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Effects of Prenatal and Postnatal Parent Depressive Symptoms on Adopted Child HPA Regulation: Independent and Moderated Influences

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Abstract

This study used a prospective adoption design to investigate effects of prenatal and postnatal parent depressive symptom exposure on child hypothalamic-pituitary-adrenal (HPA) activity and associated internalizing symptoms. Birth mother prenatal symptoms and adoptive mother/father postnatal (9-month, 27-month) symptoms were assessed with the Beck Depression Inventory in a sample of 192 families as part of the Early Growth and Development adoption Study. Child morning/evening cortisol levels and child symptoms of internalizing disorders (according to mother/father report on the Child Behavior Checklist) were assessed at 54 months, and birth mother diurnal cortisol was measured at 48 months postnatal. Hierarchical linear modeling was used to test main effects and interactions of parents' symptoms predicting child cortisol, controlling for birth mother cortisol. Prenatal exposure to birth mother symptoms predicted lower child cortisol (main effect), as did postnatal exposure to adoptive parent symptoms (interaction effects). Adoptive mother 9-month symptoms exacerbated cortisol-lowering effects of both concurrent paternal symptoms and later (27-month) maternal symptoms, and the effect of birth mother cortisol. Lower child cortisol, in turn, was associated with higher child internalizing symptoms. Implications are discussed with respect to the intergenerational transmission of depression risk.

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Keywords

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Stress response mechanisms that fail to calibrate effectively to environmental conditions are recognized as a likely link in the chain from parental depression[1] to offspring risk for disorder (Goodman & Gotlib, 1999; Meyer, Chrousos, & Gold, 2001). In particular, exposure to parents with elevated depressive symptoms both prenatally and during early postnatal development has been shown to shape the functioning of the hypothalamic-pituitary-adrenal (HPA) axis, the neuroendocrine system that in turn affects responsiveness to socially relevant stressors and risk for internalizing problems in children (e.g., Gunnar & Donzella, 2002; Oberlander et al., 2008; Murray, Halligan, Goodyer, & Herbert, 2010). Despite a large body of work addressing components of this model, there are ongoing questions about the source of parent depressive symptom effects: How much of child risk is attributable to birth parent influences (prenatal exposure and/or inherited stress dysregulation) vs. rearing parent influences (postnatal exposure)? To what extent do maternal vs. paternal symptoms and chronic vs. fluctuating symptoms derail developing stress systems? In addition, the nature of HPA dysregulation–hyper- vs. hypoactivation–conferring depression risk in a particular developmental context is still debated.

The present study was designed to follow up on previous indications that the time course of parental depressive symptoms from pre- to postnatal development influences child HPA regulation (Laurent, Ablow, & Measelle, 2011) while clarifying the sources of such influence. Specifically, we tested parental depressive symptom effects in an adoption sample to help resolve (1) whether the impact of parental depressive symptoms on child HPA depends on prenatal symptoms (from birth parents) or postnatal symptoms (from rearing parent s, or both, (2) whether effects derive from maternal or paternal symptoms (or both), (3) whether such exposure effects remain when the effect of birth mother HPA is taken into consideration (as a marker of inherited influences on HPA regulation), and (4) whether child depression risk manifests as hyper- or hypocortisolism . Below, we review available evidence for HPA dysregulation as a mechanism of depression risk transmission; prenatal and postnatal effects of parental depressive symptoms, as well as inherited influences on HPA regulation; and interactive time course and interparental effects of parent symptoms on child HPA.

Depression Transmission and HPA Regulation

The HPA axis is a stress mobilization system that varies in tonic activation over the course of the day (i.e., peak in the morning followed by decline) and plays a key role in mounting a response to physical and psychological stressors (Sapolsky, Romero, & Munck, 2000). Typically measured through circulating cortisol levels, HPA activity that is either too high or too low may signal problems. As described by the Adaptive Calibration Model of stress system development, HPA activation may adapt upward or downward to manage sustained adversity, each of which comes with costs to physical and psychosocial functioning (Del Giudice, Ellis, & Shirtcliff, 2011).

HPA dysregulation has been consistently related to elevated depressive symptoms and/or familial depression risk across a variety of ages (see Chrousos & Gold, 1992; Ehlert, Gaab, & Heinrichs, 2001; Guerry & Hastings, 2011), making this a promising mechanism for

[1]An understanding of depression risk is informed by both studies of self-reported depressive symptoms and a smaller set of studies of clinically-diagnosed syndromes. In this paper, we consider both types of studies relevant while distinguishing between “depressive symptoms” and “(clinical) depression” in discussion of relevant research.

transmission of depression susceptibility. Depressed adults show differences in diurnal cortisol output—typically, though not always, higher—and in acute stress responses—especially, impaired post-stress recovery—that may help to explain psychological and somatic symptoms (e.g., Burke, Davis, Otte, & Mohr, 2005; Lok et al., 2011). Recent reviews confirm that children show dysregulated diurnal cortisol patterns related to both concurrent and future depression similar to (but smaller in magnitude than) adult depression-related differences, and these patterns are in turn predicted by parental depressive symptoms (Guerry & Hastings, 2011; Lopez-Duran, Kovacs, & George, 2009). Maternal depression during the first years of life has been preferentially related to later cortisol reactivity to laboratory stressors in preschool (3-4 year-old) and school-aged (7-8 year-old) children (Ashman, Dawson, Panagiotides, Yamada, & Wilson, 2002; Dougherty, Klein, Rose, & Laptook, 2011). Research in infants has further demonstrated marked effects of both prenatal and postpartum (but not pre-conception) maternal depression on cortisol levels, suggesting that exposure during both periods shapes HPA axis activity (Brennan et al., 2008).

Inherited factors also play a role in associations among parent and child depression and HPA regulation, though these effects may in turn depend on environmental conditions. Moderate heritability coefficients have been found for cortisol levels, particularly in the morning, a genetic liability that can be further expressed via environmental stress-induced epigenetic processes (Bartels, van den Berg, Sluyter, Boomsma, & de Geus, 2003; Oitzl, Champagne, van der Veen, & de Kloet, 2010). Twin research has demonstrated a stronger genetic effect for morning cortisol levels in families characterized by high postnatal adversity, which authors interpreted as stress-induced exacerbation of an inherited diathesis (Ouellet-Morin et al., 2009). Additional genetically informed studies separating the child-rearing environment from inherited risk would help to clarify these processes.

Another important point to clarify is the type of HPA activity conferring depression risk in a given population. Although many of the studies cited above highlight elevated cortisol levels and reactivity as a consequence of parental depressive symptoms and/or a correlate of young children's own depressive symptoms, there is also research showing suppressed HPA activity in children and adolescents exposed to early adversity, including parental depressive symptoms (Bouma, Rise, Ormel, Verhulst, & Oldehinkel, 2011; Fernald, Burke, & Gunnar, 2008; Gunnar & Vazquez, 2001). Several developmental factors could contribute to divergent results. First, there is evidence that depressogenic HPA patterns differ in early (prepubertal) vs. later development, with cortisol hypoactivity more commonly found in the former and a shift toward hyperreactivity coinciding with puberty (Hankin, Badanes, Abela, & Watamura, 2010). Second, the time course of symptoms may make a difference, with more recent (adolescent) internalizing symptoms related to higher cortisol, but earlier (starting in childhood) symptoms related to lower cortisol (Ruttle et al., 2011). These discrepancies underline the importance of examining stress exposure over time.

Moderating Influences: Depressive Symptom Time Course and Interparental Effects

Mounting evidence suggests the influence of a parent's depressive symptoms depends not only on when the parent experiences symptoms, but also on the chronicity of symptoms–the time course–as well as on the other parent's mental health status. Several studies have demonstrated a synergistic effect of earlier and later maternal depressive symptoms on child cortisol and internalizing symptoms, with a chronic course across infancy and early childhood predicting more extreme dysregulation (manifested in higher or lower afternoon cortisol: Essex, Klein, Cho, & Kalin, 2002; Gump et al., 2009). There is also evidence that the course of maternal depressive symptoms from pregnancy to 18 months postnatal shapes

infant HPA function, though in this study a changing course of symptoms (i.e., from high to low or vice versa, rather than chronic elevation) predicted more extreme infant hyper- or hypoactivation and impaired stress recovery (Laurent et al., 2011). Still, these studies converge in showing that early exposure to elevated parent symptoms heightens the impact of subsequent exposure.

Although the majority of depression research focuses on mothers' symptoms, the importance of fathers' symptoms is gaining attention (see Lieb, Isensee, Höfler, Pfister, & Wittchen, 2002). Similarly to the studies discussed above in mothers, chronic elevation in paternal depressive symptoms across pre- and postnatal periods was shown to predict more severe child behavioral and psychological problems in early childhood (Ramchandani et al., 2008). This effect held controlling for maternal symptoms, indicating unique paths for maternal vs. paternal effects. There may also be an interactive path by which maternal and paternal depressive symptoms combine to influence child outcomes. A study showing maternal clinical depression only predicted child internalizing/externalizing symptoms in the presence of paternal psychopathology (Dietz, Jennings, Kelley, & Marshall, 2009) suggests fathers have the power to exacerbate or buffer against the effects of maternal symptoms on child risk for disorder.

The Current Study

This study was designed to follow up on earlier indications that the time course of parental depressive symptoms shapes child HPA function while addressing several crucial gaps left by that study and other depression-HPA research. Our main aim was to distinguish effects of prenatal (birth parent) vs. postnatal (rearing parent) depressive symptoms to evaluate how, controlling for birth mother HPA dysregulation (an indicator of inherited risk for HPA dysregulation), early exposure to parent depression shapes child risk. We used an adoption sample to examine effects of birth mother prenatal depressive symptoms and adoptive parent postnatal depressive symptoms (measured at 9 months and 27 months) on child diurnal cortisol levels at 54 months. By testing interactions of earlier and later parental symptoms, we could investigate time course effects both within and across parents. Birth mother cortisol measures provided a control for the effect of her HPA patterns, which could also be moderated by prenatal/postnatal symptom exposure. A secondary aim was to investigate the effects of father depressive symptoms on child cortisol, both as a direct influence and as a potential moderator of maternal symptom effects. Measures of both adoptive parents' symptoms across postnatal time points allowed us to test main and interactive effects of mother and father depressive symptoms on child cortisol. Finally, we wanted to confirm the relevance of HPA patterns (either hypo- or hyperactivation) associated with parental depressive symptoms for the child's own risk for later depression. We did this by relating children's cortisol to their concurrent symptoms of internalizing problems.

Based on depression risk transmission models and specific longitudinal studies discussed above, we hypothesized that (1) exposure to parent depressive symptoms prenatally and postnatally would impact child HPA function measured by cortisol levels, but that effects would depend on an interaction of the two. Specifically, we expected that elevated prenatal depressive symptoms (indexed in the birth mother) and/or early postnatal depressive symptoms (indexed in the adoptive parents) would strengthen effects of subsequent adoptive parent symptoms on child cortisol. (2) We further expected that the effect of one adoptive parent's depressive symptoms on child cortisol would be exacerbated by concurrent elevations in the other parent's symptoms. (3) We predicted that these associations would hold controlling for birth mother cortisol, which would independently predict child cortisol levels, particularly for children exposed to adverse (elevated parent symptom) environments. (4) Finally, we expected that child HPA patterns (hypo- or hyperactivity) associated with

parents' depressive symptoms would relate to concurrent child internalizing symptoms, consistent with a neurobiological risk transmission model.

Method

Participants

Participants were drawn from the Early Growth and Development Study, a longitudinal study of adopted children and their birth and adoptive parents. Recruitment of participants occurred between 2003 and 2006, beginning with the recruitment of adoption agencies (N = 33 agencies in 10 states located in the Northwest, Mid-Atlantic, and Southwest regions of the United States). The participating agencies reflected the full range of adoption agencies operating in the United States: public, private, religious, secular, those favoring open adoptions, and those favoring closed adoptions. Agency staff identified participants who completed an adoption plan through their agency and met the following eligibility criteria: (a) the adoption placement was domestic, (b) the infant was placed within 3 months postpartum, (c) the infant was placed with a nonrelative adoptive family, (d) birth and adoptive parents were able to read or understand English at the eighth-grade level, and (e) the infant had no known major medical conditions such as extreme prematurity or extensive medical surgeries. Of the families who met eligibility criteria, 68% (n = 361) agreed to participate. The participants were representative of the adoptive parent population that completed adoption plans at the participating agencies during the same time period (Leve et al., 2007).

The sample included male (57%) and female (43%) children with a range of racial backgrounds (57.6% White, 11.1% Black/African American, 9.4% Latino, 20.8% multiracial, .3% American Indian/Alaskan Native, .6% unknown or not reported). Adoptive parents were predominantly White (over 90% of adoptive mothers/fathers) and middle class and involved in a stable marital or marriage-like relationship (M = 18.5 years, SD = 5.2 at first assessment).[2] Birth mothers tended to be younger (M age = 24.1, SD = 5.9) than adoptive mothers (M age = 37.8, SD = 5.5) and fathers (M age = 38.4, SD = 5.8) at the time of the child's birth and of a lower socioeconomic status (typically high school or trade school education, median household income = $14,000). The current analyses are based on the subset (n = 192) of the total sample for which complete birth mother prenatal and adoptive mother/father postnatal depressive symptom information was available. A comparison of cases included vs. not included revealed nonsignificant differences on all study variables (i.e., demographics, as well as available depressive symptom scores).

Procedure and Measures

Parent and child data for this study were collected through in-person interviews, home-based questionnaires, and web-based assessments (for depressive symptoms and child behavior), as well as saliva samples (for cortisol). Further details on each measure and timing of assessments are given below.

Birth mother prenatal depressive symptoms – Pregnancy History Calendar—

Birth mothers completed an interview developed for this study based on the Life History Calendar method at their first postnatal (4 month) assessment. The measure comprised 76 questions rated on a 1-4 scale concerning health behaviors and symptoms experienced

[2]A small proportion (7.8%) of adoptive families in this sample included same-sex or divorced parents. Comparison of family compositions revealed nonsignificant differences on study variables, and a comparison of models including vs. not including these families showed they did not affect reported results. For the purposes of the present study, the primary caretaker in same sex couples was treated as the "mother" and the second parent as the "father" to fit with the typical division of caretaking responsibilities.

during pregnancy, including a subset of items from the Beck Depression Inventory (see below). Birth mothers' mean rating of the 5 depression-related questions served as an index of prenatal depressive symptoms ($M = 2.19$, $SD = .69$), as reported on in previous papers with this sample (i.e., Pemberton et al., 2010). Internal consistency for this 5-item index was found to be adequate (Cronbach's alpha = .82). Standardized (Z) scores were used in analyses to create a standard, centered metric for depressive symptom effects.

Postnatal depressive symptoms – Beck Depression Inventory (BDI; Beck & Steer, 1993)—Adoptive parents completed this widely used measure of depressive symptoms via computer-assisted interviews (adoptive mother/father 9 month and 27 month assessments). Mothers and fathers individually rated 20 symptoms of depression in the past week on a 0-3 scale (the suicidal ideation item from the original 21-item scale was eliminated to minimize situations where clinical follow-up would be required), and a summary score was computed. Compared to adoptive fathers, adoptive mothers tended to show slightly higher levels of depressive symptoms but similar variability at both 9 months ($M = 3.60$, $SD = 3.30$ vs. $M = 2.88$, $SD = 3.52$; $t[191] = 2.11$, $p = .04$) and 27 months ($M = 3.64$, $SD = 4.24$ vs. $M = 2.59$, $SD = 3.73$; $t[191] = 2.90$, $p = .004$). Although these central tendencies reflect low overall symptom levels, a small number of parents at each time point reported symptoms within the sub-syndromal (5% of mothers and 2.5% of fathers at both 9 and 27 months) or clinical (.5% of fathers at 9 months, 1% of mothers and 1.5% of fathers at 27 months) ranges. Furthermore, an extensive literature documents the stability and harmful impact of even subsyndromal states (e.g., Judd, Akiskal, & Paulus, 1997; Rapaport & Judd, 1998), and previous work has demonstrated meaningful costs to offspring adjustment associated with subclinical levels of parental depressive symptoms (Campbell, Morgan-Lopez, Cox, & McLoyd, 2009). Symptoms were correlated across time points within parents ($r = .46$ - $.65$) but were generally not correlated with other parents' symptoms; the one exception was for adoptive mother and father symptoms at 27 months, which showed a small but significant association ($r = .20$, $p = .005$). Scores were standardized for use in analyses.

Child internalizing symptoms – Child Behavior Checklist (CBCL 1½-5; Achenbach & Rescorla, 2000)—Child symptoms of DSM Affective and Anxiety Problems were assessed by adoptive parent report on the CBCL, a well-validated measure of a variety of externalizing and internalizing difficulties in children. Both parents independently rated 99 child behaviors on a scale from 0-2 at 18 months (mailed questionnaire), 27 months (mailed questionnaire), and 54 months (web-based interface). DSM-oriented scales were computed, and T-scores ($M = 50$, $T > 65$ indicates borderline to clinical range) were used to index child behavior problems. Mother and father reports showed similar overall problem levels at the 54-month assessment (Affective Problems $M = 54.88$, $SD = 5.64$ per mother; $M = 53.58$, $SD = 5.08$ per father; Anxiety Problems $M = 52.46$, $SD = 5.15$ per mother; $M = 52.34$, $SD = 4.44$ per father). At the same time, modest correlations between parent reports ($r = .34$ for Affective Problems, .49 for Anxiety Problems) suggested parents could be perceiving child problem behaviors differently. As such, mother and father reports were analyzed separately. Again, despite central tendencies in the normative range, some children scored within the borderline (3.5% for Affective, 1.6% for Anxiety) or clinical (2.3% for Affective, 2.0% for Anxiety) ranges for these problems at the 54-month assessment, and the costs of even subclinical symptoms for later depression risk have been well documented (see Garber, 2006).

Child and birth mother HPA activity – Salivary Cortisol—Morning (M time = 7:36 AM for children, $SD = 42$ minutes; M time = 8:11 AM for mothers, $SD = 107$ minutes) and evening (M time = 8:12 PM for children, $SD = 53$ minutes; M time = 10:29 PM for mothers,

SD = 90 minutes) saliva samples were collected across 3 consecutive days, and samples were sent for cortisol assay at the University of Trier Laboratory. Child samples were obtained with the help of adoptive parents at 54 months, and birth mothers contributed samples as part of their 48-month assessment. Morning samples were collected 30 minutes after awakening, and evening samples were collected at bedtime. Study parents were trained in sample collection procedures, which involved saturating salivettes before placing them in prelabeled plastic vials. Samples were then mailed to the primary study site, at which point they were frozen and stored on site until all samples for all participants had been collected and could be mailed jointly to the analysis laboratory. Samples were stored at −5° F (−20° C) until assay using a competitive solid phase time-resolved fluorescence immunoassay (DELFIA; see Dressendörfer, Kirschbaum, Rohde, Stahl, & Strasburger, 1992) with interassay coefficients of variation (CV) 7.1%-9.0%. Samples were assayed in duplicate, and mean scores used in analyses (*M* cortisol = .355 μg/dl, *SD* = .20, *M* intraassay CV = 6.04% for children; *M* cortisol = .365 μg/dl, *SD* = .31, *M* CV = 5.53% for birth mothers). Parents recorded the exact time of saliva collection and other information that could affect cortisol measurement, such as illness, medication use, and sleep time, in a collection diary. Standard data screening procedures (e.g., identifying and eliminating extreme outlying values, checks for implausible/contradictory time recording) were applied. As described further below, all 6 morning and evening sample values per individual were entered as HPA activity outcomes, with collection time entered as a covariate to allow comparability across sample values.

Control variables—Openness of adoption, based on aggregated perceived contact across adoptive families and birth mothers at 9-months (Ge et al., 2008), was considered as a control for similarities in the birth parent and adoptive family homes resulting from contact between parties. Also, birth mother postnatal depressive symptoms were assessed with the BDI at 4 months and 48 months using similar procedures to those reported for adoptive parents above. These scores were considered as controls to differentiate prenatal exposure effects from more general effects of birth mother mental health. Additional prenatal risk factors assessed in the birth mother's pregnancy history interview–indices of maternal substance use and toxin exposure during pregnancy, as well as prenatal health complications–were considered as controls to separate effects of birth mother depressive symptoms from other associated prenatal risk conditions. Finally, the cortisol collection variables outlined above (e.g., medication use) were considered as controls for evaluating cortisol values.

Analysis Overview

A dependent data structure lent itself to multilevel modeling in HLM (Raudenbush & Bryk, 2002). This approach separates variance into within-family (child and birth mother repeated cortisol measures) and between-family (different levels of parental depressive symptom exposure) components. The child cortisol outcome was modeled at Level 1 with a variable-intercept model; this allowed for the prediction of child true-score cortisol levels, based on all 6 sample scores. Birth mother cortisol was also added as a covariate at Level 1 to capture effects of birth mother HPA dysregulation.

Parental depressive symptom predictors were added at Level 2 to explain variability in child cortisol levels. Primary explanatory models tested (H1) main effects of parent depressive symptoms at all time points (birth mother prenatal depressive symptom Z-scores, adoptive mother and father postnatal depressive symptom Z-scores), and interactive *time course* effects of depressive symptom exposure (birth mother prenatal × adoptive parent postnatal, adoptive parent early postnatal × later postnatal depressive symptom Z-scores); and (H2) interactive *interparental* depressive symptom effects (adoptive mother × father depressive symptom Z-scores at postnatal time points). The setup and rationale for these interactive

explanatory models follow closely from previous work examining time course effects of birth mother depressive symptoms on infant cortisol (Laurent et al., 2011). All models controlled for birth mother cortisol (H3).

Secondary models were designed to contextualize these effects and test remaining hypotheses. The first model expanded on H3 by testing parental depressive symptoms as predictors of the birth mother HPA effect described above; this addressed whether exposure to parent symptoms exacerbated a familial predisposition to HPA dysregulation, consistent with the findings of Ouellet-Morin and colleagues (2009). Finally, (H4) child cortisol was tested as a predictor of concurrent internalizing symptoms. Examples of the two-level models testing (a) one of the primary cortisol outcome models, (b) the birth mother risk outcome model, and (c) one of the child internalizing outcome models, are given below:

a) Effect of time course of adoptive mother depressive symptom exposure on child cortisol

Level 1 (within-family)

$$\text{Child Cortisol} = \beta_0 + \beta_1(\text{collection time}) + \beta_2(\text{birth mother cortisol}) + \text{error}$$

Level 2 (between-family)

$$\beta_0 = \gamma_{00} + \gamma_{01}(\text{adoptive mother 9 month depressive symptoms}) + \gamma_{02}(\text{adoptive mother 27 month depressive symptoms} + \gamma_{03}(\text{adoptive mother 9 month} \times 27 \text{ month depressive symptoms}) + \text{error}$$

$$\beta_1 - \beta_2 \text{modeled as fixed effects}$$

b) Effect of early parent depressive symptom exposure on birth mother HPA effect

Level 1 (within-family)

$$\text{Child Cortisol} = \beta_0 + \beta_1(\text{collection time}) + \beta_2(\text{birth mother cortisol}) + \text{error}$$

Level 2 (between-family)

$$\beta_0 - \beta_1 \text{ modeled as fixed effects}$$

$$\beta_2 = \gamma_{20} + \gamma_{21}(\text{birth mother prenatal depressive symptoms}) + \gamma_{22}(\text{adoptive mother 9 month depressive symptoms}) + \gamma_{23}(\text{adoptive father 9 month depressive symptoms}) + \text{error}$$

c) Effect of child mean cortisol levels on concurrent internalizing symptoms

Level 1 (within-family)

$$\text{Child Affective Problems} = \beta_0(\text{mother report}) + \beta_1(\text{mother report } 18-54 \text{ month slope}) + \beta_2(\text{father report}) + \beta_3(\text{father report } 18-54 \text{ month slope}) + \text{error}$$

Level 2 (between-family)

$$\begin{aligned}\beta_0 &= \gamma_{00} + \gamma_{01}\,(\text{mean child cortisol}) + \text{error}\\ \beta_1 &= \gamma_{10} + \text{error}\\ \beta_2 &= \gamma_{20} + \gamma_{21}\,(\text{mean child cortisol}) + \text{error}\end{aligned}$$

$$\beta_3 = \gamma_{30} + \text{error}$$

Results

Model Setup

Cortisol scores were checked for non-normality and found to be within acceptable limits for skew (< 2), so untransformed scores were used in analyses. Although a number of the parent depressive symptom predictors showed positive skew (.5-2.7), the same model effects were obtained using raw and natural log-transformed scores, so the more interpretable raw score results are reported. Given more substantial skew in CBCL outcome scales (2.0-3.8) and greater concerns about interpretation of skewed outcome variables, natural log-transformed scores were used in analyses.

Collection time was included as a Level 1 control variable to account for time-of-day effects. This linear effect was found to adequately explain the effect of collection time on cortisol values in the present sample; the linear effect was significant, and the model was not improved by adding a nonlinear term. When morning and evening values were examined as separate outcomes, model effects were in the same direction for both morning and evening cortisol, though stronger for the former. None of the other potential cortisol control variables–sleep/wake times, steroid use, illness–were significantly related to cortisol and were therefore not included in further model testing. Birth mother cortisol scores, residualized for collection time and grand mean-centered, were added as an inherited risk control at Level 1. Including these scores (matched to child scores across samples/days) yielded a significant improvement in model fit according to the deviance statistic, $\chi^2(3) = 17.74$, $p < .001$, suggesting that some of children's unexplained cortisol variability could be predicted by their birth mothers' HPA patterns. Even though this predictor was nonsignificant overall, the association was found to vary across children and was retained for additional testing. Openness of adoption was unrelated to current study variables and so was not included in further models.

Main and Time Course Interactive Effects of Parent Depressive Symptom Exposure on Child Cortisol

The main effects model showed negative associations between parents' depressive symptoms (birth mother prenatal symptoms, adoptive father 9-month symptoms, and adoptive mother 27-month symptoms) and child cortisol levels at 54 months. Interactive model testing demonstrated support for H1: adoptive mother 9-month symptoms moderated the effect of her 27-month symptoms (see Table 1, part A). Further examination of the interaction revealed that early adoptive mother depressive symptoms heightened the cortisol-lowering effect of her later symptoms (see Figure 1 for an illustrative graph).

Contrary to hypotheses, birth mother prenatal depressive symptoms did not moderate the effects of subsequent adoptive parent symptoms, but had an independent main effect in the same direction (lowering child cortisol). Tests of later (postnatal) birth mother depressive symptoms confirmed that this effect was specific to prenatal symptoms. Other birth mother prenatal risk variables were tested as potential confounds; an effect of drug exposure (b = .

038, $SE = .019$, $p = .04$) on child cortisol was in the opposite direction (i.e., raising cortisol) and became nonsignificant with birth mother cortisol in the model, making it unlikely that drug exposure could explain the observed prenatal depressive symptom effect. Compared to the baseline model containing no depressive symptom predictors, the adoptive mother time course model yielded a marginal improvement in fit, as reflected in the deviance statistic, $\chi^2(4) = 9.22$, $p = .056$.

Interparental Interactive Effects of Parent Depressive Symptom Exposure on Child Cortisol

The model including adoptive mother × father symptom effects revealed a significant interaction at 9 months (see Table 1, part B), supporting H2. Further examination of this effect showed that early adoptive mother depressive symptoms intensified the cortisol-lowering effect of concurrent father symptoms (see Figure 2 for an illustrative graph). Compared to the baseline model, the interparental 9-month model yielded a significant fit improvement, $\chi^2(4) = 11.86$, $p = .018$.

Effects of Parent Depressive Symptom Exposure on Birth Mother HPA Effect

The fact that the above effects were significant while controlling for birth mother cortisol provided support for H3. To further explore this familial risk effect, prenatal-early postnatal parent depressive symptoms were tested as predictors of the association between birth mother cortisol and child cortisol. The only significant effect (of the 3 tested) was for adoptive mother 9-month symptoms increasing the association (see Table 1, part C and Figure 3). Because birth mothers reporting higher prenatal and postnatal depressive symptoms similarly showed low cortisol levels ($b = -.033$, $SE = .016$, $p < .05$), such heightened parent-child association was consistent with amplified risk for symptom expression.

Associations Between Child Cortisol and Internalizing Symptoms

To determine whether the cortisol-lowering effects identified above related to heightened child internalizing problems, we fit models predicting adoptive mother-reported and father-reported CBCL scale scores at the 54-month assessment. Linear models of child CBCL outcomes over time were centered at 54 months so as to predict concurrent child adjustment by mean child cortisol scores. Significant negative associations between child cortisol and mother-reported Affective and Anxiety Problems were found, as well as a marginally significant ($p = .07$) negative association with father-reported Anxiety Problems (Table 2). This finding supported the hypothesis that lower child cortisol generally reflected heightened internalizing risk in this sample.

Discussion

In this study we found evidence for effects of both birth parent prenatal and rearing parent postnatal depressive symptoms on reduced child cortisol activity, which in turn was associated with increased child internalizing problems. Early postnatal exposure to maternal depressive symptoms (at 9 months of age) appeared to exert particularly widespread effects by exacerbating effects of concurrent paternal symptoms and later maternal symptoms, as well as the effects of the birth mother HPA dysregulation. With these findings, we can be more confident that early exposure to parents' depressive symptom, and not just genetic liability, influences child risk; independent of both birth mothers' depressive symptoms and HPA activity, adoptive parents' postnatal depressive symptoms predicted young children's cortisol levels and associated affective/anxiety symptoms. Because the adoptive parents and children were unrelated, the associations between adoptive parent and child cannot be due to the effects of shared genes. While caution in extending these findings to clinical-level depression is warranted, these findings offer further insight into the nature of HPA

dysregulation in children of parents struggling with depressive symptoms. They also underline the importance of moderating time course and interparental influences, points elaborated below.

Parental depressive symptoms–measured in relation to both prenatal and postnatal development–were associated with lower child cortisol, which in turn related to child symptoms of internalizing problems in this sample. Consistent with adaptive calibration models of stress system activity (Del Guidice et al., 2011), this may be viewed as an attempt to adapt to moderately stressful conditions by downregulating HPA activation and thus sensitivity to the social environment. However, such downregulation may come at a cost, blunting the child's ability to meet interpersonal challenges and take in relevant information. Indeed, the link between lower cortisol and heightened internalizing symptoms in this study suggests the costs of diminished HPA sensitivity outweighed the benefits, perhaps because the adoptive parents generally offered a "good" environmental context in which it pays to be responsive. The fact that parental depressive symptom effects were most evident for lowered child morning cortisol levels is consistent with the flattening of daily rhythms detected in other risk samples (e.g., Gunnar & Vazquez, 2001; Ruttle et al., 2011) though the same direction of effects on evening levels suggests a general blunting rather than rhythm-specific dysregulation. Characteristics of the current sample further support observations that HPA dysregulation appears as hypo- (rather than hyper-) activation among prepubertal children. Further longitudinal work is needed to explore precisely when and how this HPA pattern becomes problematic in a particular developmental context.

The depressive symptom exposure outcomes observed here are consistent with a sensitive period for developing HPA function both in the womb and during early postnatal development. Previous work has demonstrated effects of maternal stress and depression during pregnancy on fetal expression of glucocorticoid receptors and subsequent HPA regulation (Davis, Glynn, Waffarn, & Sandman, 2011; Oberlander et al., 2008). Similarly, the quality of the early caregiving environment and frequency/severity of stressors activating HPA during a critical period of neurodevelopment has been shown to influence glucocorticoid receptor expression and sensitivity (e.g., Pryce, Aubert, Maier, Pearce, & Fuchs, 2011; Weaver et al., 2004). Importantly, we were able to rule out maternal substance use and other prenatal/neonatal complications as the reason for the prenatal symptom effect in this study, and the specificity of prenatal (as opposed to postnatal) birth mother symptom effects. We were also able to control for a more direct transmission of familial HPA dysregulation by including birth mother cortisol measures. While this did not reveal a strong birth mother risk effect overall, consistent with previous adoption studies of depression transmission (see Rice, Harold, & Thapar, 2002), between-child variability in the size of the effect suggested a possible additional mechanism for postnatal parent depressive symptom effects. This finding must be replicated to determine its reliability and practical significance, but it presents a novel and potentially useful framework for testing multiple routes of parent symptom effects early in development.

Consistent with hypotheses motivating this study, we did find a time course effect–i.e., earlier parental depressive symptoms moderating later symptom effects–though this was specific to the postnatal period and indicated a more severe effect of chronic (rather than shifting) maternal symptoms. Differing findings may depend on when child HPA function is assessed, as suggested by the convergence with previous findings in older children (Essex et al., 2002; Gump et al., 2009) as opposed to previous studies of infants. The true costs of chronic parent depression may become obvious only after a period of HPA development across the first several years of life. The reasons for not detecting a prenatal × postnatal course effect may be more complex. On the one hand, methodological issues such as differences in the measurement of birth mother prenatal and adoptive parent postnatal

symptoms (brief vs. full scale BDI) and/or the time gap between prenatal and postnatal symptom assessments could obscure a possible interaction effect. On the other hand, prenatal birth parent and postnatal adoptive parent effects on child HPA development should occur through separate paths, as suggested by previous work comparing genetically related and unrelated parent-child depression transmission (Harold et al., 2011). More detailed research at varying levels of analysis (i.e., molecular genetic, neural structure and function, neuroendocrine activity, behavioral interactions) is needed to parse such effects. Still, we can conclude from this study that both pre- and postnatal depressive symptom exposure (and birth and rearing parents) are important for later child HPA function, and that these effects are in the same direction (lowering morning cortisol levels)

We also found support for the importance of fathers' depressive symptoms as both a main effect and a moderator exacerbating the effect of mothers' symptoms. These results add weight to the contention that fathers' mental health should be considered more routinely in depression risk research. The risky constellation of not one, but two depressed parents during early postnatal development is not unlikely for several reasons. First, assortative mating for affective disorder (see Mathews & Reus, 2001) increases the chances of elevated symptoms in one parent being matched by the other. Subsequent experiences–shared environmental risk due to difficulty conceiving and/or financial stress associated with adoption, the marriage-stressing transition to parenthood for both biological and adoptive parents (Doss, Rhoades, Stanley, & Markman, 2009; McKay, Ross, & Goldberg, 2010), and the tendency for one spouse's depression to negatively impact the other's mood (Kouros & Cummings, 2010)–would only enhance such associations. In fact, previous work within this sample showed that adoptive fathers' early (9-month) depressive symptoms related to adoptive mothers' later (27-month) depressive symptoms, all of which predicted child problem behaviors (Pemberton et al., 2010). More detailed studies of the mechanisms for these interparental effects could help clarify whether paternal depression impacts children's HPA indirectly through effects on maternal symptoms and parenting, or through separate (but synergistic) effects on child stress. For now, these findings underline the need to identify and treat depression-prone mothers *and* fathers to protect children.

The present findings point to several practical and theoretical priorities in developmental stress research. One is the need for early identification and treatment of at-risk parents and expecting parents. Although the effects demonstrated in this sample were limited largely to sub-clinical internalizing symptoms, we cannot assume that later intervention with children showing clinical-level disorders is adequate; as demonstrated by this and other research, it is the earliest (prenatal-early postnatal) exposure to parental symptoms that exerts the most striking effects on the developing HPA system, which in turn confers lasting vulnerability to depression. This study also underlines the importance of attending to moderating influences, including symptom course and interparental effects, to evaluate a family risk situation. Early maternal symptoms may be particularly important as a moderating influence strengthening adverse effects of both paternal symptoms and subsequent maternal symptoms. Although a full explanation for these effects is beyond the scope of the current study, particularly since we were unable to measure children's cortisol across early development, it could be that interactions with a non-depressed mother during the first year of life calibrate the HPA in ways that buffer against dysregulating effects of stress encountered later on. From this perspective, early treatment of even sub-clinical maternal depression could be key to heading off future child problems. Finally, our results support attention to hypocortisol in daily rhythms, not just hyperreactivity, as a risk factor in children of depressed parents.

Several limitations of this study should be used to guide further research. First, while we were able to prospectively examine family risk processes across a critical period of development, we utilized only two assessments of parent symptoms at 9 and 27 months and

a single assessment of child cortisol levels at 54 months. Especially given differences between time course effects found previously in an infant sample and those found here, it will be important to trace concurrent and lagged associations between parental symptoms and child HPA function measured more intensively across infancy and early childhood. This would help to determine which aspects of HPA risk profiles are stable and which evolve in response to parent influences. To better resolve questions of when hyper- vs. hypocortisol marks risk, these effects should be further tested across pre- and postpubertal development. Another limitation involves the assessment of relatively broad psychological and neuroendocrine constructs that do not allow for a fine-grained analysis of mechanisms by which the one (parental depressive symptoms) impacts the other (child HPA). We have offered possible explanations for how these effects could unfold, but further measurement of proposed mechanisms such as parent-infant affective exchanges and changes in glucocorticoid receptor expression and sensitivity will be necessary. Finally, we chose to examine parental depression effects through a continuous range of symptoms in a normative sample not selected for depression, and child HPA through daily cortisol levels. Further work is needed to determine whether these effects apply similarly to clinical-level depression, acute HPA reactivity, and children at heightened risk for early problem behavior.

These limitations notwithstanding, this study makes an important contribution by demonstrating independent effects of birth and rearing parents' depressive symptoms on child HPA activity and internalizing symptoms, while controlling for the contribution of birth mother HPA as an index of inherited liability. Using an adoption design further allowed us to separate effects of prenatal from postnatal depression exposure, influences that are confounded in samples where the birth mother provides both the intrauterine environment and the postnatal environment. This work supports HPA dysregulation more broadly as a vector for familial depression transmission while adding to our understanding of when and how such transmission occurs.

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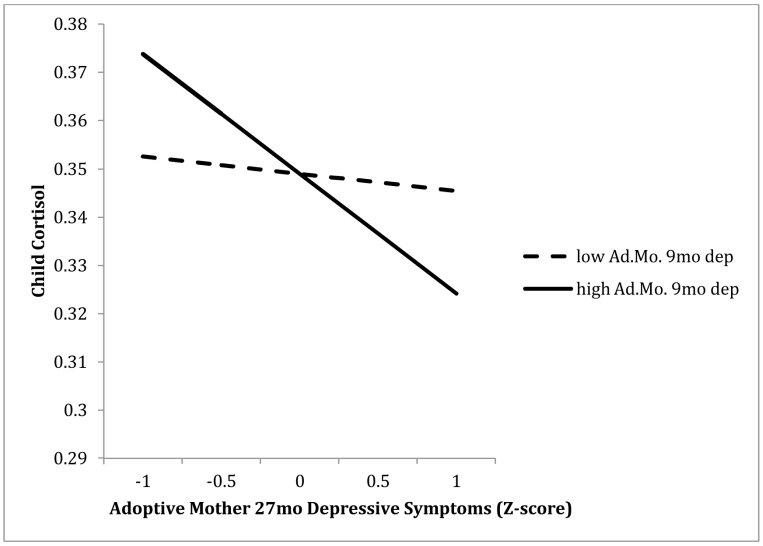

Figure 1.

Adoptive mother 9-month depressive symptoms moderate the effect of later (27-month) symptoms on child cortisol at 54 months (plotted at 25th and 75th percentile values of adoptive mother 9mo symptoms).

Note. Ad.Mo. refers to Adoptive Mother

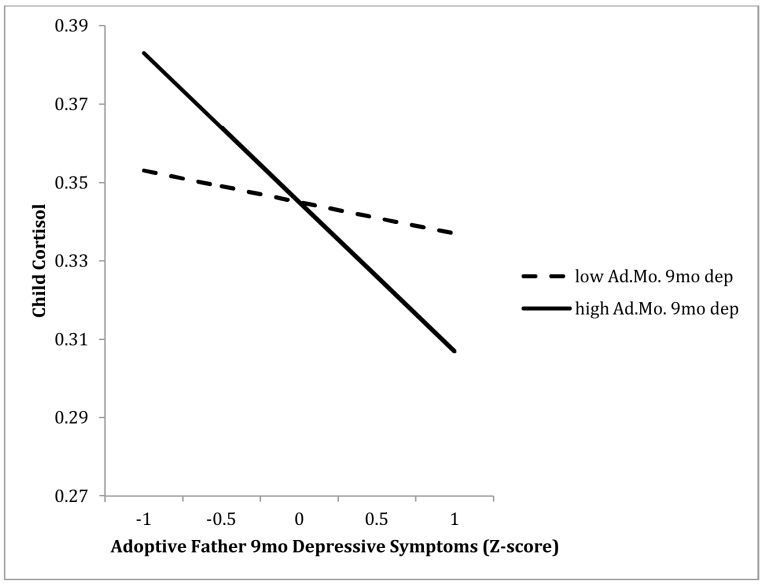

Figure 2.
Adoptive mother 9-month depressive symptoms moderate the effect of adoptive father 9-month symptoms on child cortisol at 54 months (plotted at 25th and 75th percentile values of adoptive mother 9mo symptoms).
Note. Ad.Mo. refers to Adoptive Mother

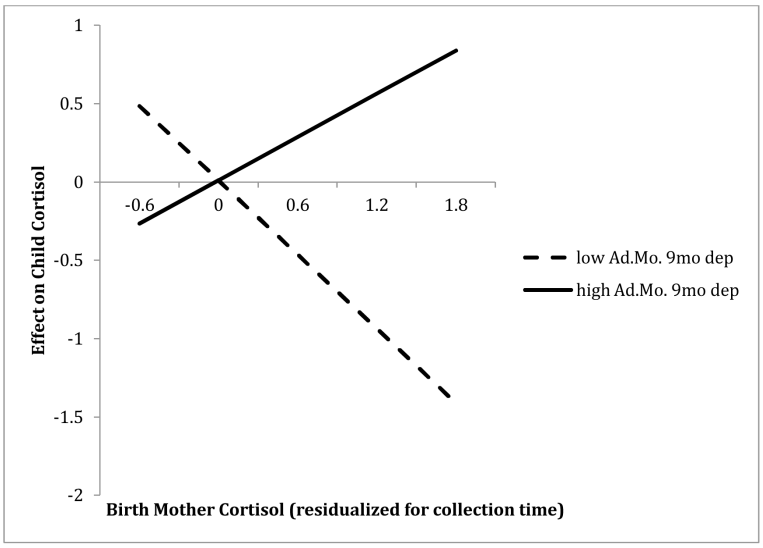

Figure 3.

Adoptive mother 9-month depressive symptoms moderate the association between birth mother and child cortisol levels (plotted at 25th and 75th percentile values of adoptive mother 9-month symptoms).

Note. Ad.Mo. refers to Adoptive Mother

Table 1

Associations between Exposure to Prenatal (Birth Parent) and Postnatal (Rearing Parent) Depressive Symptoms and Child Cortisol Levels

Predictor	Coeff (*SE*)
A. Time Course Models	
A1. Birth Mother × Adoptive Mother Course	
Child cortisol intercept γ_{00}	**.35 (.011)**
Birth Mother prenatal γ_{01}	**−.033 (.011)**
Adoptive Mother 27mo γ_{02}	**−.030 (.015)**
Birth Mother prenatal × Adoptive Mother 27mo γ_{03}	−.027 (.017)
A2. Birth Mother × Adoptive Father Course	
Child cortisol intercept γ_{00}	**.35 (.011)**
Birth Mother prenatal γ_{01}	**−.028 (.011)**
Adoptive Father 27mo γ_{02}	−.003 (.013)
Birth Mother prenatal × Adoptive Father 27mo γ_{03}	−.020 (.014)
A3. Adoptive Mother Course	
Child cortisol intercept γ_{00}	**.35 (.011)**
Adoptive Mother 9mo γ_{01}	.012 (.013)
Adoptive Mother 27mo γ_{02}	−.016 (.021)
Adoptive Mother 9mo × 27mo γ_{03}	**−.017 (.008)**
A4. Adoptive Father Course	
Child cortisol intercept γ_{00}	**.34 (.011)**
Adoptive Father 9mo γ_{01}	**−.041 (.021)**
Adoptive Father 27mo γ_{02}	.019 (.019)
Adoptive Father 9mo × 27mo γ_{03}	−.002 (.008)
B. Interparental Models	
B1. Adoptive Parents 9mo	
Child cortisol intercept γ_{00}	**.34 (.011)**
Adoptive Mother 9mo γ_{01}	.0002 (.009)
Adoptive Father 9mo γ_{02}	**−.027 (.013)**
Adoptive Mother × Father 9mo γ_{03}	**−.024 (.009)**
B2. Adoptive Parents 27mo	
Child cortisol intercept γ_{00}	**.35 (.012)**
Adoptive Mother 27mo γ_{01}	−.018 (.016)
Adoptive Father 27mo γ_{02}	.003 (.013)
Adoptive Mother × Father 27mo γ_{03}	.012 (.018)
C. Birth Mother Cortisol Covariate (inherited risk)	
Intercept γ_{20}	.0007 (.044)
Birth Mother prenatal γ_{21}	.006 (.043)
Adoptive Mother 9mo γ_{22}	**.072 (.033)**

Predictor	Coeff (*SE*)
Adoptive Father 9mo γ^{23}	−.070 (.044)

Note. Predictors are depressive symptom Z-scores. Significant effects ($p < .05$) indicated in bold. Birth mother prenatal × adoptive parent 9 month symptom effects were also tested and found nonsignificant.

Table 2

Associations between Child Cortisol Levels and CBCL Internalizing Problem Scales

	Affective Problems	Anxiety Problems
Predictor	**Coeff (*SE*)**	**Coeff (*SE*)**
Mother Report		
Intercept (level at 54 months) γ_{00}	**3.99 (.006)**	**3.94 (.005)**
Child Cortisol γ_{01}	**−.054 (.022)**	**−.047 (.016)**
Slope (18-54 months) γ_{10}	**.018 (.003)**	**.012 (.003)**
Father Report		
Intercept (level at 54 months) γ_{20}	**3.97 (.006)**	**3.95 (.005)**
Child Cortisol γ_{21}	−.017 (.032)	−.036 (.020)
Slope (18-54 months) γ_{30}	**.008 (.003)**	**.011 (.003)**

Note. CBCL outcomes are natural log-transformed T-scores to correct for positive skew. Significant effects ($p < .05$) indicated in bold.