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Elevated maternal cortisol levels during pregnancy are associated with reduced childhood IQ

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Background In animal models, there is evidence to suggest a causal link between maternal cortisol levels during pregnancy and offspring outcomes; however, evidence for this relationship in humans is inconclusive. We address important confounders of this association by estimating the relationship between maternal cortisol levels in late pregnancy and childhood IQ in a birth cohort and in a subsample of siblings.

Methods This study included 832 children who were members of the Collaborative Perinatal Project. Maternal serum collected between 1959 and 1966 during the third trimester of pregnancy was analysed for free cortisol. We investigated the relationship between maternal cortisol in quintiles and full, verbal and performance scale scores on the Wechsler Intelligence Scale for Children at age 7 years, adjusting for prenatal and family characteristics. We repeated this analysis among 74 discordant sibling pairs using a fixed effects approach, which adjusts for shared family characteristics.

Results Maternal cortisol levels were negatively related to full-scale IQ, an effect driven by verbal IQ scores. Compared with those in the lowest quintile of cortisol exposure, the verbal IQ of children in the highest quintile of exposure was 3.83 points lower [95% confidence interval (CI): −6.44 to −1.22]. Within sibling pairs, being in the highest quintile of exposure was associated with verbal IQ scores 5.5 points lower (95% CI: −11.24 to 0.31) compared with the other quintiles.

Conclusion These findings are consistent with prior human and animal studies, and suggest that exposure to high levels of maternal cortisol during pregnancy may be negatively related to offspring cognitive skills independently of family attributes that characterize the postnatal environment.

Keywords Child IQ, prenatal programming, cognitive development, pregnancy, stress, cortisol

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Introduction

Exposure to high levels of maternal cortisol during gestation has been proposed as one mechanism by which maternal experience may have lasting effects on child development.[1,2] Though there is evidence for a causal relationship between maternal cortisol levels during pregnancy and offspring outcomes in animal models,[1,2] the evidence in humans is inconsistent.[3–9] Human studies of this relationship are beset by the limitations of observational designs and vulnerable to a host of confounding factors that may predict both childhood outcomes and maternal stress during pregnancy. For example, genetic attributes of the mother may predict both childhood IQ and maternal levels of cortisol during pregnancy; however, genetic explanations for IQ differences have received less support in recent years.[10,11] Perhaps of greater concern are maternal experiences that induce stress and may result in elevated cortisol levels during pregnancy, and also characterize the environment of the developing child (e.g. low social support).[12,13] These characteristics may influence maternal cortisol levels and independently affect child outcomes. Isolating the unique effect of prenatal stress exposure is challenging as correlates of maternal stress during pregnancy likely continue to influence the child's postnatal environment.[14]

A review of animal models and human studies suggests a plausible biological mechanism by which maternal stress during pregnancy may be an important predictor of child cognitive performance. Mammals react to stress and threat through a cascade of physiological responses designed to mobilize energy stores to be used in a brief spurt of activity, promote vigilance and suppress immune responses.[15] This cascade is mediated by the hypothalamic–pituitary–adrenal (HPA) axis and ultimately results in the release of glucocorticoids from the adrenal glands, receptors for which are located in many tissues throughout the brain and body.[15] Animal models have shown that maternal stress during gestation can lead to lasting behavioural alterations among offspring, including deficits in attention, neuromotor capability and learning.[1] These effects may be mediated by the effect of maternal stress hormones on the fetal HPA axis and related brain areas. Greater prenatal stress exposure may prime the fetal HPA axis by altering the genetic expression of corticosteroid receptors in the hippocampus and hypothalamus, which are two brain regions that play a primary role in regulating the HPA axis.[1]

In humans, fetal cortisol exposure is regulated through a number of physiological pathways. The fetus is buffered from maternal cortisol by the activity of placental 11-β-hydroxysteroid dehydrogenase type 2 (11-β HSD-2), which catalyses glucocorticoids to inactive forms,[16] and increases in activity over the course of gestation.[17,18] Maternal cortisol also stimulates the production of placental corticotrophin-releasing hormone (CRH), further activating the fetal HPA axis.[19,20] Despite the multifaceted relationship between maternal cortisol levels and fetal exposure, there is some descriptive evidence that the two are moderately associated when examined *in vivo* over the course of gestation.[21] Furthermore, recent prospective studies suggest that maternal cortisol levels in the third trimester of pregnancy are positively associated with infant negative reactivity,[8] and mental and motor delays.[9] These studies suggest that maternal cortisol levels during the third trimester may be one measurable biomarker of the pre-natal environment that influences child development.

We contribute to this literature by examining the relationship between maternal cortisol levels during the third trimester of pregnancy and childhood IQ in a birth cohort and in a subsample of siblings. For obvious reasons, the effects of pre-natal stress on human development cannot be studied using an experimental design. However, one strategy that approximates experimental conditions is to supplement traditional observational studies with sibling analyses, in which siblings that are discordant for the exposure of interest are compared on their level of the outcome. In the current study, we compare sibling pairs with different levels of cortisol exposure during the third trimester of pregnancy with respect to their IQs. This approach accounts for unmeasured confounding characteristics that are shared between siblings, such as shared aspects of both the pre- and postnatal environment and shared genetic factors, but does not account for aspects that the siblings do not share, e.g. genetic susceptibility carried by only one sibling. In the current study, we investigate the association between third trimester maternal cortisol levels and child cognitive performance in a birth cohort by adjusting for potential pre- and postnatal confounding factors. We then use a fixed effects model to analyse data from siblings discordant for cortisol exposure, thereby adjusting for unmeasured familial characteristics shared by siblings.

Methods

Participants were members of the Boston and Providence sites of the Collaborative Perinatal Project (CPP), which was designed to investigate early life exposures associated with neurodevelopmental disorders of childhood.[22] Pregnant women were recruited to the study between 1959 and 1966 (usually at their first pre-natal visit). All CPP mothers were followed through their pregnancies, yielding extensive pre-natal and maternal data, which included socio-demographic characteristics of the mother at the time of childbirth. At 8 months, 4 years and 7 years, the CPP children underwent medical, neurological and psychological examinations.

The New England Family Study (NEFS) was established to locate and interview the adult CPP offspring

at the Providence, Rhode Island and Boston, Massachusetts sites. Participants in the current study were selected through a multi-stage sampling procedure and interview study, which involved a core assessment interview and three component studies. Screening questionnaires were mailed to 4579 of the 15 721 Boston and Providence CPP offspring who survived until the age of 7 years. Of the 3121 questionnaires returned (68.2%), 2271 were eligible for participation based on the combined inclusion criteria of the three component studies. Of these, we assessed 1674 CPP offspring of which 1625 completed the full study protocol [mean age 39.1 years, standard deviation (SD) = 1.9 years]. The interviewed sample had a somewhat higher level of education (e.g. 64.1% with at least some college education) than participants who were eligible but not enrolled (e.g. 51.8% with at least some college education).

Measures

Cortisol

Non-fasting maternal blood was collected at each prenatal visit in the original CPP between 1959 and 1966. Late third-trimester serum samples for this study were obtained from the CPP central repository in Bethesda, MD, and assayed for cortisol and cortisol binding globulin (CBG; for determining free cortisol levels). For each mother, a single serum sample was selected from the repository for analysis. Only samples drawn between 31 and 36 weeks following the last menstrual period and at least 14 days prior to the infant's birth date were selected. We excluded samples taken during the final 2 weeks of pregnancy because of known effects of labour and delivery on steroid hormone levels.[23–25] Weeks 31–36 were selected because: (i) these weeks provided a relatively tight window within the third trimester to examine hormone levels; (ii) these weeks included the greatest number of participants with available serum samples; and (iii) in addition to other periods of gestation, stress during the third trimester of pregnancy has been associated with offspring neurobehavioural outcomes in the prior literature.[8,9,26,27] If mothers had more than one draw during weeks 31–36, the latest draw within this window was selected.

The average length of storage of these samples was 42.5 years (SD = 1.7). The time of day at which samples were taken was not recorded. Serum samples were assayed for total cortisol and CBG levels using enzyme-linked immunoassay and radioimmunoassay, respectively (www.ibl-hamburg.com, laboratory of C. Kirschbaum). Inter/intra-assay coefficients of variability ranged from 3 to 10%. For further details of sample collection, storage and analysis, see Stroud *et al*.[28] Validity of cortisol and CBG levels after decades of storage has been described.[28]

In serum samples, 80% of cortisol is bound to CBG, making it biologically inactive and unable to affect the fetus.[29] Free cortisol was examined in this study to provide a better estimate of fetal exposure to maternal cortisol. The amount of free cortisol in a given serum sample was estimated using a formula developed by Coolens *et al*.,[30] which takes into account both total cortisol and CBG levels.

Free cortisol was examined in quintiles and treated categorically, with the lowest quintile of cortisol exposure serving as the reference group. This categorical approach was adopted to reflect our primary hypothesis that elevated levels of cortisol were inversely related with child cognitive performance in a manner consistent with the animal literature, where quite severe paradigms had been applied to illicit behavioural and neurobiological effects in offspring.[31] It is plausible that only high levels of cortisol exposure would be associated with behavioural changes detectable in childhood. Modelling quintiles of exposure allowed us to explore both the possibility of threshold effects, and model the relationship between cognitive performance and other levels of cortisol exposure.

Cognitive performance

At the age of 7 years, childhood IQ was measured using the Wechsler Intelligence Scale for Children (WISC), which has been shown to have excellent reliability and validity.[32] Full-scale IQ, and scores on the verbal and performance subscales were examined as potential outcome variables. All scores were age-standardized with a mean of 100 and an SD of 15 in the general population.

Potential confounders

Information on the mother and child at the time of birth was collected as part of the CPP follow-up procedures. Characteristics of both the mother and infant that could be independently related to maternal cortisol and child cognitive performance were included in final models for the entire sample. Typically, cortisol levels are highest 30 min after waking and then decrease over the course of the day. Because of this diurnal rhythm, maternal working conditions could be systematically related to the timing of the blood draws and cortisol levels as well as child IQ. Therefore, we included maternal work status in final models. This variable was derived from a demographic interview that included questions about current employment status as well as job type. Based on the 1960 Census Criteria (US Bureau of the Census, 1963),[33] we used these data to create a categorical variable for maternal work status that indicated whether the mother was (i) working in a manual job, (ii) working in a non-manual job or a student or (iii) not working at the time of the interview. This interview took place an average of 1.9 months (SD = 2.0) prior to the draw date. We also included a categorical variable that indicated the highest occupational level in the household. This variable was created in order to adjust for aspects of the

socio-economic environment not captured by either maternal work status or education. Paternal occupation was also assessed in the demographic interviews, and coded as non-manual, manual or unemployed/student according to the US Census.[33] Children in two-parent households were assigned to the higher parental occupation; children from single-parent families were assigned to the occupation of the parent with whom they were living. Maternal education was coded as less than high school, high school and some college or more. There were large socio-economic differences between participants from the Boston and Providence sites, so we included an indicator variable for site in all models. We also included child race (white vs other) and sex, maternal age (modelled continuously) and single motherhood. Maternal smoking during pregnancy and anaemia were also added to final models. Maternal smoking during pregnancy, measured by the maximum number of cigarettes smoked per day during the third trimester, was coded as less than one pack a day (0–19 cigarettes) and a pack or more per day (20+ cigarettes). Anaemia was coded as 1 if the mother was reported to have been anaemic at any point in her pregnancy and 0 otherwise. In the sibling analyses, we adjusted for maternal age at birth, maternal work status, child sex, birth order, maternal anaemia and smoking during pregnancy.

Analysis procedures

Because prematurity and low birth weight have been associated with both maternal stress during pregnancy[34] and with lower child IQ,[35–37] analyses were restricted to singleton births that had a gestational age of 37–42 weeks and a birth weight >2500 g. Of these participants, those who had complete data on maternal cortisol, IQ scores at the age of 7 years and covariates of interest were included in the analysis.

Because the whole cohort analysis included siblings, linear regression models with a random effect for family membership were used to account for the lack of independence within families.[38] We first examined the relationship between cognitive outcomes and maternal free cortisol in quintiles adjusting for study site only, and then estimated fully adjusted models that included all covariates. We ran these models with full-scale, verbal and performance IQ as dependent variables. For the sibling analysis, we estimated a fixed effects regression model, conditioning out the effect of family characteristics shared by siblings. Fixed effects models in this setting draw only on within-family variation and therefore yield much higher standard errors. We limited the power and precision of our analyses in this way to account for unmeasured, shared family characteristics related to both maternal cortisol levels and aspects of the postnatal environment that may independently predict child IQ. All analyses were performed using SAS version 9.1.

Results

Of the 1625 individuals participating in the NEFS, we identified and located maternal serum samples collected during weeks 31–36 of gestation for 1099 participants. Of these individuals, 901 weighed $\geqslant 2500$ g at birth and were between 37 and 42 weeks' gestation, and 832 provided complete data on cognitive outcomes and covariates of interest. The sibling analyses were conducted on 74 sibling pairs discordant for cortisol exposure where each sibling was a singleton birth.

Table 1 includes demographic data on those included and not included in the analytic sample. Since the analytic sample included only full-term, normal birth-weight infants, with a pre-natal visit during weeks 31–36 of pregnancy, these subjects were of somewhat higher socio-economic status than those excluded from the analysis. The large majority (83%) of women in our sample were not working at the time of the demographic interview. Children in the analytic sample were 60% female ($n = 500$), and came from 712 families, 113 of which had at least two children in the study.

As shown in Table 2, there was a significant relationship between quintile of maternal cortisol and full-scale IQ in the fully adjusted models. Children with cortisol exposure in the highest quintile had full-scale IQ scores 2.78 [95% confidence interval (CI): −5.36 to −0.21] points lower than those in the lowest quintile of exposure. This association was most pronounced for the verbal subscale, where those in the highest quintile of exposure had verbal IQ scores 3.83 (95% CI: −6.44 to −1.22) points lower on average than those in the lowest quintile of cortisol exposure. No significant relations were observed between cortisol level and performance IQ in either site-adjusted or fully adjusted models. Across outcomes, the addition of covariates slightly reduced the magnitude of the effect estimates.

Sibling analysis

To facilitate a comparison between the sibling and analytic sample, siblings were retained in the same cortisol quintile as they were for the analytic sample. The mean difference in the quintile of cortisol exposure within sibling pairs was 1.6 (SD = 1.1) (Table 3). There was substantial variability in full-scale, verbal and performance IQ within sibling pairs, with mean differences between 9 and 12 points or approximately two-thirds of a standard deviation. To preserve precision in the final sibling models, we did not adjust for characteristics for which there was a high rate of agreement between siblings (i.e. parental occupation, maternal education and single motherhood), but we did adjust for maternal work status. The age difference between siblings can be considered an indictor of the extent of shared early life experience.[39] The age difference between

Table 1 Socio-demographic characteristics of participants in the analytic sample and participants of the NEFS who were not included

Characteristics	Analytic sample ($n=832$)	NEFS participants not included ($n=793$)	Test of no association *P*-value (χ^2)
Socio-demographic characteristics, *n* (%)			
Child is female	60.1 (500)	58.4 (463)	0.48 (0.49)
White race	89.8 (747)	83.9 (657)	0.0005 (12.2)
Teenage motherhood	16.6 (138)	18.8 (149)	0.24 (1.4)
Single motherhood	6.0 (50)	14.4 (114)	<0.0001 (31.3)
Maternal work status, *n* (%)			
Working: non-manual	11.7 (97)	7.1 (53)	0.008 (9.6)
Working: manual	5.1 (42)	5.0 (37)	
Not working	83.3 (693)	87.9 (656)	
Parental occupation, *n* (%)			
Non-manual	61.4 (511)	52.5 (392)	0.0002 (17.6)
Manual	38.1 (317)	45.7 (341)	
Mother's education, *n* (%)			
Less than high school	42.0 (349)	50.6 (366)	0.0007 (14.6)
High school	41.1 (342)	32.2 (233)	
More than high school	16.9 (141)	17.2 (124)	

Table 2 Site-adjusted and fully adjusted estimates of maternal cortisol in quintiles on full-scale, verbal and performance IQ ($n=832$)

	Full-scale IQ	Verbal IQ	Performance IQ
Free cortisol	β (95% CI)	β (95% CI)	β (95% CI)
Site adjusted			
Lowest quintile	Reference	Reference	Reference
Second	−1.09 (−3.45 to 1.26)	−2.07 (−4.57 to 0.42)	−0.22 (−2.99 to 2.54)
Third	−1.54 (−4.23 to 1.14)	−1.83 (−4.55 to 0.90)	−1.99 (−4.91 to 0.93)
Fourth	−1.72 (−4.31 to 0.87)	−2.63 (−5.32 to 0.05)	−2.08 (−4.89 to 0.73)
Highest quintile	−3.08 (−5.76 to −0.41)	−4.33 (−7.01 to −1.64)	−3.14 (−6.07 to −0.21)
Fully adjusted[a]			
Lowest quintile	Reference	Reference	Reference
Second	−1.33 (−3.67 to 1.00)	−2.32 (−4.81 to 0.15)	−0.07 (−2.74 to 2.59)
Third	−1.12 (−3.60 to 1.35)	−1.37 (−3.93 to 1.20)	−0.64 (−3.41 to 2.13)
Fourth	−1.28 (−3.79 to 1.24)	−1.91 (−4.55 to 0.73)	−0.31 (−3.07 to 2.45)
Highest quintile	−2.78 (−5.36 to −0.21)	−3.83 (−6.44 to −1.22)	−1.16 (−4.08 to 1.76)

[a]These models are adjusted for site, maternal anaemia and smoking during gestation, maternal education, maternal work status, parental occupation, single motherhood, maternal age at birth, parental occupation, child sex and race.

discordant sibling pairs in this sample was small [mean (SD): 2.1 (1.1) years], which, in addition to the high rate of agreement on most socio-demographic characteristics examined, suggests that these siblings shared many aspects of their early childhood environment.

The models estimating the within-family associations between cortisol exposure quintile and full-scale, verbal and performance IQ suggested a similar pattern of effects to the full cohort analysis (Table 4). Again, the strongest relationship between maternal cortisol levels and IQ was with verbal IQ. In the sibling models, children in the highest quintile of cortisol exposure had verbal IQs 6.00 (95% CI: −13.31 to 1.30) points lower than those in the lowest quintile; however, the confidence intervals for all estimates in the sibling sample were very wide. We conducted a *post hoc* analysis of the verbal IQ outcome using contrast

statements and determined that the four lower categories of cortisol exposure were not substantively different from each other ($P > 0.38$ for each contrast statement). By collapsing the four lower quintiles, and identifying 23 discordant pairs (where one sibling was and one was not in the highest quintile), we estimated that being in the highest quintile of cortisol exposure was associated with a 5.5-point (95% CI: −11.24 to 0.31) lower verbal IQ score when compared with the other quintiles. Within sibling pairs, cortisol exposure did not predict either full-scale or performance IQ.

Table 3 Discordant sibling pair analyses: degree of concordance on variables of interest [$n = 74$ pairs (148 individuals)]

	Continuous	Categorical
Variable	Mean (SD) difference between two siblings	Percentage of siblings with same value for covariate
Free cortisol in quintiles	1.6 (0.9)	
Full-scale IQ	8.9 (7.2)	
Verbal IQ	9.9 (7.6)	
Performance IQ	11.8 (8.2)	
Age (years)	2.1 (1.1)	
Single motherhood		96
Mother's education		95
Parental occupation		90
Maternal work status		66

Discussion

The objective of the current study was to evaluate the effect of exposure to high levels of maternal cortisol during pregnancy on child IQ in a large, diverse sample of mothers and their children. Gestation is a critical period of development, during which pre-natal exposures can have lasting effects on child and adult outcomes.[40] There is extensive animal model evidence to suggest a plausible biological mechanism linking maternal cortisol levels during pregnancy and offspring outcomes[41–44]; however, human studies of this relationship are beset by obstacles to causal inference, including inadequate adjustment for postnatal experience, and thus far have yielded inconsistent results.[4,8,9]

We evaluated the relationship between maternal cortisol levels in pregnancy and childhood cognitive performance first by adjusting for a variety of pre-natal, socio-economic and demographic characteristics that could confound this relationship. In this analysis, higher cortisol exposure in the third trimester of gestation was associated with lower verbal IQ scores, with a 4-point lower verbal IQ observed in the highest quintile of exposure compared with the lowest. We then supplemented this analysis by looking at the effect of cortisol on IQ among siblings with different levels of cortisol exposure, which adjusts for unmeasured genetic and environmental characteristics that siblings share. This analysis supported our initial findings, suggesting that, even within sibling pairs, higher cortisol exposure during the third trimester of pregnancy was associated with lower verbal IQ scores. The estimates from this analysis were similar in both direction and magnitude when compared with the full sample. However, due to the lack of power and

Table 4 Discordant sibling pair analyses: fixed effects estimates of maternal cortisol in quintiles on full-scale, verbal and performance IQ [$n = 74$ pairs (148 individuals)]

	Full-scale IQ	Verbal IQ	Performance IQ
Free cortisol	β (95% CI)	β (95% CI)	β (95% CI)
Unadjusted			
Lowest quintile	Reference	Reference	Reference
Second	−0.89 (−5.72 to 3.93)	−2.35 (−7.41 to 2.72)	0.94 (−5.08 to 6.96)
Third	−1.96 (−7.57 to 3.65)	−1.77 (−7.66 to 4.12)	−1.80 (−8.80 to 5.20)
Fourth	−0.11 (−6.09 to 5.89)	−0.12 (−6.40 to 6.17)	0.17 (−7.29 to 7.64)
Highest quintile	−2.77 (−9.06 to 3.53)	−6.78 (−13.39 to −0.17)	2.36 (−5.50 to 10.21)
Adjusted[a]			
Lowest quintile	Reference	Reference	Reference
Second	−0.83 (−6.04 to 4.36)	−2.07 (−7.55 to 3.41)	0.80 (−5.72 to 7.63)
Third	−2.30 (−8.16 to 3.56)	−1.85 (−8.02 to 4.31)	−2.27 (−9.62 to 5.07)
Fourth	0.03 (−6.29 to 6.36)	0.63 (−6.04 to 7.29)	−0.30 (−8.23 to 7.64)
Highest quintile	−2.40 (−9.33 to 4.54)	−6.00 (−13.31 to 1.30)	2.25 (−6.45 to 10.95)

[a]These models are adjusted for maternal age at birth, work status, birth order, anaemia and smoking during pregnancy and child sex.

precision that result from estimating a fixed effects model using a smaller sample of discordant siblings, these estimates had wide confidence intervals. Nevertheless, together, the two analyses suggest that there may be a causal, negative relationship between maternal cortisol exposure during pregnancy and child verbal IQ.

Limitations

This study has several limitations, most notably that the cortisol measure was collected without noting the time of day or other factors that may affect cortisol levels. There is general agreement that the timing of cortisol measurement is important.[45] It has been shown that cortisol levels are highest 30 min after awakening, after which cortisol levels decrease until bedtime with the exception of a small spike at lunchtime. In the present study, our cortisol measure was taken on a single occasion for which the time of day was unknown. One potential influential source of bias in this regard is the effect of maternal working conditions on both the timing of pre-natal visits (and hence timing of cortisol collection) and child cognitive performance. However, our adjustment for maternal work status, as well as the fact that a relatively small proportion of women (17%) were working at the time of the demographic interview, suggests that any potential bias due to maternal working conditions in our study is minimal. In addition, we were unable to account for other factors that could influence cortisol levels including food and caffeine intake, smoking, medication use and physical activity.[46–49] Given that pre-natal visits likely took place between 1 h after waking and 6:00 p.m., and that the timing of behaviours such as smoking and food intake preceding these visits were likely uncorrelated with other maternal factors associated with childhood cognitive performance, we expect that this limitation of our cortisol measurement introduced noise, but not bias, into our study.

Another limitation is that maternal cortisol levels are not a direct measure of fetal cortisol exposure, which is determined by complex physiological processes.[2] Maternal cortisol levels may affect fetal exposure through the production of placental CRH, further activating the fetal HPA axis.[19] Also, the activity of the enzyme 11-β-HSD-2 in the placenta, which reduces fetal cortisol exposure by catalysing active maternal glucocorticoids to inert forms, increases over the course of gestation.[17,18] These factors suggest that a third trimester measure of maternal cortisol may be a limited proxy for fetal exposure, as 11-β-HSD-2 activity during this period is high. Furthermore, there are certainly other periods of gestation (i.e. the first and second trimester) during which neurological development is also vulnerable to the effects of maternal stress hormones.[2] However, recent evidence linking maternal cortisol levels in the third trimester with infant outcomes indicates that this is still an important and sensitive period during gestation worthy of investigation.[8,9] Furthermore, a study linking paired venous measures of maternal and fetal cortisol suggests that 40% of the variance in fetal cortisol is accounted for by variation in maternal cortisol.[21] Though this study was not designed to make a causal argument about the relationship between maternal and fetal cortisol levels, it does suggest that maternal and fetal levels are positively correlated.

Furthermore, it is possible that there are additional confounding variables not available to us that are associated with both maternal cortisol and child cognitive performance, such as maternal depression. Women who are depressed are more likely to have abnormal cortisol levels over the day,[50] and also less likely to provide stimulating, nurturing environments for their children.[51,52] Though unmeasured and residual confounding could be a cause for concern in this study, the within-family analysis controls for environmental factors shared between siblings. Therefore, chronic maternal depression would be accounted for if present throughout the lives of both siblings. Nevertheless, residual confounding due to characteristics that are both unmeasured and unshared between siblings, such as other pre-natal exposures that might have varied between gestations, is still a concern. However, our adjustment of maternal smoking and anaemia, which are known correlates of child IQ, strengthens this analysis.[53,54]

A final limitation is the external validity or generalizability of the findings. The CPP cohort was not designed to be a representative sample of all births in Rhode Island and Massachusetts, and the individuals who were included in the NEFS were sampled on the basis of multiple inclusion criteria consistent with the goals of the component studies. Furthermore, we restricted our analysis to children born at term and with normal birth weights, which led our analytic sample to be of slightly higher socioeconomic status than the NEFS. Finally, the discordant sibling analysis included individuals that were once again selected from a larger group and had special characteristics (i.e. siblings came from families with at least two children enrolled in the CPP study and were exposed to different levels of cortisol during gestation). Overall, these design elements suggest that the children in this study are not representative of all children in Massachusetts and Rhode Island, especially not those born low birth weight or outside the gestational ages of 37–42 weeks.

Implications of our findings for understanding the relation between maternal stress and childhood outcomes

Our finding in both the full and sibling sample of a negative relationship between maternal cortisol

levels and child IQ are consistent with studies of self-reported maternal stress during pregnancy and child behaviour, neurodevelopmental outcomes and academic achievement.[34] These studies generally report greater behaviour problems, and poorer neurodevelopmental outcomes with increasing self-reported stress.[34] Of the few studies that have examined maternal cortisol levels during pregnancy and child outcomes, two have found a negative relationship with infant neurodevelopment,[8,9] but none has found effects that persist through childhood.[4–7] Ours is the first study of this relationship in a large, socio-economically diverse sample that both addresses a wide range of confounding factors through statistical adjustment, and attempts to control for unmeasured, shared aspects of the family environment through a sibling analysis. In this study, the results of these two analyses are in agreement, suggesting there may be a causal, negative relationship between levels of maternal cortisol exposure in gestation and child verbal IQ.

The mechanisms that underlie the association between maternal stress hormones and cognitive outcomes in children born fullterm and normal birth weight remain unclear, but are informed by both human and animal studies. Maternal cortisol secretion, which increases vessel tone, may reduce blood flow to the fetus.[55] Reduced supply of oxygen may, in turn, activate the fetal HPA axis, increasing fetal cortisol exposure. Maternal stress may also lead to the production of placental CRH, further activating the fetal HPA axis.[19] Though fetal exposure to glucocorticoids is essential for some aspects of normal maturation in the central nervous system,[2] excess glucocorticoid exposure has widespread effects on neuronal structure and synapse formation,[56] and is particularly toxic to neurons in the hippocampus, which is the primary regulator of the HPA-axis in the limbic region.[2,44,57] It appears that these effects on the hippocampus disrupt its regulatory actions on the HPA axis, such that prenatally stressed animals show prolonged and stronger responses to novel experiences in offspring,[44] as well as deficits in hippocampal-related spatial tasks.[31] There is some evidence to suggest that pre-natal stress alters HPA axis functioning in humans as well.[5,58] All of these mechanisms depend on fetal (and/or childhood) exposure to excess levels of glucocorticoids, which has damaging effects on hippocampal structure and function.[59]

Though few studies have made direct links between deficits specific to verbal skills, cortisol exposure and hippocampal structure and/or function in the general population, a recent study found a positive relationship between hippocampal volume and verbal IQ, but not performance IQ.[60] This association may in part be explained by the important role the hippocampus plays in the formation of declarative memory,[61] which refers to the explicit knowledge of facts and information and requires conscious reflection to retrieve.[62,63] Though not considered an explicit test of declarative memory, verbal IQ certainly draws on declarative memory skills. The verbal IQ subscale includes tests of general knowledge and vocabulary, which require the use of declarative memory to retrieve factual information and the definitions of words. This stands in contrast to the performance subscale, which assesses reasoning, pattern recognition and spatial skills, drawing minimally on the memory and retrieval of facts and information. Declarative memory deficits have been found in individuals who show both increasing cortisol exposure over a 5-year period[64,65] and those who were on long-term corticosteroid treatment.[49] In both populations, individuals with higher glucocorticoid exposure also had smaller hippocampal volumes.[49,66]

In studies of clinical populations for which exposure to high levels of cortisol and reduced hippocampal volume is a proposed mechanism, there is also evidence supporting a relationship between cortisol, hippocampal volume and verbal IQ. For example, adults with Cushing disease, which is marked by hypersecretion of cortisol and reduced hippocampal volume, have pervasive deficits in verbal IQ when compared with healthy controls.[67] Though there is debate about whether reduced hippocampal volume precedes[68] or is an outcome of post-traumatic stress disorder (PTSD),[69] reduced hippocampal volume has been proposed as a potential biological pathway through which traumatized individuals go on to develop PTSD. Two separate studies indicate that trauma-exposed individuals with PTSD have greater deficits on verbal (but not performance) IQ sub scales when compared with trauma-exposed PTSD-negative subjects.[70,71] The cognitive profile of individuals with PTSD, which is consistent with deficits related to hippocampal functioning, is similar to, if less severe than, the pattern of cognitive performance in the current study.[72]

In sum, our study suggests that exposure to high levels of maternal cortisol in the third trimester of gestation may have a small but lasting effect on child verbal skills; a relationship that may be explained by the effects of cortisol exposure in early life on the hippocampus and declarative memory. This relationship was found to be independent of aspects of the postnatal environment and genetic factors that are shared by siblings, suggesting that this relationship may be causal. Our findings need to be replicated in studies with diverse populations that are representative of the US population at the present time.

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KEY MESSAGES

- Exposure to high levels of maternal stress hormones during pregnancy is one mechanism by which the uterine environment may have lasting effects on child development.
- We examined the relationship between maternal cortisol levels during the third trimester and child IQ in a large birth cohort that included a subset of siblings discordant for maternal cortisol level.
- In fully adjusted models and sibling analyses, we found that higher maternal cortisol levels were associated with lower verbal but not performance IQ.
- Maternal stress hormone exposure during pregnancy may have a small but persistent effect on child cognitive skills that draw on declarative memory.

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