analyses. We controlled for time of day by regressing each cortisol sample at 7- and 15-month visits onto the time of day (24-hour clock) at which the first saliva sample was taken and saving the unstandardized residuals. These natural log-transformed and time-of-day-corrected cortisol values were then used in all correlation and regression analyses. For descriptive purposes, however, we report the raw cortisol values in Table 1.

Following this, we conducted a series of descriptive and preliminary analyses. We used paired samples t-tests to examine differences in infants' cortisol levels at baseline (before administration of the emotion challenge task), 20-minutes post-peak emotional arousal, and 40-minutes post-peak emotional arousal at both 7- and 15-month visits. For descriptive purposes, we computed delta scores to assess cortisol change (i.e., the difference between 20-minutes post-peak and baseline) and included these variables in the zero-order correlation analyses in Table 2.

To address our primary research aim, the prediction of infant cognitive development from cortisol, we conducted an Ordinary Least Squares (OLS) regression model using Mplus 7 software [43]. MDI scores at 15 months were regressed onto 7- and 15-month baseline cortisol levels, as well as on cortisol levels collected at 20-minutes and 40-minutes post-peak emotional arousal following exposure to the emotion challenge task. Thus, baseline and reactivity cortisol levels were included as separate predictors of the MDI. In this same model, socio-demographic, child, parent, and obstetric covariates were included. The covariates listed above were included in the model on an *a priori* basis. All continuous predictors were mean-centered. In supplementary analyses we present several modifications to the analyses, which serve as robustness checks.

Results

Descriptive analyses

As shown in Table 1, Bayley scores of mental development were slightly lower and less variable than in the reference population (M = 96.27, SD =10.69 vs. M = 100, SD = 15.00). With regard to obstetric variables, approximately 4% (n = 41) of primary caregivers reported that their child had visited the NICU after birth. Children in the study sample were in the normal range of birth weight (M = 3,276.12 grams, SD = 578.18 grams). 8% (n = 87) of infants were low birth weight (< 2,500 grams). Mothers reported breastfeeding their children for 2.58 months post-birth, on average, although 52% (n = 572) of mothers reported having never breastfed their child. Of those who reported breastfeeding, only 12% (n = 64) reported breastfeeding past 12 months post-birth. 16% (n = 172) of mothers reported that they had smoked cigarettes every day for at least three months of their pregnancy. Maternal mental health symptoms were low, on average, as measured by the Brief Symptoms Index.

Cortisol patterns at 7 and 15 months

Preliminary analyses indicated that at 7 months, infants displayed a physiological response to the emotional stressor indicated by increases in cortisol levels from baseline to 20-minutes post-peak arousal (paired $t(886) = -4.23$, $p < .001$), followed by a decrease in cortisol levels from 20 to 40 minutes post-peak arousal (paired $t(797) = 6.22$, $p < .001$). Baseline and 40 minutes post-peak arousal cortisol levels were not statistically different from one another (paired $t(829) = -0.11$, *ns*). At 15 months, infants displayed a significant increase in cortisol from baseline to 20-minutes post-challenge (paired $t(839) = -7.72$, $p < .001$); however, in contrast to the 7-month visit, toddlers' 15-month cortisol levels did not decline, on average, from 20- to 40-minute post-peak arousal (paired $t(765) = 1.26$, *ns*) and 40-minute post-peak levels remained significantly higher than baseline levels (paired $t(783) = -6.13$, $p < .001$). Baseline cortisol at 7-months was higher, on average, than baseline cortisol at 15-months (paired $t(865) = 4.91$, $p < .001$).

Table 2 depicts correlations between study variables. At 7- and 15-months, cortisol values were moderately to highly correlated within visit (*r*s ranged from .41 to .79 *p*s < 0.01), but there is little evidence of intra-individual stability between visits. Both 7-month ($r = -.11$, $p < 0.01$) and 15-month ($r = -.12$, $p < 0.01$) baseline measures of cortisol were associated with scores on the MDI at 15 months. Correlations between delta scores (20-minute post peak sample minus baseline sample) and baseline levels indicated that lower baseline cortisol levels were associated with increased cortisol reactivity at both time points ($r = -.50$ $p < .001$ at 7 months; $r = -.35$ $p < .001$ at 15 months). Cortisol reactivity at 7 ($r = .08$, $p < 0.05$) and 15 months ($r = .12$, $p < .01$) was associated with the MDI at 15 months. The child temperament factors, affect/attention ($r = .15$, $p < .01$) and activity/social responsiveness ($r = .10$, $p < .01$), were associated with cortisol reactivity to the emotional stressor at 15-months. There were few significant relations among cortisol and socio-demographic risk. Having been in the NICU was associated with higher baseline cortisol at 7 months ($r = .09$, $p < .01$) and there was a modest inverse correlation between maternal education and baseline cortisol at 15 months ($r = -.08$, $p < .05$). Birth weight ($r = .15$, $p < .01$), duration of breastfeeding ($r = .16$, $p < .01$), maternal education ($r = .21$, $p < .01$), maternal mental health symptoms ($r = -.10$, $p < .01$), and income ($r = .20$, $p < .01$) were each associated with the MDI.

Associations of Cortisol with Cognitive Development

7 months—Results of the OLS regression model predicting MDI scores at 15 months are included in Table 3. Baseline cortisol at 7 months was uniquely negatively associated with MDI at 15 months ($b = -0.988$, $SE = 0.487$, $p < 0.05$) over and above the effects of 15-month cortisol and covariates. In terms of effect size, a one standard deviation increase in baseline cortisol was associated with a 0.07 standard deviation decrease in MDI scores. Cortisol at 20-minutes post-peak arousal at 7 months was positively associated with mental development at 15 months ($b = 1.569$, $SE = 0.753$, $p < 0.05$). A one standard deviation increase in cortisol reactivity at 20-minutes post peak arousal was associated with a 0.11 standard deviation increase in MDI scores. Cortisol at 40-minutes post-peak arousal was marginally negatively associated with MDI scores, suggesting that lower cortisol at 40-

minutes following peak emotional arousal to the emotion challenge tasks was associated with higher MDI at age 15 months net of all other predictors in the model.

15 months—Baseline cortisol at 15 months was inversely associated with mental development at 15 months ($b = -1.605$, $SE = 0.561$, $p < 0.01$) over and above the effects of 7-month cortisol and covariates. A one standard deviation increase in baseline cortisol levels was associated with a 0.11 standard deviation decrease in MDI scores. In contrast to the patterns of 7-month cortisol and the zero-order correlations in Table 2, 20-minute and 40-minute samples (cortisol reactivity and regulation) at 15-months were not associated with MDI scores.

Socio-demographic and Obstetric Risk and Cognitive Development at 15 Months

Several covariates were also uniquely associated with infant cognitive development. MDI scores were significantly negatively associated with age, low birth weight (using the < 2500g cut-off), and being a member of the North Carolina sample. MDI scores were significantly positively associated with being female, income-to-needs ratio, maternal education, and temperamental affect/attention and activity/social responsiveness. Obstetric and postnatal variables including NICU visit, being a first-born child, duration of breastfeeding, and smoking during pregnancy were not associated with MDI scores. The full model accounted for approximately 26% of the variance in Bayley MDI scores at 15 months.

Supplementary analyses

Supplementary analyses were carried out to test the robustness of the model and examine exploratory hypotheses. First, an alternative model using birth weight as a continuous variable resulted in substantively identical findings. Second, we re-ran the model excluding those infants with a birth weight below 2500g or who were admitted to the NICU (n=104). The parameter estimates changed minimally (for baseline cortisol at 15 months, $b = -1.492$, $SE = 0.589$, $\beta = -0.104$, $p = .01$; for baseline cortisol at 7 months, $b = -0.933$, $SE = 0.524$, $\beta = -0.061$, $p < .10$) and the coefficient for the 7-month reactivity measure was no longer significant at $p < .05$ (details available from the first author). We also considered the possibility that the cortisol prediction was moderated by child sex or birth weight, two factors frequently included in research on cortisol; there was no evidence of moderation. Additionally, given the wide age range of infants in the sample, we reran the final model with a restricted sample that included only those infants who ages fell within one standard deviation of sample mean at both 7- and 15-month time points. The associations between baseline cortisol levels and MDI scores became stronger (15 months, $b = -2.366$, $SE = 0.719$, $\beta = -0.177$, $p = 0.001$; 7 months, $b = -1.385$, $SE = 0.594$, $\beta = -0.096$, $p = 0.02$). The coefficient for the 7-month reactivity was no longer significant at $p < .05$.

To test estimates from our final model against another parameterization of cortisol reactivity, we computed residual change scores [44] (regressed 20-minute cortisol levels on baseline levels and saving the residuals for both 7- and 15-months). Estimates changed minimally (baseline cortisol at 15 months, $b = -1.231$, $SE = 0.417$, $\beta = -0.085$, $p = 0.003$; baseline cortisol at 7 months, $b = -0.760$, $SE = 0.426$, $\beta = -0.05$, $p < .10$) in a model that included

residual change scores along with baseline levels predicting MDI. Coefficients for the 7- and 15-month reactivity residual change scores were not significant at $p < .05$.

Because time of day of saliva collection varied between and within participants in the sample, we reran our models with subgroups of the full sample in which saliva was collected either in the morning or in the afternoon/evening. First, analyses were rerun in a subsample of cases that provided 7-month saliva samples in the morning (n = 359). Controlling for 15-month cortisol levels, 7-month baseline cortisol levels sampled in the morning were not associated with MDI scores ($b = 0.35$, $p = .65$). 20-minute ($b = 0.08$, $p = .95$) and 40-minute cortisol levels ($b = -1.24$, $p = .33$) at 7 months were also not associated with MDI scores. Next, the analysis sample was restricted to include only those cases that provided their 7-month saliva samples in the afternoon/evening (n = 639). In this time window, the analysis yielded results that were consistent with those obtained in the analysis of the full sample. Specifically, controlling for 15-month cortisol levels, 7-month baseline cortisol levels sampled in the afternoon/evening were significantly associated with MDI scores ($b = -1.67$, $p = 0.007$). 20-minute ($b = 2.68$, $p = 0.006$) and 40-minute cortisol levels ($b = -2.08$, $p = 0.04$) at 7 months were also significantly associated with MDI scores. Next, analyses were rerun in a subsample of cases that provided 15-month saliva samples in the morning (n = 299). Controlling for 7-month cortisol levels, 15-month baseline cortisol levels sampled in the morning were associated with MDI scores at trend-level significance ($b = -1.74$, $p = 0.06$). Consistent with the analysis of the full sample, neither 20-minute nor 40-minute cortisol levels sampled in the morning were associated with MDI scores at 15 months. Finally, the analysis sample was restricted to include only those cases that provided their 15-month saliva samples in the afternoon/evening (n = 639). In this time window, the analysis yielded results that were similar to those obtained in the analysis of the full sample. Specifically, controlling for 7-month cortisol levels, 15-month baseline cortisol levels sampled in the afternoon/evening were associated with MDI scores ($b = -1.60$, $p = 0.02$). Consistent with the analysis of the full sample, neither 20- nor 40-minute cortisol levels sampled in the afternoon/evening were associated with MDI scores. In summary, supplementary analyses indicated that the associations observed between baseline cortisol levels and MDI scores were relatively robust across many different model specifications.

Discussion

There is considerable theoretical interest in the relation between stress physiology and cognitive and social-emotional development in infancy. In part, this is due to the concern that early stress exposure may have an adverse impact on neurocognitive development. Cortisol has been a particular focus of research as a mediator of stress exposure, but evidence indicating that cortisol in infancy is associated with cognitive development has been lacking. Findings from this large-scale sample of high-risk families contribute to this literature by demonstrating that HPA activity at 7 and 15 months is associated with cognitive ability at 15 months of age, after accounting for psychosocial and demographic covariates. Specifically, we found that the prediction derived primarily from basal or resting cortisol levels rather than from cortisol reactivity to an acute stressor.

An important feature of our results is that the inverse association between basal cortisol and cognitive development was found at both the 7-month and 15-month assessments. The consistency of this association – which was stronger at the 15-month assessment – should be considered in light of the absence of rank-order stability in cortisol between the two assessments. This may imply an allostatic process [45] in which re-occurring stress in the child's environment is understood to alter basal cortisol levels in ways that are injurious to early cognitive development. Findings from the current study regarding relations between HPA functioning at two time points and cognitive development may be interpreted in view of prior research and theory concerning influences on the development of the HPA axis during infancy and early childhood. Experiential input from both inside and outside of the home influences the developing HPA axis in ways that may optimize the child's fitness within their particular environment [46]. In contexts characterized by high stress, however, these processes may not be without certain costs to early cognitive development [46]. In a previous study using the same sample reported here, Blair and colleagues [47] reported an inverse association between children's basal cortisol levels averaged across the first two years of life and children's executive functioning at 36 months of age. The current findings, relating infants' basal cortisol levels to cognitive outcomes at 15 months, thus provide an incremental step in our understanding of the mechanisms of very early cognitive development in infancy and toddlerhood.

The allostatic load framework for the interpretation of our findings suggests a mechanistic association between glucocorticoids and cognitive development. Glucocorticoids bind to receptors in the hippocampus and at elevated levels impair neurogenesis, increase vulnerability to insults, and decrease dendritic branching [48,49]. Glucocorticoids also alter hippocampal structure and function by inducing oligodendrogenesis [50]. Glucocorticoid receptors also proliferate in the prefrontal cortex, which is involved in the control of attention and the development of executive function abilities [51]. This neurobiology, however, would only partially account for lower cognitive performance at age 15 months in this sample. Reduced stimulation for development in the context of socioeconomic risk as well as other potential factors such as reduced speed of information processing associated with low birth weight may also contribute to observed associations – but the prediction from cortisol shown in Table 3 is independent of these additional processes. Our findings are notable in a developmental context in showing that (at least some) of the mechanisms linking cortisol with cognitive function are extant in infancy, and that this is so despite the changes in cortisol production and considerable volumetric changes in the infant brain within the first years of life [52].

Furthermore, as with a prior study with a smaller sample [21], we found that cortisol reactivity in response to an acute stressor at 7 but not at 15 months was positively associated with mental development at 15 months. Notably, however, this association was seen at 7 months but not at 15 months. This is despite a zero order correlation between cortisol reactivity at 15 months and MDI (see Table 2). We suggest that the inverse association of basal cortisol with cognitive development is a more robust and directly interpretable association, likely indicative of the cumulative effect of stress on development, because it replicates at both assessments and because the basal cortisol prediction is significant after accounting for reactivity (the reverse was not the case).

An additional feature of the analyses is that we covaried child, parent, psychosocial, and obstetric risks, which enhances the robustness of the cortisol prediction by ruling out possible confounds and adds to the research on stress and neurocognitive development. Prior studies suggest that socioeconomic status is associated with neurodevelopment [5] and elevated morning cortisol in very young children [11]. The current findings replicate and extend that work by showing that socio-demographic stress is associated with child cognitive development as early as 15 months. The findings from regression analyses show that cortisol predicts cognitive development after accounting for socio-demographic stress.

We are also mindful of the limitations of our analysis. Time of day of saliva collection varied between and within participants in this study across time. Measuring cortisol levels at varying times of day is potentially problematic for interpretation of the results not only because of the diurnal rhythm of cortisol levels across the day, but also because reasons for cortisol elevations in the morning may be different than reasons for cortisol elevations in the afternoon/evening. For example, prior studies have shown certain forms of severe stress including maltreatment and neglect to be associated with lower morning levels [22] and other forms of stress including maternal emotional unavailability to be associated with higher cortisol levels in the morning [53]. Exposure to chronic forms of stress have been associated with elevated afternoon/evening levels of cortisol [54]. Although the variation in time of sampling is a limitation of the current analysis, concerns are reduced somewhat through our robustness checks. Robustness checks restricting the sample to specific times of the day indicated that results were stronger for samples collected in the afternoon. Given prior studies indicating that elevations in afternoon and evening cortisol levels may be associated with more chronic stress exposure [54], relations found in the current analysis between heightened cortisol levels in the afternoon and reduced cognitive development may be indicative of the chronic stressors faced by families in the sample that have implications for both physiological functioning and cognitive development in infants and children. Prior analyses of this sample indicate that chronic exposure to household risks including instability in caregivers and economic hardship are positively associated with cortisol levels in infancy and toddlerhood and that the magnitude of this relation increases as children grow [10]. Additional analyses of this sample indicate that cortisol levels mediate the relation between household risk and early executive function development [47].

Although findings from the current study are consistent with prior literature, other saliva sampling strategies including measuring cortisol levels over multiple days and within shorter time windows may have been preferable and would have increased the reliability of our estimates. Similarly, collecting other measures of HPA axis functioning including diurnal cortisol levels may also have been preferable given their precedence in the literature and relative ease of interpretation.

Another limitation concerns the generalizability of our findings, given the large proportion of low-income families in the sample. Additionally, a single assessment of infant cognitive development and the correlational nature of our analyses limit our ability to infer causality with respect to relations among variables. It may be that infant cortisol levels covary with other unmeasured variables including prenatal maternal distress [13,14], mode of delivery [55], and prematurity [20], which may or may not covary with cognitive development.

Broader settings-level factors such as whether or not a child attends childcare outside of the home may also be relevant for understanding very early HPA axis functioning. For instance, prior work has established associations between the childcare setting and cortisol regulation [56] and also shown that exposure to out-of-home childcare interacts with household risk to influence cortisol levels in childhood [57]. Given the design of the current study, we cannot rule out the possibility of omitted third variables and stress the need to interpret findings with caution. These limitations are offset by several strengths, including a large and representative sample of high-risk families, repeated assessment of cortisol at two stages in infancy, and detailed assessment of multiple types of psychosocial and obstetric confounds.

The Bayley MDI scale assesses a more general measure of cognitive function than measures used in studies of cortisol and cognition in adults, which tend to focus on specific cognitive capacities like working memory. It may be that distinguishing cognitive capacities in infants may illuminate more subtle features for a role of cortisol in cognitive development. That being said, we note the considerable interest in trying to operationalize working memory in infants and its relation to brain circuits [58]. Additionally, further research is needed to challenge the model that elevated cortisol is linearly associated with poorer cognitive performance. A non-linear model of cortisol and cognitive function has been demonstrated [3], and elevated cortisol may be associated with enhanced memory, perhaps especially to emotionally arousing events [59].

Interventions to influence cortisol levels have proliferated in recent years [60,61]. Although it is not yet clear what would constitute elevated and therefore an at-risk range of cortisol for cognitive development in the young child, findings from the current study reinforce the potential value in incorporating biomarkers of stress such as cortisol in early interventions by suggesting that the biological impact of early stress exposure relevant for cognitive development may be evident as early as infancy.

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Lay Summary

In a large sample of infants from primarily low-income families in the U.S., higher cortisol levels at 7 and 15 months of age were found to be associated with poorer cognitive development at 15 months of age. This study provides some of the earliest evidence that the stress response system is associated with cognitive development in infants and suggests how subsequent interventions may promote healthy brain development in young children.

Table 1

Descriptive statistics of the analysis variables (N = 1,091)

	n	Mean/%	*SD*	Min.	Max.
Child variables					
Bayley MDI	1091	96.27	10.69	59.00	132.00
Salivary cortisol					
Baseline 7 months μg/dl	998	0.21	0.21	0.02	1.58
20-minutes post peak 7 months μg/dl	904	0.24	0.26	0.02	2.12
40-minutes post peak 7 months μg/dl	845	0.21	0.21	0.02	1.81
Baseline 15 months μg/dl	938	0.19	0.20	0.01	1.63
20-minutes post peak 15 months μg/dl	892	0.23	0.27	0.01	2.06
40-minutes post peak 15 months μg/dl	834	0.23	0.25	0.02	2.16
Time of day 7 months (24-hour clock)	998	13.61	2.88	8.18	20.08
Time of day 15 months (24-hour clock)	938	14.02	2.91	8.75	20.40
Child race (% Caucasian)	1091	57%			
State of residence (% NC)	1091	59%			
Child's sex (% female)	1091	50%			
Child's age (7-month visit)	1069	7.67	1.42	5.02	13.71
Child's age (15-month visit)	1091	15.68	1.29	13.98	22.32
Birth weight (grams)	1089	3276.12	578.18	453.59	5443.10
% low birth weight (< 2,500 grams)	1089	8%			
NICU visit (% yes)	1081	4%			
First-born child (% yes)	1091	39%			
Duration of breastfeeding (months)	1090	2.58	4.24	0.00	18.00
Family and Maternal variables					
Household income					
% Below poverty line (INR < 1)	983	34%			
% Low income (INR between 1 and 2)	983	33%			
% Middle income (INR ≥ 2)	983	33%			
Education (% highest level is HS graduation)	1091	50%			

	n	Mean/%	*SD*	Min.	Max.
Smoked every day during pregnancy (% yes)	1086	16%			
Brief Symptoms Index (GSI)	1090	6.77	7.47	0.00	60.00

Note: MDI = Mental Development Index; NC = North Carolina; HS = High School; IBR = Infant Behavior Record; NICU = Neonatal Intensive Care Unit; INR = income-to-needs ratio

Table 2

Zero order correlations among the analysis variables (N = 1,091)

Variables	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1. MDI	1																	
2. Cort B 7	−.11**	1																
3. Cort 20 7	−.04	.48**	1															
4. Cort 40 7	−.05	.41**	.79**	1														
5. Cort B 15	−.12**	.02	.07*	.00	1													
6. Cort 20 15	−.02	.00	.05	.05	.63**	1												
7. Cort 40 15	−.01	.03	.06	.03	.54**	.79**	1											
8. Cort Δ 7	.08*	−.50**	.52**	.38**	.01	.05	.04	1										
9. Cort Δ 15	.12**	−.01	.00	.06	−.35**	.51**	.34**	.04	1									
10. BW	.15**	−.03	−.01	.00	.02	−.01	.02	.00	.00	1								
11. NICU	−.07*	.09**	.04	.02	.00	−.04	−.04	−.03	−.05	−.29**	1							
12. Breastfeed	.16**	−.02	.04	.03	.00	−.05	−.02	.05	−.03	.13**	.03	1						
13. Mat. Ed.	.21**	−.04	−.03	−.02	−.08*	−.07*	−.03	.01	.01	.18**	−.01	.36**	1					
14. Affect	.06*	.03	.02	.03	−.09**	.07*	.02	.01	.15**	−.02	.01	−.03	−.02	1				
15. Activity	.29**	.00	.01	.07*	−.04	.03	−.01	.02	.10**	.05	−.01	.06*	.11**	.19**	1			
16. BSI	−.10**	.04	.02	−.02	.01	.03	−.03	−.01	.01	−.05	.02	−.06*	−.20**	−.04	−.08*	1		
17. Smoke	.02	−.03	−.07*	−.06	−.01	.00	−.04	−.03	−.01	−.15**	.02	−.12**	−.22**	−.08*	−.01	.06*	1	
18. INR	.20**	−.04	−.03	−.02	−.01	−.03	.01	.02	−.02	.11**	.01	.28**	.52**	−.08*	.09**	−.16**	−.12**	1

Note:

** $p < 0.01$;

* $p < 0.05$;

MDI = Mental Development Index; Cort B 7 = Cortisol baseline sample taken at 7 months; Cort 20 7 = Cortisol 20-minute sample taken at 7 months; Cort 40 7 = Cortisol 40-minute sample taken at 7 months; 15 = 15 months; Cort Δ = cortisol difference score (20-minute post peak sample minus baseline sample); BW = birth weight; NICU = Neonatal Intensive Care unit; Breastfeed = duration of breastfeeding; Mat. Ed. = years of maternal education; Affect = Affect factor extracted from principal component analysis of Infant Behavior Record; Reactivity = Reactivity factor extracted from principal component analysis of Infant Behavior Record; BSI = Brief Symptoms Index; Smoke = maternal smoking during pregnancy; INR = household income-to-needs ratio; Affect = Affect/Attention factor; Activity = Activity/Social responsiveness factor

Table 3

Regression predicting Bayley Scale of Infant Development at 15 months of child age (N = 1,091)

Variable	*b*	*SE*	β	*p*
Intercept	95.714	0.920	8.958	< .001
Cortisol (ln)				
Baseline 7 months	−0.988	0.487	−0.066	.042
20-minutes post peak 7 months	1.569	0.753	0.110	.037
40-minutes post peak 7 months	−1.373	0.784	−0.091	.080
Baseline 15 months	−1.605	0.561	−0.112	.004
20-minutes post peak 15 months	0.122	0.750	0.009	.871
40-minutes post peak 15 months	0.560	0.708	0.041	.429
Covariates				
Income-to-needs ratio	0.625	0.217	0.100	.004
Mat. Education	0.287	0.129	0.075	.026
Mat. Mental health symptoms	−0.073	0.039	−0.051	.059
Low birth weight	−3.521	1.143	−0.089	.002
NICU visit	−1.419	1.599	−0.025	.375
First-born child	0.666	0.595	0.030	.263
Duration of breastfeeding	0.056	0.075	0.022	.456
Smoke during Pregnancy	0.911	0.826	0.031	.270
Affect/Attention	1.001	0.329	0.085	.002
Activity/Social responsiveness	2.230	0.321	0.194	<.001
Child’s ethnicity (Caucasian)	1.233	0.781	0.057	.114
Child’s sex (female)	2.434	0.568	0.114	<.001
Child’s age	−1.874	0.236	−0.225	<.001
NC	−2.429	0.782	−0.112	.002
Total R^2		0.26		

Note: ln = natural log transformed; NC = North Carolina; Mat. = Maternal; NICU = Neonatal Intensive Care Unit