Development and Psychopathology (2025), **37**, 1707–1720
doi:10.1017/S0954579424001287

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Regular Article

Timing sensitivity of prenatal cortisol exposure and neurocognitive development

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Abstract

Prenatal glucocorticoid exposure has been negatively associated with infant neurocognitive outcomes. However, questions about developmental timing effects across gestation remain. Participants were 253 mother-child dyads who participated in a prospective cohort study recruited in the first trimester of pregnancy. Diurnal cortisol was measured in maternal saliva samples collected across a single day within each trimester of pregnancy. Children (49.8% female) completed the Bayley Mental Development Scales, Third Edition at 6, 12, and 24 months and completed three observational executive function tasks at 24 months. Structural equation models adjusting for sociodemographic covariates were used to test study hypotheses. There was significant evidence for timing sensitivity. First-trimester diurnal cortisol (area under the curve) was negatively associated with cognitive and language development at 12 months and poorer inhibition at 24 months. Second-trimester cortisol exposure was negatively associated with language scores at 24 months. Third-trimester cortisol positively predicted performance in shifting between task rules (set shifting) at 24 months. Associations were not reliably moderated by child sex. Findings suggest that neurocognitive development is sensitive to prenatal glucocorticoid exposure as early as the first trimester and underscore the importance of assessing developmental timing in research on prenatal exposures for child health outcomes.

Keywords: cognitive development; executive functioning; HPA axis; prenatal cortisol; prenatal programming

(Received 19 August 2023; revised 3 June 2024; accepted 12 June 2024; first published online 6 November 2024)

Introduction

The prenatal programming hypothesis states that maternal experiences during pregnancy can shape offspring biology and behavior, including disease onset later in life (Barker, 1998; Gluckman & Hanson, 2005). A core component of the model is the premise that the fetus adapts to prenatal exposures to maximize evolutionary fitness in a particular postnatal environment (Barker, 1998). Although initially proposed in the context of nutritional risk for cardiovascular and metabolic-related outcomes (Barker, 1998; Gluckman & Hanson, 2005), this hypothesis has been expanded to include multiple exposures, such as stress physiology, and additional outcomes, including neurodevelopment and non-infectious diseases (Bock et al., 2015; Zijlmans et al., 2015).

The hypothalamic–pituitary–adrenal (HPA) axis and its key products corticotrophin-releasing hormone (CRH), ACTH, and cortisol, which, among many other biological functions, help regulate the body's stress response, have been well described in pediatric and adult samples (Gunnar & Quevedo, 2007; Howland et al., 2017; Lupien et al., 2009). In response to environmental, interpersonal, or psychological stress, CRH is released from the hypothalamus, which stimulates the release of ACTH from the pituitary gland (Karin et al., 2020). ACTH activates the adrenal gland to produce the glucocorticoid cortisol, which is the end product of the HPA axis (Karin et al., 2020). Cortisol concentrations in circulation follow a natural circadian rhythm characterized by a peak at the transition from sleep to waking, a gradual decline throughout the day, and an increase during sleep (Weitzman et al., 1971). Additionally, maternal cortisol concentrations naturally increase over the course of pregnancy in response to placental secretion of CRH into the bloodstream (Duthie et al., 2013; Robinson et al., 1988).

To protect the developing fetus from excessive exposure to maternal cortisol, the placenta produces 11 β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), an enzyme that serves as a partial barrier to maternal cortisol by converting active cortisol into inactive cortisone (Schoof et al., 2001). In general, placental production of 11β-HSD2 mirrors the increase in maternal cortisol across pregnancy; 11β-HSD2 production is lowest in early

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Cite this article: Womack, S. R., Murphy, H. R., Arnold, M. S., Duberstein, Z. T., Best, M., Qiu, X., Miller, R. K., Barrett, E. S., & O'Connor, T. G. (2025). Timing sensitivity of prenatal cortisol exposure and neurocognitive development. *Development and Psychopathology* **37**: 1707–1720, https://doi.org/10.1017/S0954579424001287

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https://doi.org/10.1017/S0954579424001287 Published online by Cambridge University Press

pregnancy and increases throughout gestation (Robinson et al., 1988). At the end of gestation, maternal cortisol levels are, on average, 3–5 times higher than pre-pregnancy levels (Sandman et al., 2006), and placental production of 11β-HSD2 drops (Schoof et al., 2001). The resulting increase in fetal exposure to cortisol at the end of gestation is thought to promote the maturation of vital organs and the central nervous system (Drake et al., 2007; Trejo et al., 2000).

Notwithstanding the important functional role of glucocorticoids in healthy fetal development, excessive exposure may have a negative impact on fetal development and disrupt postnatal development (Lautarescu et al., 2020; O' Donnell et al., 2009). Maternal stress and anxiety in pregnancy have attracted research interest, in part, because of their impact on patterns of cortisol production throughout the day (Murphy et al., 2022; Vergara-Lopez et al., 2021) and throughout pregnancy (Bublitz et al., 2014; Murphy et al., 2022; Stephens et al., 2021). As placental production of 11β-HSD2 is lowest in the first trimester (Robinson et al., 1988), the developing fetus and core aspects of brain development (e.g., formation of the neocortex, neuronal migration, and establishment of early neuronal connections (Monk et al., 2019; Vlasova et al., 2021) may be particularly vulnerable to elevations in maternal cortisol levels. Furthermore, in animal models, maternal experimental exposure to synthetic glucocorticoids has been found to downregulate placental 11β-HSD2 production (Cuffe et al., 2012; Wieczorek et al., 2019) and in humans, maternal prenatal anxiety has been linked to downregulation of 11β-HSD2 gene expression (O'Donnell et al., 2012). Therefore, elevations in maternal cortisol early in pregnancy may impact placental production of 11β-HSD2 long-term, leading to increased fetal exposure to glucocorticoids at later gestational stages.

Consistent with the prenatal programming hypothesis, several studies have found that higher levels of prenatal cortisol exposure are associated with poorer neurocognitive development (Bergman et al., 2010; Caparros-Gonzalez et al., 2019; Davis & Sandman, 2010; LeWinn et al., 2009; Nazzari et al., 2020). Developmental programming models make broad predictions about the timing sensitivity by focusing on *in utero* exposures. However, few studies of glucocorticoid exposure and neurocognitive development have focused on the more specific developmental question of timing across gestation, and the few that have produced inconsistent findings in terms of the timing of risk sensitivity (Caparros-Gonzalez et al., 2019; Davis & Sandman, 2010; Huizink et al., 2003). For example, hair cortisol levels in the second trimester (thought to reflect first-trimester exposures) have been unrelated or positively related to cognitive and language development in infancy, controlling for exposure at subsequent trimesters (Caparros-Gonzalez et al., 2019; Mariño-Narvaez et al., 2023). Alternatively, Huizink and colleagues (2003) found maternal waking salivary cortisol levels in late gestation (37–38 weeks), but not early (15 – 17 weeks) or mid-gestation (27 – 28 weeks) to predict lower Bayley mental development scores at 3 months. In contrast, higher afternoon salivary cortisol levels in early gestation (15.1 weeks) were associated with a slower trajectory of cognitive development between 3 and 12 months, whereas higher afternoon salivary cortisol concentrations in late gestation (37 weeks) were associated with faster cognitive growth trajectories and higher 12 months cognitive scores (Davis & Sandman, 2010). Exposure to elevated maternal cortisol levels in the third trimester has been linked to higher cognitive ability scores in some samples (Davis & Sandman, 2010; Davis et al., 2017) and lower cognitive scores in other samples (LeWinn et al., 2009; Nazzari et al., 2020).

Inconsistencies in the literature regarding the role of gestational timing may be explained by methodological limitations or analytic differences in measuring and analyzing cortisol (Zijlmans et al., 2015). For example, few studies testing timing hypotheses have included first-trimester measurements. Furthermore, the limited research including first-trimester assessments has relied on hair samples (Caparros-Gonzalez et al., 2019; Mariño-Narvaez et al., 2023), which correlate only moderately with salivary cortisol measurements and may begin to degrade after one month, potentially introducing noise into estimated levels over longer time periods (Sugaya et al., 2020). Other studies of gestational timing effects have used limited assessment models, for example, samples collected at only one timepoint in the day, which will not provide a detailed or thorough index of fetal exposure throughout the day.

The current study advances research on developmental or gestational timing effects of cortisol on child neurodevelopment in several ways. First, we include a detailed assessment of prenatal maternal cortisol at each trimester: we calculate cortisol area under the curve with respect to the ground (AUCg) from five diurnal saliva samples starting in the first trimester of pregnancy. Cortisol AUCg reflects the total maternal cortisol output during a period of time (Khoury et al., 2015) and provides an estimation of total fetal glucocorticoid exposure throughout a day.

Second, leveraging the cortisol assessments across gestation, we provide a strict test of the timing sensitivity. A timing sensitivity model proposes that there are particular gestational periods where fetal exposure has a greater or diminished impact on neurocognitive development. In contrast, a "general exposure" model would predict that cortisol exposure is similarly/equally predictive of neurocognitive outcomes across gestation. A key requirement in these studies is to account for stability in cortisol levels across gestation, which has not been incorporated into prior analyses, but which has been shown in several commonly used cortisol measures (e.g., cortisol awakening response, diurnal slope, AUCg; Murphy et al., 2022). For example, the multiple regression approach of including all measures of prenatal maternal cortisol as simultaneous predictors assumes that repeated cortisol measures are independent. Hierarchical linear modeling approaches can identify the impact of the rate of change in maternal cortisol across pregnancy on neurocognitive development but do not address a fundamental question of timing sensitivity, which requires isolating the unique contribution of cortisol at each gestational timepoint. This study makes a novel contribution to the literature by applying simplex (autoregressive) models to isolate the independent contribution of maternal cortisol AUCg at each trimester, and we compare this model to a general exposure model in which the independent contributions of maternal cortisol at each trimester are constrained to contribute equally to neurocognitive development.

Third, we advance this line of research by examining multiple neurodevelopmental phenotypes across multiple occasions of measurement in the child's first two years. The "programming" model proposes that prenatal exposure effects would not be transient but would instead persist. Longer-term outcomes of prenatal maternal stress, anxiety, and depression on child psychopathology have been reported (O' Donnell et al., 2014). However, few studies examine neurodevelopmental outcomes on multiple occasions. Much of the previous research on cortisol exposure and cognitive outcomes has focused on infancy (Bergman et al., 2010; Caparros-Gonzalez et al., 2019; Davis & Sandman, 2010; Huizink et al., 2003), with fewer assessing neurodevelopmental outcomes in later developmental stages (Buss et al., 2011; LeWinn et al., 2009). An emphasis on cognitive

https://doi.org/10.1017/S0954579424001287 Published online by Cambridge University Press

Table 1. Sample collection times and raw cortisol measurements

	Time (SD)	*n*	Raw cortisol mean nmol/L (SD)
Trimester 1			
Wake	07:47 (87.7)	108	9.50 (5.77)
45 mins post-wake	08:34 (87.5)	108	9.76 (5.37)
2 hours post-wake	10:30 (91.4)	107	4.76 (2.84)
8 hours post-wake	16:31 (124.0)	107	3.00 (2.35)
12 hours post-wake	18:40 (280.3)	90	2.79 (3.03)
Trimester 2			
Wake	07:34 (88.3)	134	12.09 (5.85)
45 mins post-wake	08:22 (88.1)	134	12.13 (5.99)
2 hours post-wake	10:21 (93.5)	133	7.26 (4.02)
8 hours post-wake	16:19 (140.1)	133	5.09 (5.10)
12 hours post-wake	18.56 (233.4)	103	3.96 (5.21)
Trimester 3			
Wake	07:44 (93.1)	150	11.98 (5.82)
45 mins post-wake	08:31 (93.5)	148	13.71 (6.70)
2 hours post-wake	10:25 (97.0)	149	8.92 (3.97)
8 hours post-wake	16:12 (114.3)	149	6.19 (3.84)
12 hours post-wake	19:42 (113.3)	120	4.82 (3.64)

Note. Standard deviations for time are presented in minutes.

development in early infancy may contribute to inconsistencies in extant findings as cognitive assessments within the first year are typically not strongly associated with cognitive abilities in later developmental stages (Bishop et al., 2003; Womack et al., 2022). Measurements of cognitive ability stabilize over the second year of life, and cognitive abilities in toddlerhood are moderately to highly stable into adolescence (Friedman et al., 2011; Yu et al., 2018). In the current study, we include assessments of neurocognitive development through the first two years, and include multiple measures of neurocognitive development including cognitive ability language, and executive functioning.

Finally, a further consideration for research on prenatal cortisol exposure and child neurocognitive development is sex and gender differences. Human and animal studies suggest that males and females may respond differently to prenatal stress exposure (Campbell et al., 2019; Glover & Hill, 2012; Graham et al., 2019). Findings from animal models suggest that males are more likely than females to show learning and memory impairments following exposure to prenatal stress (Glover & Hill, 2012), but there are comparatively few empirical examples for neurocognitive outcomes in children (Campbell et al., 2019). We examine if child gender moderates the association between prenatal cortisol and neurocognitive outcomes.

Methods

Participants

Participants were 253 mother-child dyads recruited as a part of the Understanding Pregnancy Signals and Infant Development study, a prospective longitudinal pregnancy cohort study conducted in Rochester, New York (O'Connor et al., 2021). The cohort is a part of the Environmental Influences on Child Health Outcomes program (Knapp et al., 2023). Mothers were recruited during the first trimester of pregnancy from outpatient obstetric clinics affiliated with the university. Recruitment spanned from December 2015 to April 2019. To be eligible, mothers had to be 18 years or older, at less than 14 weeks gestation, carrying a singleton, and able to communicate in English. Mothers with a history of psychotic illness, known substance abuse problems, and major endocrine disorders were not eligible. The study was approved by the local IRB; all participants provided signed consent. Of the 326 mothers initially recruited, 294 (90%) were retained through birth. Only full-term infants were included in follow-up assessments after birth. Families that were missing prenatal cortisol measurements and postnatal assessments at 6, 12, and 24 months were not included in analyses ($n = 41$). Thus, the study sample included participants with at least one cortisol or cognitive measurement.

Independent variable: salivary cortisol samples

Participants provided salivary cortisol samples at five timepoints across a single typical day once per each trimester. We employed the standard passive drool protocol and the timepoints suggested by the MacArthur Network (MacArthur research network on socioeconomic status and health, http://www.macses.ucsf.edu/research/allostatic/notebook/salivarycort.html). Samples were collected at wake and then at + 45 min, +2 hr, +8 hr, and +12 hr after wake-up. Time of collection and day of collection was recorded for every sample (see Table 1 for mean collection times for each sample). Detailed instructions were provided to avoid collection within 30 min of eating, drinking, brushing teeth. Collection, storage, and assay procedures followed established protocol and employed standard commercial kits (Salimetrics, LLC). The assay

https://doi.org/10.1017/S0954579424001287 Published online by Cambridge University Press

utilized a capture antibody-coated plate and involved competition with cortisol and horseradish peroxidase-conjugated anti-cortisol. The plate was incubated in the dark, and the reaction was stopped using stop solution. Spectrophotometry at 450 nm with a secondary correction filter at 490 – 492 nm was employed to measure cortisol levels. Quality and accuracy were ensured with checks for R2 value, duplicate CV%, and control values within kit ranges, resulting in average intra- and inter-assay coefficients of variation of 2.40% and 11.75%, respectively. Saliva samples were frozen at − 80 °C until analysis. AUCg values with reference to the ground were calculated using a trapezoidal formula (Pruessner et al., 2003). AUCg was selected over other indicators of cortisol output (e.g., awakening response, diurnal slope) as it represents an estimate of total maternal cortisol output (and thus total potential fetal exposure, which is of greatest interest; Fekedulegn et al., 2007). AUCg calculations were restricted to participants who had at least four viable daily cortisol values including the waking sample (other laboratory and data quality information is provided in Murphy et al., 2022).

Outcome variables: mental development and executive functioning

Mental development

Infant cognitive abilities were assessed by trained research assistants at approximately 6, 12, and 24 months using the Bayley Scales of Infant Development, Third Edition (BSID-III) (Bayley, 2006). The BSID-III yields a standardized score for cognitive and language development. The cognitive scale assesses emerging play skills, memory, and information processing; language scale assesses expressive and receptive language skills (Bayley, 2006). Scores on the Bayley are standardized to have a mean of 100 and a standard deviation of 15.

Executive functioning

Executive functioning was assessed at 24 months from performance on three tasks. The first task, snack delay (Kochanska et al., 2000), is a task of inhibition in which a trained examiner placed an M&M under a cup and told the child that they could eat the M&M after the examiner rang a bell. A total of 6 trials were administered with varying pause lengths from immediate to 30 s. A trial is considered successful if the child waits the allotted amount of time before consuming an M&M. The task is scored by summing the total number of successful trials. Spin the pots is a task of working memory (Hughes & Ensore, 2005). A trained examiner placed stickers in six of eight uniquely colored cups on a lazy susan, covered the cups, and spun the lazy susan. The child was then asked to select a cup with a sticker in it. As soon as a cup was chosen by the child and the sticker was removed, the cup was then returned to the tray. The administrator then covered the cups again with the scarf and the next trial began. A trial was considered successful if the child was able to accurately recall which cups held stickers. The score reflected the total number of successful trials divided by the total trials administered. Reverse categorization is a task of set shifting in which a child first learns a simple rule, followed by a rule reversal (Carlson, 2012). During the learning trial, the child was taught to sort toys into two different colored bins. The sorting rule was then reversed for the rule reversal trials. The task was scored by the total number of toys correctly sorted during the rule reversal trial divided by the number of toys available. For all of the executive functioning tasks, higher scores indicated better performance on the task.

Data integrity

Video recordings of the Bayley and executive functioning assessments were reviewed by trained research assistants and a clinical psychologist and scored for integrity issues on a 0–2 scale; assessments were made blind, as much as possible, to other data. Scores of 0 indicated no threats to data integrity, scores of 1 indicated mild threats to data integrity (e.g., parent provides support, but the child did not change their response), and scores of 2 indicated potential serious threats to integrity (e.g., the child changed their response based on parent input; the administration was prematurely terminated because of child behavior or other circumstance). Cases with an integrity score of 2 were removed for primary analyses (3 six-month cognitive, 3 six-month language, 2 twelve-month cognitive, 1 twelve-month language, 8 twenty-four-month cognitive, 8 twenty-four-month language). For executive functioning, 14 snack delay, 35 reverse categorization, and 43 spin the pots scores received an integrity score of 2 and were omitted from primary analyses. We conducted sensitivity analyses including these cases, and no substantial differences in findings were noted.

Covariates

We created a directed acyclic graph (DAG) to identify potential confounding variables in the association between prenatal cortisol exposure and neurocognitive development (see Supplementary Figure S1). DAGs are graphical representations of causal relationships between exposure and outcome variables and are useful to identify potential confounding variables and guide covariate selection (Digitale et al., 2022; Greenland et al., 1999). Variables in the DAG were selected based on theoretical knowledge and empirical evidence. Covariates included family socioeconomic status, maternal age, maternal anxious and depressive symptoms, maternal pre-pregnancy BMI, gravidity, infant sex, and neighborhood dangerousness. Family income-to-needs ratio was used as a proxy for family SES and was calculated by dividing a family's income by the poverty threshold calculated by the Department of Health and Human Services (United States Department of Health & Human Services, 2022). Neighborhood dangerousness was measured using an abbreviated nine-item version of the Me & my Neighborhood Questionnaire (Pittsburgh Youth Study, 1991). Mothers reported on the frequency of experiences in the neighborhood (e.g., "I heard adults arguing loudly on my street") over the past year on a four-point Likert scale from Never (0) to Often (3). Scores were summed to create a cumulative neighborhood dangerousness score. Maternal depressive symptoms were assessed using the Edinburgh Postnatal Depression Scale (EPDS; Cox et al., 1987) at each trimester across pregnancy. Maternal prenatal anxious symptoms were assessed using the Penn State Worry Questionnaire (PSWQ; Meyer et al., 1990). Repeated EPDS and PSWQ measurements were highly correlated (r's = 0.70–0.72 and 0.74–0.85 for the EPDS and PSWQ, respectively) and were therefore averaged across pregnancy.

Postnatally, caregivers completed the EPDS and PSWQ at 6, 12, and 24 months. Postnatal EPDS and PSWQ scores were also highly correlated over time (0.46–0.65 for EPDS and 0.78–0.80 for PSWQ) and were averaged to create mean postnatal depressive and anxious symptom scores. Because prenatal and postnatal depressive and anxious symptoms scores were highly correlated ($r = 0.72$ for EPDS and $r = 0.81$ for PSWQ), postnatal scores were revisualized on prenatal scores to adjust for multicollinearity. Caregivers also completed the Vocabulary subtest from the

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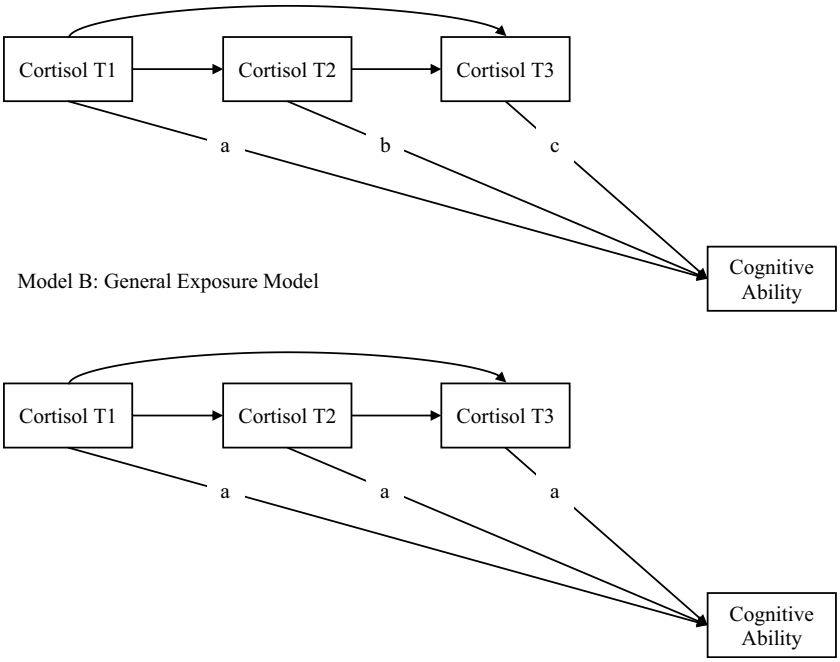


Figure 1. Conceptual diagrams of competing theoretical models.

Wechsler Intelligence Scale for Adults, Fourth Edition (WAIS-IV; Wechsler, 2008) at the 24-month assessment. Caregiver Vocabulary scores were also included as a covariate to adjust for aspects of the postnatal environment that may be associated with caregiver vocabulary abilities.

Data analysis

Data preparation and descriptive analyses were conducted using the 'base' package in R version 4.2.2 (R Core Team, 2022). Structural equation models were fit using the 'lavaan' package version 0.6-14 in R (Rosseel, 2012) to test the timing sensitivity and general exposure models. We fit a simplex model to the repeated cortisol AUCg measurements (see Supplementary Figure S2 for a path diagram). Specifically, we regressed trimester 2 cortisol AUCg onto trimester 1 cortisol AUCg, and trimester 3 cortisol AUCg onto trimesters 1 and 2 cortisol AUCg. The use of a simplex model allowed us to isolate cortisol exposure unique to each trimester (e.g., trimester 3 was adjusted for cortisol levels at trimesters 1 and 2) and test independent associations between cortisol exposure at each trimester and neurocognitive outcomes within the same model. This allowed us to take a conservative approach to testing timing sensitivity as models were adjusted for potential multicollinearity among repeated cortisol measurements.

Neurocognitive outcomes were regressed onto cortisol AUCg at trimesters 1, 2, and 3. Models were fit separately for cognitive (Bayley) and executive functioning outcomes. Although not depicted in Figure 1 for clarity, all six Bayley scores (cognitive and language at 6, 12, and 24 months) were included as individual outcomes in a single model. Similarly, snack delay, spin the pots, and reverse categorization scores were included as individual outcomes in a single executive functioning model. We compared the fit of two models: a timing sensitivity model (see Model 1a in Figure 1) and a general exposure model (see Model 1b in Figure 1). In the timing sensitivity model, all regression paths from the cortisol AUCg measurements were freely estimated. In the general exposure model, the regression paths from cortisol at each trimester and each neurocognitive outcome were constrained to be equal (e.g., cortisol AUCg at trimesters 1, 2, and 3 were constrained to have an equal association with 12-month language abilities). Associations were estimated freely for different outcomes within the same model (e.g., the association between cortisol and 12-month language abilities was allowed to differ from the association between cortisol and 12-month cognitive abilities). The general exposure and timing sensitivity models were nested and, therefore, could be compared using a chi-square difference test (Satorra, 2000). A significant difference in model fit would indicate that the more constrained model (the general Exposure model) had a poorer fit to the data relative to the timing sensitivity model. Wake time and post-conception age at time of cortisol collection for each sample set were included in the models as time-varying covariates.

To test whether infant sex moderated associations between cortisol AUCg and neurocognitive outcomes, we fit multi-group structural equation models. Before testing moderation by sex, we confirmed the homogeneity of means and variances assumption by constraining the means and variances for all independent and dependent variables to be the same for males and females, and then compared the fit of the constrained model to a model where the means and variances were freely estimated by sex. We also constrained the autoregressive paths to be equal by sex. Finally, we tested moderation by individually constraining the paths from cortisol AUCg to the cognitive and executive functioning outcomes to be equal by sex and testing differences in model fit. If constraining a regression path from one of the AUCg to a neurocognitive outcome to be equal by sex resulted in a significant worsening of model fit, then that would indicate the presence of moderation (Maruyama, 1998).

Missing data

Data were missing on independent and dependent variables. Regarding cortisol measurements, 61 participants (24.1%) had no

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valid measurements, 63 (24.9%) had one valid measurement, 66 (26.1%) had two valid measurements, and 63 (24.9%) had three valid measurements (these estimates also include missing due to laboratory exclusions/extreme values, see Murphy et al., 2022). Of the six Bayley outcomes (cognitive and language at 6, 12, and 24 months), 41 (16.2%) had no scores, 37 (14.6%) had two scores, 5 (2.0%) had three scores, 61 (24.1%) had four scores, 7 (2.8%) had five scores, and 102 (40.3%) had six scores. Rates of missing data (because of no administration or exclusion for incomplete assessment) were higher for executive functioning tasks: of the 217 individuals included in the executive functioning analyses, 93 (42.9%) had no executive functioning assessments, 30 (13.8%) had one executive functioning measurement, 47 (21.7%) had two executive functioning measurements, and 48 (22.1%) had three executive functioning measurements. A heatmap depicting patterns of missingness for all the independent and dependent study variables is depicted in Supplementary Figure S3.

Models were fit using maximum likelihood estimation and missing data were accounted for using full information maximum likelihood estimation (FIML; Enders & Bandalos, 2001). Under conditions of high rates of missingness, FIML has been found to perform similarly to other missing data techniques (e.g., multiple imputation) and yield unbiased parameter estimates when the model is correctly specified (based on RMSEA values), even in instances where there are high rates of missing data (Lee & Shi, 2021).

An assumption of using FIML is that data are missing at random (MAR; Enders & Bandalos, 2001). MAR occurs when missingness is related to observed constructs, but not related to the missing value itself (Rubin, 1976). For example, under MAR conditions, missing 12-month Bayley Language scores may related to family income, but MAR would be violated if children with stronger language abilities at 12 months were more likely to be missing the 12-month Bayley Language score. Empirically testing for MAR patterns of missingness is not possible as doing so would require knowledge of the missing value (e.g., 12-month Baley Language scores in the previous example; Enders, 2013). To explore patterns of missingness, we fitted a series of *t* tests to explore whether missingness on each of the cortisol measurements or Bayley scores was related to any continuous study covariates (chi-square tests were used for categorical covariates). In exploring patterns of missingness, we also tested whether missing cortisol values and Bayley scores were associated with cortisol values and Bayley scores at other waves (e.g., if missing cortisol AUCg at trimester 1 was associated with cortisol AUCg values at trimesters 2 or 3). To the extent that repeated cortisol and Bayley measurements were associated with one another, this provided an approximation of whether missingness was related to the missing value itself. Results of attrition analyses are presented in Supplementary Tables S1–S2 for attrition analyses.

Missing cortisol and cognitive scores were associated with several covariates. Missing trimester 1 cortisol AUCg was not associated with cortisol AUCg at trimesters 2 or 3 and missing trimester 2 cortisol measurements were not associated with cortisol AUCg at trimesters 1 or 3. Individuals missing cortisol AUCg at trimester 3 had lower trimester 2 cortisol AUCg scores ($t = 2.4$, $df = 60.0$, $p = .022$, Cohen's $d = -0.41$). Missing Bayley scores at 6, 12, and 24 months were not associated with missing Bayley scores at other waves. Therefore, we proceeded to analyze the data using FIML under the assumption that data are MAR.

Power analyses

Monte Carlo simulations were conducted in Mplus (Muthén & Muthén, 2017) to test the power of detecting the observed associations between cortisol AUCg at each trimester and each neurocognitive outcome. Power analyses were based on 2,500 simulated datasets of 253 individuals for the Bayley model (218 individuals for the executive functioning model). We coded patterns of missingness in the Monte Carlo simulations to reflect patterns of missingness in the data.

Results

Characteristics of the study sample are presented in Table 2. This sample was racially, ethnically, and socioeconomically diverse. Participants belonged to the following racial and ethnic groups: 7.9% Hispanic, 60.9% non-Hispanic White, 22.9% non-Hispanic Black, 4.3% Asian, and 4.0% other (including Native American, Pacific Islander, biracial, and multi-racial). The average household income was 3.2 times the poverty level, but about a quarter of the sample (23.5%) was living at or below 150% of the poverty line.

Supplementary Figure S4 depicts the raw cortisol concentrations calculated with each sample at each point in pregnancy. Diurnal patterns of cortisol concentrations followed the expected pattern characterized by elevated levels in the morning and a gradual decline over the course of waking hours. Mean cortisol levels (based on AUCg) increased across pregnancy, with the largest increase observed between trimesters 1 and 2 (see Table 2, supplementary Figure S4).

Bivariate correlations

See Table 3 for bivariate correlations between cortisol concentrations and neurocognitive outcomes. AUCg measurements were weakly to modestly positively correlated across pregnancy trimesters. Bayley scores (with the exception of 6-month language) were moderately positively correlated with each other. The executive functioning tasks did not correlate significantly with one another, but better performance on the snack delay and reverse categorization tasks was associated with higher 24-month Bayley scores. There was a general pattern of first and second-trimester measures of maternal cortisol AUCg to be inversely associated with Bayley scores at 12 and 24 months; that contrasted with the findings with third-trimester cortisol AUCg. Associations with executive function measures were generally weaker and less consistent. Supplementary Figure S5 depicts the bivariate associations between cortisol AUCg by trimester and Bayley scores.

Simplex model of cortisol AUCg across pregnancy

The simplex model was fully saturated and, therefore, had perfect fit to the data. Higher cortisol AUCg in trimester 1 was associated with higher cortisol AUCg in trimester 2 ($B = 0.38$, $SE = 0.19$, $p = .044$) and trimester 3 ($B = 0.54$, $SE = 0.13$, $p < .001$). Additionally, higher cortisol AUCg in trimester 2 was associated with higher cortisol AUCg in trimester 3 ($B = 0.20$, $SE = 0.08$, $p = .016$).

Prenatal cortisol exposure and cognitive development

The timing sensitivity model fit the cognitive data well ($X^2 = 192.0$, $df = 169$, $p = .108$, RMSEA = 0.02, CFI = 0.97). Constraining the associations between cortisol AUCg and Bayley outcomes to be

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Table 2. Descriptive statistics of the study sample

Categorical variables					
	N (%)				
Infant race/ethnicity					
Hispanic	20 (7.9%)				
Non-Hispanic White	154 (61.6%)				
Non-Hispanic Black	58 (22.9%)				
Asian	11 (4.3%)				
Other (Native Alaskan, Hawaiian/Pacific Islander, includes more than 1 race)	10 (4.0%)				
Infant sex					
Male	127 (50.2%)				
Female	126 (49.8%)				
Continuous variables					
	N	Mean (SD)	Range	Skew	Kurtosis
Income to Needs Ratio	212	3.2 (2.5)	0.4, 12.7	1.5	2.4
Maternal Age (years)	253	29.3 (4.6)	18.0, 41.0	−0.1	−0.3
Maternal Prenatal Anxiety	251	44.1 (12.7)	17.3, 78.7	0.4	−0.6
Maternal Postnatal Anxiety	215	45.4 (13.8)	16, 80	0.2	−0.8
Maternal Prenatal Depression	251	5.7 (4.4)	0.0, 20.7	0.9	0.3
Maternal Postnatal Depression	213	6.1 (4.7)	0, 19.5	0.7	−0.1
Maternal Pre-Pregnancy BMI	253	27.8 (7.0)	18.4, 49.1	1.1	0.5
Maternal WAIS-IV Vocabulary (Raw)	167	36.3 (11.4)	5.0, 56.0	−0.6	−0.3
Gravidity	253	1.8, (1.8)	0, 9	1.6	3.1
Birth Weight (kg)	252	3.4 (0.5)	1.3, 4.7	−0.2	0.6
Cortisol AUCg (nmol/L)					
Trimester 1	105	55.1 (28.3)	7.3, 177.2	2.0	5.7
Trimester 2	132	81.4 (42.4)	2.4, 288.7	1.9	5.6
Trimester 3	147	92.6 (40.3)	8.4, 311.5	1.5	5.6
Post-conceptual age (weeks)					
Trimester 1	105	12.7 (1.1)	8.6, 13.9	−1.7	3.0
Trimester 2	132	23.7 (2.1)	19.6, 26.9	−1.1	1.1
Trimester 3	146	34.7 (3.0)	26.1, 41.1	0.0	−0.7
Bayley scales of infant development-III					
Cognitive (6 mos)	194	107.0 (14.2)	55, 145	−0.4	1.0
Language (6 mos)	191	100.2 (13.1)	56, 130	−0.4	0.4
Cognitive (12 mos)	172	101.9 (14.2)	70, 145	0.3	0.4
Language (12 mos)	173	92.4 (11.2)	59, 124	0.2	−0.2
Cognitive (24 mos)	126	98.8 (14.2)	60, 145	0.4	0.6
Language (24 mos)	124	101.9 (20.3)	47, 147	0.0	−0.4
Executive functioning measures					
Snack delay	113	2.73 (1.23)	0, 4	−0.5	−1.0
Spin the pots	89	0.32 (0.15)	0, 1	0.7	0.2
Reverse categorization	64	0.59 (0.38)	0, 0.67	0.6	−0.9

Note. For analyses, race/ethnicity was recoded as White = 1, nonwhite = 0 due tosmall cell sizes of many of the race/ethnicity categories. AUCg = cortisol area under the curve withrespect to the ground.

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Table 3. Bivariate correlations between maternal prenatal cortisol and infant mental development

	AUCg T1	AUCg T2	AUCg T3	COG 6	LAN 6	COG 12	LAN 12	COG 24	LAN 24	Snack delay	Spin the pots	Reverse cat
AUCg T1	–	72	79	76	75	69	69	56	56	49	38	29
AUCg T2	0.15	–	104	100	98	87	89	67	65	61	44	33
AUCg T3	0.24*	0.25*	–	113	111	108	107	81	81	76	56	46
COG 6 mos	−0.16	0.15	0.06	–	161	140	140	110	108	103	79	59
LAN 6 mos	−0.10	−0.09	−0.01	0.30*	–	138	138	108	107	102	78	58
COG 12 mos	−0.24*	−0.07	0.04	0.23*	0.06	–	146	110	110	102	84	60
LAN 12 mos	−0.39*	−0.24*	−0.13	0.36*	0.17*	0.47*	–	108	108	101	82	60
COG 24 mos	−0.03	−0.14	0.07	0.22*	0.01	0.26*	0.40*	–	117	102	82	60
LAN 24 mos	0.10	−0.22	0.12	0.20*	0.01	0.21*	0.41*	0.71*	–	102	82	60
Snack delay	−0.27	0.16	0.21	0.07	0.04	0.00	0.08	0.31*	0.22*	–	81	58
Spin the pots	−0.15	0.03	−0.04	0.13	0.15	−0.07	0.07	0.04	0.16	0.01	–	52
Reverse cat	0.03	−0.01	0.27	0.03	0.20	0.23	0.10	0.22	0.39*	0.20	−0.24	–

Note. Pearson correlation coefficients are presented below the diagonal. The *n* included in each correlation is presented above the diagonal. AUCg = cortisol area under the curve with respect to the ground; T1–T3 = trimesters 1–3; COG = Bayley Cognitive subscale; LAN = Bayley Language subscale. Reverse Cat = Reverse Categorization. *$p < .05$

equal across trimester (general exposure) resulted in a significant reduction in model fit ($X^2 = 21.8$, $df = 12$, $p = 0.040$). Associations between cortisol AUCg at each trimester and all Bayley scores are presented in Table 4. Higher first-trimester cortisol AUCg was associated with lower 12-month cognitive ($B = -0.18$, $SE = 0.07$, 95% C.I. = −0.30, −0.05) and 12-month language ($B = -0.16$, $SE = 0.05$, 95% C.I. = −0.24, −0.06) scores, but not at 6 or 24 months.

Second-trimester cortisol AUCg was significantly negatively associated with lower language scores at 24 months ($B = -0.15$, $SE = 0.06$, 95% C.I. = −0.26, –0.03). Second-trimester cortisol AUCg was positively associated with cognitive scores at 6 months ($B = 0.09$, $SE = 0.04$, 95% C.I. = 0.02, 0.16); significant associations were not found for 6-month language or 12-month cognitive or language scores.

Third-trimester AUCg was not significantly related to cognitive or language outcomes at any age.

Power analyses revealed that there was sufficient power to detect the observed association between first-trimester cortisol AUCg and 12-month language abilities (80.2%) and the observed association between second-trimester cortisol AUCg and 24-month language abilities (80.8%). The study was slightly underpowered to detect the observed association between second-trimester cortisol AUCg and 6-month cognitive abilities (68.0%) and the observed association between first-trimester cortisol AUCg and 12-month cognitive abilities (70.1%).

Prenatal cortisol exposure and executive functioning

See Table 5 for parameter estimates for the prenatal cortisol AUCg models predicting child executive functioning at 2 years of age. The timing sensitivity model also fit better than the general exposure model for executive functioning ($X^2 = 14.2$, $df = 6$, $p < .028$). Higher first-trimester AUCg was associated with poorer performance on the snack delay task ($B = -0.14$, $SE = 0.06$, 95% C.I. = −0.26, −0.03) but not on spin the pots or reverse categorization. Second-trimester cortisol exposure was not significantly associated with executive functioning measures. In contrast, one positive association was found: third-trimester cortisol concentrations was positively associated with reverse categorization scores ($B = 0.06$, $SE = 0.02$, 90% C.I. = 0.02, 0.09).

Power analyses revealed that the study was sufficiently powered to detect the association between third-trimester cortisol concentrations and reverse categorization scores (95.7%). Analyses were underpowered to detect the association between first-trimester cortisol exposure and the snack delay score (58.6%).

Moderation of associations by sex

There was limited evidence of sex moderation. Sex did not significantly moderate any of the paths between trimesters 1, 2, and 3 cortisol AUCg and Bayley scores (see Supplementary Table S3). Only one path between cortisol exposure and an executive functioning outcome was moderated by sex: third-trimester cortisol AUCg was associated with higher snack delay scores for males relative to females (see Supplementary Table S4).

Sensitivity analysis

Sensitivity analyses were conducted including all Bayley and executive functioning scores initially assessed to have a serious threat to integrity. The magnitude and direction of associations between cortisol AUCg and neurocognitive outcomes remained stable after

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https://doi.org/10.1017/S0954579424001287 Published online by Cambridge University Press

Table 4. Parameter estimates of the association between cortisol AUCg across pregnancy and Bayley-III scores at 6, 12, and 24 months

Autoregressive paths						
	B (SE) [95% C.I.]					
AUCg T1 à AUCg T2	0.32 (0.20) [−0.08, 0.71]					
AUCg T1 à AUCg T3	0.54, (0.14) [0.28, 0.81]					
AUCg T2 à AUCg T3	0.21, (0.08) [0.05, 0.36]					
Associations with cognitive outcomes						
	LAN 6 months	COG 6 months	LAN 12 months	COG 12 months	LAN 24 months	COG 24 months
	B (SE) [95% C.I.]	*B* (SE) [95% C.I.]	*B* (SE) [95% C.I.]	*B* (SE) [95% C.I.]	*B* (SE) [95% C.I.]	*B* (SE) [95% C.I.]
AUCg T1	−0.08 (0.07) [−0.22, 0.07]	−0.09 (0.08) [−0.24, 0.07]	−0.16 (0.05) [−0.25, −0.06]	−0.18 (0.07) [−0.30, −0.05]	0.10 (0.09) [−0.08, 0.29]	−0.02 (0.07) [−0.12, 0.15]
AUCg T2	0.04 (0.03) [−0.02, 0.10]	0.09 (0.04) [0.02, 0.16]	−0.03 (0.03) [−0.09, 0.03]	−0.01 (0.04) [−0.07, 0.08]	−0.15 (0.06) [−0.26, −0.03]	−0.07 (0.05) [−0.16, 0.03]
AUCg T3	−0.03 (0.04) [−0.11, 0.05]	0.01 (0.04) [−0.09, 0.08]	−0.03 (0.03) [−0.08, 0.03]	0.04 (0.04) [−0.03, 0.12]	0.10 (0.05) [−0.00, 0.21]	0.04 (0.04) [−0.04, 0.12]
Residual correlations						
	LAN 6 months	COG 6 months	LAN 12 months	COG 12 months	LAN 24 months	COG 24 months
	r [95% C.I.]	*r* [95% C.I.]	*r* [95% C.I.]	*r* [95% C.I.]	*r* [95% C.I.]	*r* [95% C.I.]
COG 6 months	0.28 [0.14, 0.42]	–				
LAN 12 months	0.19 [0.02, 0.37]	0.37 [0.20, 0.54]	–			
COG 12 months	0.05 [−0.13, 0.23]	0.17 [−0.01, 0.34]	0.39 [0.24, 0.53]	–		
LAN 24 months	−0.03 [−0.24, 0.19]	0.09 [−0.13, 0.31]	0.28 [0.06, 0.50]	0.12 [−0.12, 0.36]	–	
COG 24 months	−0.12 [−0.34, 0.10]	0.16 [−0.06, 0.39]	0.29 [0.08, 0.51]	0.25 [0.03, 0.47]	0.56 [0.41, 0.70]	–

Note. Beta coefficients are unstandardized. Significant associations are bolded for clarity. Covariates included family income-to-needs ratio, maternal age, prenatal and postnatal maternal depressive symptoms, prenatal and postnatal maternal anxious symptoms, neighborhood dangerousness, gravidity, maternal pre-pregnancy BMI, maternal WAIS Vocabulary scores, and infant sex. LAN stands for Bayley language, COG stands for Bayley cognitive, AUCg stands for cortisol area under the curve with respect to the ground, and T1–T3 stand for trimester 1–trimester 3, respectively.

Table 5. Parameter estimates of the association between cortisol AUCg across pregnancy and executive functioning scores at 24 months

Autoregressive paths			
	B (SE) [95% C.I.]		
AUCg T1 à AUCg T2	0.38, (0.19) [0.01, 0.74]		
AUCg T1 à AUCg T3	0.57, (0.13) [0.32, 0.83]		
AUCg T2 à AUCg T3	0.17, (0.08) [0.01, 0.33]		
Associations with cognitive outcomes			
	Snack delay	Spin the pots	Reverse categorization
	B (SE) [95% C.I.]	*B* (SE) [95% C.I.]	*B* (SE) [95% C.I.]
AUCg T1	−0.14 (0.06) [−0.26, −0.03]	−0.01 (0.01) [−0.03, 0.01]	−0.05 (0.03) [−0.11, 0.02]
AUCg T2	0.04 (0.04) [−0.04, 0.12]	0.01 (0.01) [−0.00, 0.03]	−0.03 (0.02) [−0.07, 0.02]
AUCg T3	0.05 (0.04) [−0.02, 0.12]	−0.00 (0.01) [−0.01, 0.01]	0.06 (0.02) [0.02, 0.09]
Residual correlations			
	Snack delay	Spin the pots	Reverse categorization
	r [95% C.I.]	*r* [95% C.I.]	*r* [95% C.I.]
Spin the pots	−0.17 [−0.41, 0.07]	–	
Reversecategorization	0.17 [−0.11, 0.46]	0.03 [−0.38, 0.43]	–

Note. Beta coefficients are unstandardized. Significant associations are bolded for clarity. To improve the interpretability of the regression coefficients, AUC values were divided by 10 so they were on a similar scale as the executive functioning measures. Covariates included family income-to-needs ratio, maternal age, prenatal and postnatal maternal depressive symptoms, prenatal and postnatal maternal anxious symptoms, neighborhood dangerousness, gravidity, maternal pre-pregnancy BMI, maternal WAIS Vocabulary scores, infant sex, and infant age at the time of assessment. AUCg stands for cortisol area under the curve with respect to the ground and T1–T3 stand for trimester 1–trimester 3, respectively.

including neurocognitive assessments with serious threats to integrity. Findings for Bayley scores and executive functioning results are presented in Supplementary Tables S5–S6, respectively.

Discussion

In this racially and socioeconomically diverse community sample, we found reliable evidence of a developmental timing effect of prenatal maternal cortisol on child neurodevelopment. Exposure to higher cortisol concentrations in the first trimester was reliably associated with poorer cognitive and language abilities at 12 months in both bivariate correlations and structural equation models which accounted for cortisol exposure in later gestation. First-trimester maternal cortisol was also negatively associated with inhibition at 24 months. Additionally, higher second-trimester cortisol concentrations were associated with poorer language abilities at 24 months. Finally, there was limited evidence of a positive association between mid-gestation cortisol levels of 6-month cognitive scores and late gestation cortisol levels and set shifting abilities at 24 months. These findings extend previous research (Bergman et al., 2010; Caparros-Gonzalez et al., 2019; Davis & Sandman, 2010) by demonstrating sensitivity of early neurocognitive development to maternal cortisol beginning in the first trimester and in suggesting that early exposure effects had independent, persisting effects on multiple measures of child neurodevelopment.

There are several reasons why cortisol exposure early in gestation may be more reliably associated with poorer language and cognitive performance and inhibition than cortisol exposure at later points in gestation. For example, exposure to elevated maternal cortisol early in gestation may be more detrimental to fetal development as concentrations of the barrier enzyme 11β-HSD2 are lowest early in pregnancy (Schoof et al., 2001). Furthermore, the fetal blood–brain barrier, which serves as a secondary barrier for the developing fetal brain after the placenta, is not fully developed until the second trimester (Goasdoué et al., 2017). Thus, stronger prediction from glucocorticoid exposure in early gestation may reflect a greater effect on, or greater vulnerability of, early brain development (Lautarescu et al., 2020; O' Donnell et al., 2009). In humans, neurogenesis and gliogenesis begin in the first trimester and precipitate the formation of the neocortex and other brain structures (Leibovitz et al., 2022; Monk et al., 2019). Early disruption to the development of these structures may have cascading effects on subsequent development of more complex structures, and eventually early cognition (Vlasova et al., 2021). Glucocorticoid receptors (GR) and mineralocorticoid receptors (MR), which are necessary structures for maternal glucocorticoids to have a direct impact on fetal brain development, are fully developed in humans by 24 weeks gestation (Noorlander et al., 2006). However, 24 weeks gestation represents the lower limit at which fetuses have been tested for the presence of GRs or MRs, and GRs and MRs are likely present earlier in gestation (Noorlander et al., 2006).

Alternatively, the placenta may be a structure by which exposure to elevated maternal glucocorticoids early in gestation may contribute to neurocognitive development. Maternal depression and stress have been associated with elevated cortisol production during pregnancy (Murphy et al., 2022) and over time, maternal stress has been found to downregulate placental production of 11β-HSD2 (O' Donnell et al., 2012). Downregulation of placental 11β-HSD2 production early in gestation may result in lower placental production of 11β-HSD2 throughout gestation, resulting in prolonged fetal exposure to elevated glucocorticoids. In turn, chronic fetal exposure to elevated levels of glucocorticoids may impair fetal neurodevelopment (Samarasinghe et al., 2011) and restrict fetal growth (Gur et al., 2004), ultimately leading to poorer performance on early neurocognitive assessments. Recent twin study research has found that prenatal environmental experiences account for most of the

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phenotypic association between birth weight and early cognitive development (Womack et al., 2024), potentially implicating impaired fetal growth in a developmental cascade from which early maternal glucocorticoid production downregulates placental 11β-HSD2 which leads to restricted fetal growth and ultimately compromised neurocognitive development. Elucidating the mechanisms by which early prenatal maternal cortisol leads to impaired neurodevelopment remains an important avenue for future research.

There are parallel lines of evidence emphasizing early prenatal exposure for neurodevelopmental outcomes, perhaps because of neural development and greater permeability of barriers to protect the fetus. One is the maternal immune activation hypothesis, which consistently demonstrates that maternal illness and infection in early pregnancy are associated with neurodevelopmental disorders (Brown et al., 2004; Weir et al., 2015) and with individual differences in neurodevelopment (Ghassabian et al., 2018). The stronger and more consistent effects on cognitive and executive function found for cortisol earlier in gestation may reflect the relatively weaker role of protective mechanisms such as barrier enzymes or a greater vulnerability of early brain development, but there are alternative explanations. For example, maternal cortisol levels naturally increase across gestation and peak near parturition (Duthie et al., 2013; Robinson et al., 1988), presumably reflecting a greater influence of maternal-placenta biology of pregnancy; elevations in maternal cortisol concentrations early in pregnancy may reflect a greater deviation from typical levels relative to elevations at later gestational ages. We are unable to differentiate among these explanations, but our findings do underscore the value in formally testing much-needed developmental timing hypotheses in studies of prenatal exposures.

In line with previous research (Davis & Sandman, 2010; Davis et al., 2017), there was suggestive evidence that elevated levels of maternal cortisol in later gestation had a positive impact on select neurocognitive outcomes. In the present study, this was seen with performance on the reverse categorization task, a task of cognitive flexibility and set shifting abilities. Slight elevations in maternal glucocorticoids in late gestation have been linked with fetal maturation (Drake et al., 2007; Trejo et al., 2000) and postnatal cortical thickness in the frontal regions of the brain (Davis et al., 2017), suggesting that exposure to glucocorticoids late in gestation may promote brain development. However, the lack of a reliable association between third-trimester cortisol concentration with other cognitive, language, or executive functioning outcomes in the present study suggests that this may not be a robust effect; furthermore, these findings are in contrast with other studies reporting negative associations between maternal cortisol and cognitive development (LeWinn et al., 2009).

The developmental timing of child neurodevelopmental outcomes is also notable. We observed generally stronger associations at the latter assessments, which agrees with one report indicating that prenatal cortisol exposure was unrelated to cognitive outcomes until 12 months (Lautarescu et al., 2020). Despite being more proximal to prenatal exposures, cognitive abilities assessed at 6 months differ significantly in complexity and may be more confounded with sleep/wake and other behavioral artifacts than assessments conducted at 12 and 24 months (Graham et al., 2019). At a minimum, increased error of measurement of cognitive abilities in early infancy at least underscores the need for ongoing assessments past infancy.

Sex did not reliably moderate associations between cortisol exposure and neurocognitive outcomes through age 2 years. A recent meta-analysis of 22 studies observed a modest negative association between maternal stress and anxiety (a proxy for HPA axis physiology) and cognitive outcomes but did not observe any moderation by sex (Delagneau et al., 2023), which conflicts with animal studies suggesting that sex may moderate the association between prenatal cortisol exposure and learning and memory development (see Glover & Hill, 2012 for a review). Further research in humans that incorporates prenatal sex steroids and other plausible explanations for sex moderation. This is particularly important as studies (including the present study) are often powered to detect main effects of prenatal exposures on developmental outcomes but are underpowered to detect interactions.

This study benefited from several strengths, including a comparatively large and diverse sample for research of this kind, multiple measurements of prenatal cortisol exposure from the first trimester, and a conservative modeling approach to test developmental timing. However, findings should be considered in the context of several limitations. First, although the sample size was large relative to comparable studies, results from a Monte Carlo simulation suggested that the study was underpowered to detect select hypotheses. Second, there were significant rates of missing data on exposures and outcomes, which highlights the challenges in collecting intensive longitudinal data in a community sample, and particularly the burden of collecting diurnal salivary samples. Approximately half of the sample was missing two or more prenatal cortisol measurements, which may have led to inflated standard errors around parameter estimates. Notably, patterns of missingness did not violate the MAR assumption and the FIML approach to handling missingness allowed covariates to inform patterns of missingness, reducing bias in parameter estimates. Third, most of the first-trimester cortisol assessments were collected relatively late in the first trimester; sampling data even earlier in gestation is needed to provide broader coverage of gestational exposure. Fourth, there are limits of the sample, as the collection of diurnal cortisol is burdensome on participants and thereby creates selection biases. Our approach to collecting cortisol measurements over a single day in each trimester represents a snapshot of overall maternal cortisol output over a typical day. Previous research suggests that within-person, cortisol output does not vary significantly when measured on consecutive days (O'Donnell et al., 2013), and collecting saliva samples across multiple days in each trimester would increase participant burden. Nonetheless, collecting additional cortisol samples within trimester may have provided additional information on within-person fluctuations. Additionally, although our indicator of cortisol (AUCg) is thought to reflect total cortisol output (and total potential fetal exposure over a day), AUCg is agnostic to individual differences in the rate and shape of diurnal cortisol trajectories. Fifth, although we controlled for postnatal maternal anxious symptoms, depressive symptoms, and vocabulary abilities, we cannot rule out the possibility that other exposures contributed to the observed effects. For example, our focus here was on prenatal cortisol exposure because of its dominance in the developmental programming research; other prenatal biological exposures, including other steroid hormones and immune markers, require attention moving forward because of their associations with the HPA axis.

In conclusion, we observed a reliable negative association between cortisol exposure in early- to mid-pregnancy, but not late pregnancy, and early problem-solving, language, and inhibition abilities. These findings provide further evidence for the need to collect multiple exposure periods within pregnancy and test developmental timing hypotheses within the prenatal exposure period. Clinical applications of the findings are intriguing but indirect (Knap et al., 2023). For example, if neurocognitive development is more vulnerable to early cortisol exposure, then

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there is a concomitant need to start prenatal interventions early in pregnancy. That may be challenging; nonetheless, (Branum & Aherns, 2017) recruiting at-risk participants prior to conception may be an important way forward (Finer & Zolna, 2016; Urizar & Muñoz, 2011) if implemented early in gestation.

Supplementary material. For supplementary material accompanying this paper visit https://doi.org/10.1017/S0954579424001287

Funding statement. Funding was provided by NIH grants T32HD101392, OD023349, HD083369, NIEHS grant P30 ES005022 and The Wynne Center for Family Research; the project described in this publication was supported by the University of Rochester CTSA award number UL1 TR002001 from the National Center for Advancing Translational Sciences of the National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Competing interests. The authors declare no conflicts of interest.

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