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Prospective Relations Between Prenatal Maternal Cortisol and Child Health Outcomes

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Abstract

Objective: To investigate prospective, longitudinal associations between maternal prenatal cortisol response to an interpersonal stressor and child health over the subsequent three years.

Methods: 123 women expecting their first child provided salivary cortisol samples between 12–32 weeks gestation ($M=22.4\pm4.9$ weeks) before and after a videotaped couple conflict discussion with their partner. Mothers reported on overall child health and several indicators of child illness (sick doctor visits, fevers, ear and respiratory infections) when children were 6 months ($n=114$), 1 ($n=116$) and 3 ($n=105$) years old. Associations between maternal prenatal cortisol reactivity and recovery and later child health at each of the three time points were analyzed using longitudinal regression models.

Results: Greater cortisol reactivity in response to the couple conflict discussion was associated with maternal self-report of better overall child health ($p = 0.016$, 95% CI = [0.06, 1.30], Cohen's $f = 0.045$) across the study period. Greater cortisol reactivity was also associated with lower incidence rate ratios (IRRs) for maternal reports of sick doctor visits (IRR 95% CI = [0.25, 0.83], $p = 0.006$), fevers (CI = [0.25, 0.73], $p = 0.002$), ear infections (CI = [0.25, 0.58], $p < 0.001$), and respiratory infections (CI = [0.08, 1.11], $p = 0.073$). Cortisol recovery was unrelated to study outcomes (all $ps > 0.05$). Maternal prenatal depressive symptoms moderated the association between cortisol reactivity and overall child health ($p = 0.034$, 95% CI = [0.07, 1.87] for interaction term) but no other health outcomes ($ps > 0.05$). Among women with lower depressive symptoms, cortisol reactivity was not associated with overall child health; among women with higher levels of depressive symptoms, greater cortisol reactivity was associated with better overall child health.

Conclusions: This study provides longitudinal evidence that greater maternal cortisol reactivity to a salient interpersonal stressor during pregnancy is associated with fewer child health problems and better maternal report of overall child health during infancy and into early childhood.

Keywords

maternal prenatal cortisol; child health; Family Foundations; cortisol reactivity; maternal prenatal depression

Maternal psychological stress during pregnancy has been linked to adverse consequences with respect to offspring physical health and development, including low birthweight (1), infant and child health problems (2,3), and delayed infant motor and cognitive development (4). Although this work is suggestive of a critical role of prenatal maternal stress in offspring development, prospective longitudinal studies that assess physiological indicators of stress, such as maternal prenatal cortisol, are needed to better understand the causal link between maternal stress during pregnancy and later child health.

Existing research implicates the maternal hypothalamic-pituitary-adrenal (HPA) axis as a likely mechanism connecting maternal psychological stress to offspring health and development (5). The HPA axis coordinates the human physiological stress response in addition to serving many other functions (6). Maternal HPA axis functioning plays a critical role in fetal development (7). During pregnancy, the maternal HPA axis undergoes several normative changes, including an overall increase in cortisol production over the course of pregnancy (8,9). The maternal HPA axis is also known to play an important role specifically in programming the offspring HPA axis (10), thereby influencing early child development in terms of cognitive, behavioral, and physical development (11–13). For example, disrupted maternal cortisol profiles during pregnancy are associated with adverse offspring outcomes, such as preterm birth (14) and disrupted HPA axis functioning among offspring (15,16). Conversely, previous research has shown that a psychosocial coparenting intervention was effective in *reducing* adverse birth and offspring outcomes (i.e., lower birth weight) among women reporting high levels of psychological and economic stress when compared to a control group (17). The same intervention was further linked to reduced adverse birth outcomes among women with higher levels of diurnal cortisol levels when compared to a control group (18). Taken together, these studies suggest that exposure of the fetus to prenatal maternal cortisol represents a plausible link between maternal psychological stress and later child health outcomes, including, among others, metabolic functioning, insulin resistance, and asthma (13,19,20).

Some important influences on the maternal HPA axis are being exposed to psychological stressors and experiencing poor psychological well-being, such as depression. Among the most salient stressors for women during pregnancy is couple relationship conflict. Much research has focused on the strains and stresses of the transition to parenthood, both for individuals and couple relationships (21,22). For example, in addition to a prior history of depression, conflict with and lack of support from a partner predict new mothers' risk of postpartum depression. Experiencing depression itself has also been linked to altered HPA axis functioning (23) and poorer child development among offspring of women experiencing

depression during pregnancy (24). Seeing as relationship conflict is an important source of stress among new parents, and both relationship conflict and maternal depression are known to result in HPA axis activation (24,25), we assessed maternal cortisol reactivity and recovery in response to a couple conflict discussion, an ecologically valid mild stressor, while additionally examining the role of maternal prenatal depressive symptoms.

Importantly, most studies to date have considered effects of maternal diurnal cortisol production, not maternal cortisol reactivity in response to a stressor, on child outcomes. Thus, even though it is known that greater exposure to psychological stress during pregnancy is associated with adverse health outcomes among offspring (2,3), not enough is known about the extent to which the maternal physiological response to as well as recovery from stressors influences offspring development and well-being. Despite the normative rise in cortisol levels across pregnancy, HPA reactivity to psychological stress appears to be attenuated during pregnancy, particularly during the second and third trimesters (26–28). This attenuation of the HPA stress response may help protect the developing fetus from exposure to potentially harmful glucocorticoid levels. Given that exposure to relatively higher levels of diurnal cortisol during pregnancy has been linked to a host of adverse infant and child health outcomes (2,20) increased maternal reactivity to stressors as well as slower recovery from stressors may be associated with indicators of poorer child well-being and development. Nonetheless, research on adult samples also suggests potential adverse effects of ‘blunted’ stress responses on health (29,30), suggesting that hyper- as well as hyporeactivity may be undesirable and that there may be an optimal ‘middle ground’ which is associated with the most beneficial health and developmental outcomes.

Existing research that has examined the links between maternal prenatal psychological and physiological stress and offspring health suffers from several limitations. First, many such studies assess maternal stress during pregnancy solely based on psychological instruments, without the inclusion of physiological stress assessments. However, self-reported levels of psychological stress often correlate only modestly with physiological stress markers (31) and reports of psychological distress are also lower among pregnant compared to non-pregnant women (26). Second, most studies only assess the effects of maternal stress during pregnancy in infancy and thus little is known about the influence of maternal stress during pregnancy on more distant offspring outcomes during childhood. Third, much research to date has included only HPA axis assessments via a single saliva sample or focused only on diurnal patterns of maternal HPA axis functioning (e.g., diurnal cortisol) rather than the maternal HPA axis response to naturalistic stressors. The latter is important given that resting levels of cortisol are not strongly associated with HPA axis reactivity (32). For example, one study links maternal diurnal cortisol levels during the third trimester to greater infant health problems (2), but does not include information on maternal reactivity to and recovery from stressors or on outcomes among their children beyond the first 12 months of life. It is possible that relatively greater HPA axis reactivity during pregnancy is indicative of better overall HPA axis regulation and an ability to mount appropriate physiological responses to stressors. A better-regulated maternal HPA axis in turn may portend a better-regulated HPA axis among offspring and consequent better offspring health.

The Current Study

The aim of the present study was to assess whether the maternal prenatal physiological stress response to a naturalistic, common, and highly salient stressor – a couple conflict discussion in the home – is linked to later infant and child health. In addition, we examined whether the association between the maternal physiological stress response and subsequent child health varied as a function of maternal prenatal depressive symptoms. This prospective, longitudinal study extends existing research by examining the relation of maternal prenatal cortisol levels and child health outcomes over the subsequent three years; by assessing the independent effects of cortisol reactivity and recovery; and by employing a stressor that is especially salient for first-time, expectant couples, i.e., couple conflict.

Methods

Participants

The sample consisted of 169 heterosexual couples residing in two cities in central Pennsylvania, living together, and expecting a first child, who were recruited as part of a randomized controlled trial evaluating the effects of the Family Foundation (FF) prevention program. FF consists of four sessions before birth and four sessions after birth for groups of primiparous couples and focuses on enhancing coparenting relations. Existing research has shown that FF improves maternal mental health, parenting quality, coparenting, and child adjustment (33–35). At study entry, mothers had a mean age of 28.3 ± 5.1 years and had completed an average of 15.1 ± 1.8 years of education. Ninety-two percent of mothers were non-Hispanic White and 85% were married. To be eligible for this study, mothers had to be at least 18 years old and be able to provide cortisol data between 12–32 weeks gestation. See Table 1 for additional information regarding our participants.

Cortisol was collected from a sub-sample of 136 mothers. Of these, 128 (59 from the control and 69 from the intervention condition) met initial criteria for these analyses by reporting requisite data. An additional five families (2 intervention, 3 control) were excluded from the present analyses because of severe parent and infant health problems (e.g., severe congenital defect, death of mother) or multiple births. Thus, our analytic sample consists of 123 families (65 treatment, 58 control).

Procedure

Participants were recruited into a study evaluating the effects of the FF intervention between August 2003 and October 2005. FF consists of four prenatal and four post-natal classes focusing on conflict management, problem solving, communication, and mutual support strategies that foster positive joint parenting of an infant. Control group couples were mailed literature on quality childcare and child development. Saliva and other baseline data were collected during pregnancy at the pretest visit before randomization into condition; later follow-up data were collected in posttest waves after birth and after the completion of the post-natal portion of the intervention.

Home visits were scheduled to occur in the afternoon or early evening to limit variability in cortisol based on time of day (mean time= 17.9 ± 2.3 hours), with 90% of samples being

collected after 2 p.m. and 80% of samples after 5 p.m. Study measures were collected from couples at pre-test (wave 1), when mothers' gestational ages averaged 22.4 ± 5.3 weeks (range 12–32 weeks), as well as at three follow-up periods when children were approximately 6 months (wave 2), 1 year (wave 3), and 3 years old (wave 4). Cortisol data were collected by trained research assistants during the pretest home visit before and following a videotaped couple conflict discussion task. Respondents were interviewed in their homes by trained research assistants for all waves except wave 2, when data was collected via a mailed questionnaire. At waves 2, 3, and 4, respectively, 114, 116, and 105 participants completed interviews. Further study details are available elsewhere (33,34,36). This study was approved by The Pennsylvania State University Institutional Review Board.

Measures

Couple conflict discussion task.—Couples participated in a 12-minute videotaped conflict discussion task. Specifically, couples were asked to discuss three problems in their relationship. These problem areas were chosen by research assistants based on which items each partner had previously rated highly on a list of potentially conflictual topics (e.g., couple relationship difficulties, financial strain).

Maternal prenatal cortisol.—Mothers provided three saliva samples using salivettes during the pretest home visit. Specifically, a baseline sample (t_0) was collected shortly after obtaining informed consent. Two subsequent samples were collected to assess cortisol reactivity and recovery in response to a mildly stressful couple interaction. During a 12-minute discussion period, couples discussed up to three previously-indicated topics where they wanted to see change in their partner's behavior (33). The second sample (t_1 , reaction) was collected 15 minutes after the end of the conflict discussion (on average 64 minutes after the baseline sample). The third sample (t_2 , recovery) was collected 20 minutes after the 2nd sample (on average 84 minutes after the baseline sample). Participants were instructed to not eat during the hour leading up to the visit; if eating occurred, cortisol-related tasks were delayed.

Following collection, saliva samples were stored within 8 hours at -20°C until they were shipped to Salimetrics laboratories (State College, PA) where they were stored at -70°C until assaying. At that time, samples were thawed, centrifuged at 3,000 rpm for 15 minutes, and then assayed using a commercially available immunoassay for salivary cortisol (Salimetrics LLC) following the recommended protocol. All samples were tested in duplicate. Assay sensitivity ranged from 0.007 to $3.0\mu\text{g/dL}$ and average intra-and inter-assay coefficients of variation were below 5 and 10%, respectively.

For the present study, cortisol measurements at t_0 constitute *baseline cortisol* (pre-discussion levels). *Cortisol reactivity* is the difference in cortisol level at t_1 from t_0 ($t_1 - t_0$) and reflects maternal cortisol change immediately following the couple's discussion of relationship stressors. *Cortisol recovery* is the difference in cortisol from t_1 to t_2 ($t_1 - t_2$) or the decline in maternal cortisol 20 minutes after the relationship discussion ended. See Table 1 for details regarding participants' cortisol levels.

Maternal-Reported Child Health Outcomes.—Mothers reported on child health over the past six months at six months, one year, and three years after birth (waves 2–4). Child health indicators included an overall health rating (7-point ordinal scale, ranging from poor to excellent), and counts of the following over the prior six months: a) fevers, b) doctor visits due to child illness/health problems, c) cold or respiratory illness, and d) ear infections. Existing research suggests that mothers provide reliable accounts of their young children's symptoms and health care utilization (37,38).

Covariates.—During pre-test visits, mothers provided data on their age, education (highest grade completed), marital status (cohabitating vs. married), overall health rating (ranging from 1–4, with '1' being poor and '4' being excellent), height and pre-pregnancy weight. At wave 2, mothers reported on their child's birth weight and sex. At the pretest, mothers also reported on illicit drug use during the past five years, current tobacco use, and lifetime history of alcohol-related problems. Finally, as daycare attendance is known to be associated with child illness rates (39–41), we include a time-varying covariate for the mother's number of weekly work hours at each wave. Paternal work was not included here because 90% of fathers reported working full-time (35 hours/week or more) at all postnatal waves of data collection.

Maternal Prenatal Depressive Symptoms.—During the in-home visit, mothers completed a 7-item subset of the Center for Epidemiological Studies Depression Scale (CESD), reporting on symptoms of depression occurring during the prior week (e.g., 'How often during the past week did you feel sad?') on a 4-point scale (42). Responses were averaged across all items, with higher scores indicating greater depressive symptoms. This subset of items was selected based on high correlations ($r > .90$) with the total score of the full scale to reduce participant burden. Cronbach's alpha for prenatal maternal depression symptoms in the present sample was acceptable at $\alpha = 0.79$.

Analyses

Data transformations.—To reduce the influence of outliers, we truncated high incidence rates for reported frequencies of child illness based on regression diagnostics and examination of distributional plots. The following outcomes were adjusted (number of cases listed in parentheses at waves 2/3/4): doctor visits (3/3/4); cold/respiratory illness reports (0/0/4); ear infection reports (2/1/4); fevers (4/2/2).

Prenatal cortisol values were residualized to address the heterogeneity in cortisol values arising from (a) time-of-day for cortisol collection and (b) degree of negativity expressed in wave 1 conflict discussions. Mothers' raw cortisol values at each collection time point were similarly and highly correlated with time of day ($r \sim -0.60$, $p < .001$). Smaller, but significant correlations were also observed between collection time and maternal raw cortisol reactivity ($r = 0.33$, $p < .001$) and cortisol recovery ($r = 0.24$, $p = 0.002$). To residualize cortisol values for the degree of negativity, we used a measure of negative communication created by having trained coders rate observed behavior during the videotaped interactions for the degree of contempt, hostility, and demandingness separately for both mother and father. A 5-point Likert scale was used, and scores were averaged across

couples to create a couple-level negative communication score; Cronbach's alpha for the six items was 0.84 (33).

The residualized scores were used in all statistical models. To reduce the impact of outliers, four values were truncated (i.e., set to threshold levels based on distributional box plots) for baseline cortisol, two for cortisol reactivity, and one value for cortisol recovery. Residualized scores were also multiplied by a factor of ten to enable more comparable variation across variables. See Table 1 for additional details regarding residualized cortisol levels.

Analytic strategy.—We used multilevel modeling (MLM) techniques to examine the association between prenatal maternal cortisol reactivity and recovery and subsequent maternal reports of overall child health and child illness. Specifically, we examined child health and illness measures 6 months, 1 and 3 years following birth, using a random slope at the individual level while adjusting for child age to account for clustering related to reports of child health and illness over time. We used MLM to examine the effect of prenatal maternal cortisol on mother's overall reported child health. Negative binomial regression models (appropriate for analysis of count outcomes) were used to model frequency of sick doctor visits, fever, cold/respiratory infection, and ear infections as a function of prenatal maternal cortisol. Results are presented as Incidence Rate Ratios (IRRs), representing the relative increase or decrease (compared to 1) in the likelihood of the outcome (not percentage changes). For example, if mean cortisol reactivity were associated with four sick doctor visits over the past 6 months, an IRR of 0.25 would suggest that a one standard deviation increase in cortisol reactivity would be associated with one sick doctor visit over the same time period.

Other variables that could impact child health were adjusted for included: intervention condition (which was unrelated to health outcomes), child sex, child birth weight, pretest marital status, mother's years of education, age, pre-pregnancy BMI, self-rated mother health, illicit drug use, tobacco use, history of alcohol problems, and gestational age at pretest. To adjust for illness related to children being cared for outside the home, we added the mother's total work hours at each post-test wave. We analyzed the relation between mother's prenatal cortisol levels and child health/illness in two sequential models that included the following predictor variables: (1) cortisol reactivity adjusting for baseline cortisol (and covariates), and (2) cortisol recovery adjusting for reactivity and baseline cortisol. To address heteroscedasticity, Huber-White standard errors were estimated.

To test whether any observed effects of cortisol reactivity or recovery were dependent on gestational age at the time of pretest data collection, we considered both linear and non-linear moderation, by examining linear and quadratic gestational ages, using gestational age as a continuous variable (number of weeks) and categorical variable (by dividing the sample into thirds: 12–20 weeks, 20–24 weeks, 25–32 weeks).

Finally, we examined whether maternal prenatal depressive symptoms moderated the association between cortisol reactivity/recovery and child health using the basic MLM regression framework and covariates described above.

Results

Table 2 displays results for the main effects of prenatal maternal cortisol measures on indicators of child health and illness. Mean cortisol levels across the entire sample declined across the three assessment timepoints, in line with previous research that did not find a strong salivary cortisol response in response to a standard laboratory stressor among pregnant women (26); thus, findings presented here speak to relative differences across participants.

Cortisol Reactivity

In Model 1, we examine the association between prenatal maternal cortisol reactivity and child outcomes while adjusting for the mother's baseline cortisol level. Greater cortisol reactivity was associated with a 0.72-point increase in the mother's overall child health rating ($p = 0.016$, 95% CI = [0.06, 1.30]). Over the range of residualized cortisol reactivity values, maternal report of child health increases by two points as reactivity levels rise.

Increased cortisol reactivity was also associated with a reduced incidence of several child illness measures. Specifically, a one standard deviation increase in cortisol reactivity was associated with a reduction in doctor sick visits by a factor of 0.49 ($p = 0.006$, 95% CI = [0.29, 0.83]), a reduction in reported fevers by a factor of 0.43 ($p = 0.002$, 95% CI = [0.25, 0.73]), a reduction in reported ear infections by a factor of 0.38 ($p < 0.001$, 95% CI = [0.25, 0.58]), and a marginally significant reduction in reported colds/respiratory infections by a factor of 0.31 ($p = 0.073$, 95% CI = [0.08, 1.11]).

Cortisol Recovery

In Model 2, we examined the association between maternal cortisol recovery and child health/illness, while adjusting for baseline cortisol and cortisol reactivity. We did not observe significant main effects for cortisol recovery on any child health and illness measures (all $ps > .05$).

Association Between Gestational Age with Cortisol Reactivity

To determine whether mother's gestational age at pretest influenced cortisol reactivity and recovery, we tested the role of gestational age as a possible moderator. We found no significant moderation patterns of gestational age with respect to cortisol reactivity and recovery (β s from -0.98 to 1.04 , all $ps > .05$). Linear and quadratic interaction terms for the continuous measure of gestational age also did not indicate significant moderation patterns (β s from 0.008 to 0.043 , all $ps > .05$).

Analyses Using Raw Cortisol Values

We also considered cortisol reactivity and cortisol recovery values based on raw cortisol data, with added covariates regarding the time of sample collection. When using cortisol reactivity and recovery values based on raw cortisol data, our findings were consistent with those reported above for residualized reactivity and recovery scores. That is, increased reactivity to relationship stressors was associated with maternal report of better overall child

health and reduced incidence of child health problems. Maternal prenatal cortisol recovery remained unrelated to our outcomes of interest.

Moderation by Prenatal Maternal Depressive Symptoms

Maternal prenatal depressive symptoms moderated the association between cortisol reactivity and mother-rated overall child health ($p < 0.034$, 95% CI=[0.07, 1.87]), see Figure 1. Specifically, among mothers with lower depressive symptoms (shown at $-1SD$), mother-rated overall child health was consistently high, increasing only slightly with increasing levels of reactivity. In contrast, among mothers with higher levels of depressive symptoms (shown at $+1SD$), mother-rated overall child health was lower when cortisol reactivity was also lower. Thus, the joint concurrence of reduced cortisol reactivity and greater maternal prenatal depressive symptoms is linked with poorer overall child health as rated by their mothers.

Maternal prenatal depressive symptoms did not moderate the associations between cortisol reactivity and maternal reports of specific child health problems ($p > 0.05$) or between cortisol recovery and any of our outcomes ($p > 0.05$). For a graph depicting maternal prenatal cortisol levels by maternal depressive symptoms, see Figure 2.

Discussion

The present study extends prior work by directly linking maternal prenatal cortisol reactivity between 12–32 weeks gestation to health outcomes among offspring over the first three years of life. Specifically, we found that relatively greater maternal cortisol reactivity in response to a conflict discussion task with their romantic partner was a strong and consistent predictor of greater overall child health (as assessed by maternal report) as well as fewer illness reports at 6 months, 1 year and 3 years following birth. The association between greater cortisol reactivity and better overall child health was further moderated by maternal prenatal depressive symptoms, such that the described association was only seen among women reporting higher levels of depressive symptoms. We found no association between cortisol recovery following the conflict discussion task and subsequent reports of child health. Taken together, these findings suggest that a relatively more responsive maternal HPA axis during pregnancy may portend better offspring health over the first few years of life.

Our findings suggest that greater reactivity in response to an acute interpersonal stressor during pregnancy is beneficial with respect to later child health. These findings may seem counterintuitive in light of the prevailing understanding that heightened psychological stress levels are linked with adverse offspring development and health (2,43). Among pregnant women, maintaining a comparatively greater cortisol response in reaction to a stressor may perhaps be indicative of better HPA axis regulation and more appropriate stress responses, which in turn may be associated with healthier cortisol exposure of the developing fetus. This is also in line with research linking moderate amounts of psychological stress during pregnancy to potential long-term benefits with respect to healthy child development (44). In addition, previous research that has found attenuation to acute stressors among pregnant women has primarily focused on less naturalistic, laboratory-based stressors (26,45). Thus, it

is possible that even in a generally higher-cortisol prenatal environment marked by a potentially reduced range of maternal cortisol reactivity, the fetus benefits from a relatively greater degree of maternal HPA responsivity to psychological stress.

Maternal stress responsivity and resulting fluctuations in cortisol, even if attenuated during pregnancy, may be critical for healthy fetal and later child development. The fetal programming hypothesis suggests that maternal HPA axis regulation during pregnancy is an important influence on future HPA axis regulation among offspring themselves (7). Because HPA axis regulation and consequent cortisol production influence the developing organism, infants who themselves have a less well-regulated HPA axis may have a greater propensity towards experiencing future health problems because of the wide range of relevant physiological processes, e.g., regulation of inflammatory and metabolic processes, prefrontal cortex functioning, that are influenced by HPA axis activity (46). In addition to physiological mechanisms, behavioral pathways may also account for our results. For example, it is possible that better HPA axis regulation during pregnancy is indicative of mothers' greater ability to cope with stressors and thus a lower likelihood of taking their child to see a physician.

It is furthermore of interest that maternal prenatal depressive symptoms only moderated the association between cortisol reactivity and mothers' ratings of their child's overall health, not more specific, countable outcomes, such as the number of physician visits. Although mothers also self-reported the frequency of physician visits and specific child health problems, this raises the possibility that greater maternal depressive symptoms may primarily change mothers' subjective assessments of their children's health, rather than the number of times children actually do get sick and require to be taken to the doctor. These results also support a large body of research linking a blunted salivary cortisol response following an acute stressor to psychiatric problems, such as major depression, particularly among women (23,47). Given that decreased stress reactivity in response to stressors has been linked to depression, and that maternal depression in turn is also known to alter parenting and child health (48–50), it is possible that lower HPA axis reactivity in the presence of other maternal problems, such as greater depressive symptoms, may carry negative consequences for the offspring.

Finally, we did not find effects of maternal stress *recovery* on infant and child health. One possible explanation for this is that the recovery period following the stressor was insufficiently long for us to capture recovery and full variability in recovery in our sample in their entirety. This is of particular concern as salivary cortisol recovery has previously been shown to be longer among pregnant women in the second and third trimester (51). In addition, much research has shown cortisol recovery to be influenced by both the social context in which it occurs (52) as well as individual differences, such as coping styles (53), which were not assessed as part of the present project. It is possible that taking into account additional information, e.g., with respect to individual differences, would have brought to light potential influences of cortisol recovery following acute stress but this was beyond the scope of the present report.

This study has several strengths. First, we were able to take advantage of a naturalistic, ecologically valid, and highly salient stressor for pregnant women, specifically, a couple conflict discussion conducted in the home. This represents an important extension of previous research, almost all of which has exclusively focused on the use of laboratory-based stressors which have substantially less ecological validity (26,45). Second, we were able to adjust for the degree of negativity couples expressed during the couple conflict discussion talk, based on observer-coded assessments of expressed negativity. Thus, we focused on responsivity of the HPA axis to whatever level of negativity was elicited in the discussion, rather than on absolute levels of cortisol production to a standard stressor stimulus (which, while being standardized as a stimulus, may not be equally salient to all individuals). Third, unlike most previous research we were able to focus specifically on maternal reactivity to and recovery from an acute stressor, rather than on basal or diurnal cortisol levels. Further, we were able to evaluate HPA axis reactivity and recovery in the late afternoon and early evening. This is particularly important as it has been previously suggested that afternoon/evening measurements of cortisol is preferred among pregnant women, as the largest changes to the diurnal cortisol rhythm among pregnant women can be found early in the day during the cortisol awakening response (28). Finally, we were able to follow our participants until children had reached the age of three years and to assess data collected at three different time points following childbirth, thus limiting the risk of recall bias on the part of mothers when asked about their child's recent health problems.

Nonetheless, we also acknowledge some limitations. Although families were prospectively followed, our measures of child health are based on maternal report, not medical records or physiological measures (e.g., child immune response). However, previous research suggests that retrospective parental reports regarding child health (when compared to medical records) are generally reliable for up to a year, especially for parents of younger children (37,38). In addition, our sample consisted of women who were either married or cohabitating with their partner. Thus, these findings may not generalize to single pregnant women with potentially less access to social support than those living with romantic partners, which is known to buffer the negative impact of acute stressors (54). Similarly, the sample was predominantly white and highly educated, further limiting the generalizability of the present findings. The sample also included pregnant women at different gestational ages at the time of cortisol sampling. Although we adjusted for gestational age in our analyses and found no evidence of moderation by gestational age, future research may benefit from exploring the importance of timing of exposure. Finally, our stressor did not result in an overall mean increase in salivary cortisol in this sample, which may be a function of sample characteristics. Recent evidence suggests that women show smaller increases in cortisol following acute stressors compared to men (55) and two different samples of pregnant women have previously been shown to not have had a marked salivary cortisol response to an acute stressor (26,56). Nonetheless, comparing relative HPA axis responses to an ecologically valid acute stressor among pregnant women and considering possible consequences, fills an important gap in the literature.

Conclusions

This study provides novel longitudinal evidence that increased maternal prenatal cortisol reactivity in response to an interpersonal stressor (couple conflict) is associated with better overall child health and lower illness rates of common childhood health problems over the three-year period following pregnancy. This highlights the importance of considering not only basal cortisol among pregnant women but also HPA responsivity to stressors. Although these findings need to be replicated and these general associations, as well as the potential moderating role of maternal prenatal depressive symptoms, better understood, they may be indicative of opportunities to improve infant and early child health by focusing on maternal stress and perhaps particularly family relations during pregnancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Conflicts of Interest and Source of Funding:

Drs. Roettger, Schreier, and Jones declare no conflicts of interest. Dr. Feinberg, the principal investigator of the study, developed the Family Foundations program and is the owner of a private company, Community Strategies, which disseminates the program. This research is based on data from a trial of the program (NIH grant MH064125; MEF), but this report does not concern program effects. This research is supported by NIH grant HL137809 (HMCS).

Acronyms used in text:

BMI	body mass index
CI	confidence interval
FF	Family Foundations
HPA	hypothalamic-pituitary-adrenal
kg	kilograms
kg/m²	kilograms-per-square-meter
OLS	Ordinary Least Squares
SD	standard deviation
wks	weeks

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Figure 1. Moderation of the association between cortisol reactivity and mother-rated overall child health by maternal prenatal depressive symptoms

Note: Depressive symptoms moderate the effect of maternal prenatal cortisol reactivity and mother-rated overall child health ($b=0.97$, $p = 0.034$, $95\% \text{ CI} = [0.07, 1.87]$). Results based on MLM regression models. Mother-rated child-health is a 7-point ordinal scale denoting the mother's overall health rating for her child (ranging from '1' = 'poor' to '7' = 'excellent'). Lower and higher maternal prenatal depressive symptoms are plotted at $-/+1$ SD, respectively. $SE=0.28$ for the plotted lines.

Figure 2. Maternal prenatal cortisol by maternal depressive symptom quartile.

Note: Maternal prenatal salivary cortisol is presented at baseline, before and after the couple conflict discussion task. Depression quartiles are arranged by increasing number of depressive symptoms as reported on the CESD.

Table 1.

Descriptive statistics (N = 123)

	N (%) or Mean $\pm$ SD
Marital status (% married)	104 (84%)
Mother education (highest grade completed)	15.05 $\pm$ 1.87
Maternal age (years)	28.10 $\pm$ 5.50
Mother's pre-pregnancy BMI (kg/m ²)	24.99 $\pm$ 5.25
Mother's self-rated health	3.40 $\pm$ 0.54
Number of weeks gestation	22.37 $\pm$ 4.98
Time of day of cortisol collection (24 hrs)	17.96 $\pm$ 2.32
Mother's tobacco use (# of times, prior month)	0.53 $\pm$ 2.13
Observed negative couple communication	-0.01 $\pm$ 0.63
Mother's drug use, prior 5 years (# of times)	1.70 $\pm$ 1.45
Mother's history of alcohol problems	1.03 $\pm$ 2.73
Child birth weight (kg)	3.27 $\pm$ 0.66
Child sex (male)	72 (59%)
Mother weekly total work hours	
Wave 2	26.80 $\pm$ 19.21
Wave 3	25.61 $\pm$ 18.68
Wave 4	26.90 $\pm$ 19.49
Prenatal maternal depression	0.43 $\pm$ 0.45
Salivary cortisol	
Maternal baseline cortisol at t ₀ (µg/dL)	0.17 $\pm$ 0.11
Maternal cortisol at t ₁ (µg/dL)	0.14 $\pm$ 0.08
Maternal cortisol at t ₂ (µg/dL)	0.13 $\pm$ 0.08
Maternal cortisol reactivity (t ₁ -t ₀) (µg/dL)	-0.03 $\pm$ 0.05
Maternal cortisol recovery ((t ₁ -t ₂) (µg/dL)	-0.01 $\pm$ 0.02
Maternal baseline cortisol at t ₀ , residualized	-0.01 $\pm$ 0.76
Maternal baseline cortisol at t ₁ , residualized	0.00 $\pm$ 0.61
Maternal baseline cortisol at t ₂ , residualized	-0.00 $\pm$ 0.58
Maternal cortisol reactivity, residualized	0.01 $\pm$ 0.39
Maternal cortisol recovery, residualized	0.00 $\pm$ 0.21
Child health/illness	
Mother-rated overall health	
Wave 2	6.33 $\pm$ 0.91
Wave 3	5.97 $\pm$ 1.04
Wave 4	6.16 $\pm$ 1.03
Number of sick doctor visits (6 mo.)	
Wave 2	1.91 $\pm$ 2.02
Wave 3	2.32 $\pm$ 2.21
Wave 4	1.78 $\pm$ 2.56

	N (%) or Mean $\pm$ SD
Number of fevers (6 mo.)	
Wave 2	1.26 $\pm$ 1.91
Wave 3	2.46 $\pm$ 1.92
Wave 4	1.67 $\pm$ 1.80
Number of ear infections (6 mo.)	
Wave 2	1.16 $\pm$ 1.21
Wave 3	2.82 $\pm$ 2.10
Wave 4	2.20 $\pm$ 1.81
Number of colds/respiratory infections (6 mo.)	
Wave 2	0.30 $\pm$ 0.78
Wave 3	1.18 $\pm$ 1.83
Wave 4	0.79 $\pm$ 1.65

Note: kg = kilograms; kg/m² = kilograms-per-square-meter; μ g/dL= micrograms-per-deciliters; t₀ = time of initial cortisol measurement; t₁ = time of cortisol measurement, after exposure to relationship stressor; t₂ = time of cortisol measurement, after recovery period. Exact number of participants varied by data collection wave. Wave 2 (6 months following birth): n = 112; wave 3 (1 year following birth): n = 114; wave 4 (3 years following birth): n = 105.

Table 2.

Multilevel regression coefficients/IRRs and standard deviations for residualized maternal prenatal cortisol predicting change in child health outcomes across the study period.

	<u>Model 1</u>		<u>Model 2</u>	
	Baseline	Reactivity	Baseline	Reactivity
<u>Child Health (Coefficients)</u>				
Overall health	0.90 (0.14)	0.72* (0.28)	0.08 (0.15)	0.81** (0.30)
<u>Illness measures (Incident Rate Ratios)</u>				
Sick doctor visits	0.91 (0.12)	0.49** (0.13)	0.88 (0.12)	0.46** (0.12)
Fevers	0.76* (0.10)	0.43** (0.11)	-0.77+ (0.11)	0.43** (0.12)
Ear infections	0.70** (0.07)	0.38*** (0.08)	0.70** (0.07)	0.38*** (0.08)
Colds/respiratory infections ^b	1.06 (0.36)	0.31 [†] (0.22)	1.03 (0.36)	0.32 [†] (0.22)

Note:

[†] p < 0.10;

* p < 0.05;

** p < 0.01;

*** p < 0.001.

All multilevel models adjusted for clustering of individuals within waves. Multivariate-normal ML regression models were used for modeling mother-reported child health. Negative binomial ML regression models were used to model count-based child illness measures. Model 1 = baseline cortisol + cortisol reactivity + covariates. Model 2 = cortisol recovery + Model 1. Illness measure coefficients are reported as Incident Rate Ratios (IRRs).