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Cancer experience modulates the relationship between child and parent Hypothalamic Pituiatary Adrenal (HPA) axis functioning

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CANCER EXPERIENCE MODULATES THE RELATIONSHIP BETWEEN CHILD AND PARENT HYPOTHALAMIC PITUIATARY ADRENAL (HPA) AXIS FUNCTIONING

by

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Child Cancer Experience Modulates the Relationship Between Child and Parent Hypothalamic-Pituitary Adrenal (HPA) Axis Functioning

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Abstract

Objective: We examine how parental stress and pediatric cancer might jointly predict child HPA function using a non-invasive method of cortisol assessment (hair samples).

Methods: Parents and children from healthy control and pediatric cancer survivor families participated. Multilevel modeling was applied to data from a nested-design study (85 children, 5-18 years old, from 64 families, healthy controls: n=32; cancer survivors: n=32) to determine the relationship between parent salivary and child hair cortisol measures.

Results: No main effect of the cancer experience on child cortisol was found. Parental cortisol positively correlated with child cortisol levels within healthy controls, while there was no association within pediatric cancer survivor families. For cancer survivor children given corticosteroids, there was a negative association between parent and child cortisol levels. Among cancer survivor children not given corticosteroids, the relationship between parent and child was the same as for healthy control families.

Conclusion: Only when children are exposed to corticosteroids, the relationship between parent and child HPA function is significantly changed by the cancer experience. This study provides no evidence that the cancer illness alone alters child HPA function. However, direct perturbation of the child's HPA axis by corticosteroid exposure may have lasting effects on children's stress physiology.

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INTRODUCTION

The preponderance (66%) of pediatric cancer survivors experience at least one "late effect", an outcome related to the disease process or treatment that occurs more than six months after the completion of treatment. These late effects may manifest as either physical or psychological impairments and are, in a substantial minority of cases, severe or life threatening (Institute of Medicine, 2003; Oeffinger et al., 2006). Psychological late effects include both neurocognitive (Moore, 2005) and psychosocial effects (Patenaude & Kupst, 2005). Psychological late effects are highly variable, with common manifestations including but not limited to behavior problems, depression, anxiety, and post-traumatic stress symptoms, as well as deficits in attention, executive functioning, memory, and general intelligence (Moore, 2005; Moore, Ater, & Copeland, 1992; Mulhern, Wasserman, Fairclough, & Ochs, 1988; Schultz et al., 2007; Stam, Grootenhuis, & Last, 2001).

The pediatric cancer experience encompasses a series of ongoing interrelated stressors, such as painful and long-term treatment, frequent and unpredictable hospital stays, the threat of mortality, and late effects associated with treatment (Kazak & Noll, 2015). Treatment severity, in particular, has received ample attention as this component of the cancer experience has influences on child outcomes (Anderson, Smibert, Ekert, & Godber, 1994; Brinkman et al., 2012; Moleski, 2000; Moore, 2005; Peterson et al., 2008; Reddick et al., 2006). This research has found that as the severity of treatment increases, children are more likely to suffer from late effects (Moleski, 2000). However, while treatment severity related to radiation, chemotherapy and neurosurgery has direct effects

on pediatric cancer survivor outcomes, it is currently unknown the extent to which these effects may also be caused via increased stress or dysregulation of the HPA axis.

Chronic stress associated with pediatric cancer may influence several different child developmental outcomes, including global symptoms of stress and distress as well as child HPA axis functioning. HPA function is an essential outcome measure for child development not only because it can be impacted by the amount of stress to which an individual is exposed (Del Giudice, Ellis, & Shirtcliff, 2011), but also because dysfunction of the HPA axis is associated with many common psychological health problems such as depression (Spijker & van Rossum, 2012) and anxiety (Faravelli et al., 2012; Ising et al., 2012). Previous research suggests children who suffer from chronic diseases such as wasting disorders and HIV (Zeitler, Travers, & Kappy, 1999) as well as children who have been maltreated (Fisher, Van Ryzin, & Gunnar, 2011) have altered HPA function. Survivors of pediatric cancer generally have higher levels of global distress than children who experienced few health problems (Lesko, 1990; Zeltzer et al., 2008) as well as higher rates of PTSD than healthy controls and children who have a history of abuse (Pelcovitz et al., 1998).

As these findings reveal differences in pediatric cancer survivors' anxiety and PTSD symptomology compared to healthy controls, it is logical to consider that these psychological processes may be related to changes in HPA axis function. Research investigating whether pediatric cancer may affect child HPA axis function has found that survivors of pediatric Acute Lymphoblastic Leukemia (ALL) demonstrate altered HPA function (Gordijn et al., 2012). Yet, it is virtually impossible to untangle the effects of corticosteroid treatment from those of the cancer experience during treatment. Treatment

studies examining corticosteroid exposure both within the cancer and non-cancer literatures show similar increased levels of anxiety and an increased risk for behavioral and psychiatric problems (Drozdowicz & Bostwick, 2014; Pound et al., 2012), as well as increased treatment related anxiety (Pound et al., 2012). The cancer experience is no doubt a prolonged stressor, which can alter HPA regulation; alternatively, or additionally, some cancer treatments, particularly corticosteroids, have the potential to directly influence the development of the HPA axis, particularly during childhood. A focus on child cancer survivors provides an opportunity to inform the study of stress regulation as survivors are no longer being treated with medications that disrupt HPA function.

Contextual factors may impact how children respond to the experience of a chronic illness such as cancer. When examining the contextual effect of parent stress and distress, it is found that non all pediatric cancer survivors are equally negatively affected by the cancer experience, and that parental stress may mitigate the negative effects of cancer. Previous research examining the effect of parental distress on child day-to-day functioning after cancer found that for ALL survivors, high parent distress was associated with high child functional impairment (Hile, Erickson, Agee, & Annett, 2014). Thus, children's ability to function in everyday life after having cancer is related to stress in their family environment. In contrast to the above findings, at least one study reports that depression symptomology in children with cancer is less well predicted by parental distress than in healthy control children (Robinson, Gerhardt, Vannatta, & Noll, 2007). Yet, both of these studies are limited to parent proxy reports, of child functioning, which may bias the results. This methodological problem highlights the need for research to

examine both parent and child stress using alternative measures that can assess physiological markers of stress.

Literature exists that supports the impact of early life stress interaction with parental cortisol levels to shape child HPA functioning. This research (Clearfield, Carter-Rodriguez, Merali, & Shober, 2014; Hibel, Granger, Blair, Finegood, & Investigators, 2014) highlights that as child stress exposure increases, the concordance between parental factors and child cortisol levels decrease. Mothers and children in low socioeconomic status (SES) families demonstrate less concordance between their cortisol levels than high SES families (Clearfield et al., 2014). This may be attributed to the increased stress of being in a low socioeconomic environment, but additionally, these mothers may not spend as much time with their infants and therefore may not have as many shared experiences with the infant, leading to a decreased relationship with the child. Experimental manipulation of cortisol synchronicity by Hibel and colleagues (2014), found that the concordance between parent and child cortisol decreases as the child is exposed to stress. Given that cancer is both a major adversity and one that removes children from the home environment for significant periods of time, it can be hypothesized that children with cancer might not only have elevated cortisol but may also exhibit weaker correlations with their parents than healthy controls.

The aim of the present study was to investigate how the early experience of the chronic stress of cancer, in addition to parental stress, might predict child HPA function as expressed in cortisol production. In order to study this relationship we examined parent and child cortisol is both healthy control and pediatric cancer survivor populations. Specifically, we test the following hypotheses: (1) early experience of cancer will affect

child cortisol levels; and (2) early experience of cancer modifies the association between parental and child cortisol levels. Specifically, we predict that parental and child cortisol levels will be positively associated among healthy controls, but that this association will be reduced among child cancer survivors. We also compare to healthy controls cancer survivors who have and have not been treated with corticosteroids to determine whether any cancer related effects can be attributed to the experience of cancer itself or to potential steroid interference with HPA development.

METHODS

Participants

Participants (N=64 families, 85 children, children mean age=11 years, SD=4) included two distinct groups: 32 families with children who were pediatric cancer survivors (CS; child mean age in cancer survivor group=12 years, SD=4), and 32 families with children who were healthy controls (HC; child mean age in healthy control group=10 years, SD=3). Each child was assessed along with a primary caregiver (n=3, 2 sisters, 1 grandmother) or parent (n=61, 58 mothers, 3 fathers). Eligibility criteria for children in both groups included: (a) age between 5 and 18 years, and (b) ability to follow instructions in English. As this study involved additional components not reported here, individuals were excluded from the study at the discretion of the investigator if they could not adequately complete the tasks (e.g., child with visual impairment) or if they had a diagnosis that interferes with cognitive or functional abilities (e.g. Learning Disorder, IQ<70). Child cancer survivors also needed to have had a cancer diagnosis and be at least one-year post treatment at the time of testing. Healthy control individuals were excluded if they had been diagnosed with a chronic illness.

Recruitment. A trained research assistant recruited potential cancer survivor participant families during the child's routine clinic visit at pediatric cancer follow-up clinics within a children's hospital. If the family indicated interest, they were either immediately scheduled or contacted within a week to set up a time to return for the study. HC families were recruited via online advertisements on Craigslist that included a brief description of the study, compensation, and contact information.

Procedure

Study procedures were conducted with approval from the University of New Mexico's Institutional Review Board. The procedure is outlined in detail in Figure 1. Here we report findings on only one (child cortisol) of several outcome measures, which include: measures of child day-to-day impairment, executive functioning, and intelligence were also collected. Once the family dyad arrived for the study visit, consent/assent was obtained and hair samples collected. Next, the parent (or caregiver) and child were separated for additional study procedures. The child completed a number of measures for intelligence, executive functioning and functional impairment not included in the current analyses. The parent was asked to give a saliva sample, complete an amended version of the Trier Social Stressor Task (TSST; Kirschbaum, Pirke, & Hellhammer, 1993) and provide a second saliva sample after answering demographic questions as well as questions related to socioeconomic status (Barratt, 2012). The parent then completed other measures not included in the current analyses. Upon completion of the study measures, both parent and child received a gift card as compensation.

Measures

Cortisol Measures. Within this study we examined cortisol collected from both hair and saliva. Salivary and hair cortisol measurements are two conceptually different measures of the same hormone. Salivary cortisol measurements assess circulating cortisol levels at the time of sample collection and are used as measures of stress regulation, allowing us to gauge participant stress response related to the TSST. The hair measure allows one to assess the individual's average exposure to perceived stressful situations over approximately the past three months (Gow et al., 2010; Wennig, 2000).

For data analysis, we utilized the parent's hair and both saliva samples, giving us three different measures of parental cortisol, a baseline and a post-stress salivary cortisol measure, as well as a measure of cumulative stress from hair. In addition, we calculated a measure of normalized evoked cortisol, which evaluates the relative rise in cortisol from baseline to post-stress. This normalized evoked cortisol measure was calculated by the following formula: $(CORT_{POST\text{-}STRESS} - CORT_{BASELINE})/ CORT_{BASELINE} X100 = CORT_{NORM\_EVOKED,}$ and assesses the relative change in cortisol from baseline to post-stress (Tang, Reeb-Sutherland, Romeo, & McEwen, 2012). Individual differences in HPA function can manifest as either variation in baseline cortisol, or variation in the magnitude of response to a stressor, so we attempted to assess both measures in the parent.

Hair cortisol. Parent and child cortisol levels were measured in hair samples. This measurement of hair cortisol is a non-invasive technique, useful in assessing long-term cortisol production (Russell, Koren, Rieder, & Van Uum, 2012; Staufenbiel, Penninx, Spijker, Elzinga, & van Rossum, 2012). It is insensitive to fluctuations in

cortisol concentration due to short-term psychosocial stress or diurnal rhythm. Hair cortisol ($CORT_{HAIR}$) analysis captures the average cortisol secreted over a few months (the assessment time period varies based upon hair length, the target is 3 months = 3 cm). As hair dye may change the concentration of cortisol in the hair (Sauvé, Koren, Walsh, Tokmakejian, & Van Uum, 2007), we statistically controlled for whether the parent's hair was dyed.

Approximately 150 strands of hair were taken from the vertex posterior of the head (if the participant's hair was too short for this collection method, small samples were collected from multiple places on the head) from both parent and child. Hair was cut with sanitized scissors as close to the scalp as possible. Cortisol was assayed in the Hominoid Reproductive Ecology Laboratory at the University of New Mexico. The hair samples were first ground to a fine powder using a Retsch ball mill, and then methanol was used to extract cortisol from the samples. We added 2 ml of methanol to the ground hair and incubated the sample overnight at 52°C in a water bath. The sample was centrifuged for 15-20 minutes, and the supernatant was dispensed into a new test tube and centrifuged for a second time for 15-20 minutes. Then, 1.5 ml of the supernatant was pipetted into a clean glass tube and dried under nitrogen gas for 20-30 minutes. Lastly, 200ul of the assay diluent from Salimetrics was added to the dry sample and then this mixture was vortexed to re-suspend the cortisol. Once the cortisol was extracted, cortisol concentration was assessed in duplicate using Salimetrics ELISA cortisol assays (Gow, Thomson, Rieder, Van Uum, & Koren, 2010; Sauvé et al., 2007; Yamada et al., 2007). Two parents and seven children refused or did not have long enough hair for collection, leaving 62 parent and 78 children who consented for us to obtain hair samples. The inter-

assay CVs for cortisol controls (across both hair and saliva assays) were 1.71% and 6.53% for high and low controls, respectively, while the intra-assay CV for hair samples was 7.14%.

Salivary cortisol. Salivary cortisol was collected in conjunction with an amended version of the TSST. The TSST is a well-validated laboratory stressor requiring participants to encounter psychosocial stress induced by a public speaking task. In the classic TSST, participants are asked to give a 5-minute job talk after preparing for 10 minutes, and are then immediately given a mental arithmetic task (Kirschbaum et al., 1993). In the present study, only the speech portion, rather than the speech and arithmetic portions, of the TSST was utilized as previous research has shown that public speaking elicits a greater overall physiological response than mental arithmetic (Al'Absi et al., 1997). During the amended version of the TSST, participants were given 5 minutes to prepare a 5-minute speech about their qualifications and reasons why they should be hired for their dream job. If they could not speak for the whole 5 minutes, they were prompted by questions from the researcher. Two saliva samples were collected in conjunction with the TSST: the first immediately before the start of the TSST ($CORT_{BASELINE}$), and the second 5 minutes after the completion of the stressor ($CORT_{POST\text{-}STRESS}$). The delay between baseline and post-stress sample collection was approximately 10 minutes. This duration was chosen to ensure that the rising phase of the stress response was captured for all participants, as the cortisol response to a stressor peaks 10-30 minutes after the end of a stressor (Del Giudice, Ellis, & Shirtcliff, 2011). Saliva was stored at -25 degrees Celsius until analysis, then vortexed and centrifuged to

separate mucins. Salimetrics cortisol ELISAs were used to process samples in duplicate. The intra-assay CV for duplicate aliquots of saliva samples was 6.30%.

The majority of samples were collected in the afternoon (mean time= 2:48 PM) however; because the participant families determined scheduling, there was a wide range of sample times (10:18 AM-5:50 PM). Since salivary cortisol levels are affected by time of day (Gamble, Berry, Frank, & Young, 2014), we controlled for time of day in our analyses.

Treatment severity. The researchers identified whether each cancer survivor received cranial radiation therapy (CRT), intrathecal methatrexate (IT MTX), systemic chemotherapy (SC), neurosurgery, or corticosteroid treatment via examining medical records. Typically indexes of treatment severity exclude corticosteroid treatment, but the present study examines HPA functioning, which may be affected by large doses of corticosteroids (Gordijn et al., 2012; Kuperman et al., 2001; Mendoza-Cruz, Wargon, Adams, Tran, & Verge, 2013)(for information regarding timing and dosage see Table 1). Scores of 0 or 1 (0 if not given treatment, 1 if given treatment) were assigned for CRT, IT MTX, SC, neurosurgery, and corticosteroid treatment. Treatment severity was derived by summing these categorical treatment scores based on the procedure developed by Vannatta, Gerhardt, Wells, and Noll (2007). Thus each cancer survivor was given a treatment severity score ranging from 0-5.

Statistical Analyses

Data was first checked for normality and log-transformed when necessary. Only cortisol measures required log transformation. Next, descriptive statistics were evaluated

to assess for the presence of systematic differences between groups on demographic variables such as child age, ethnicity, and sex.

As 13 of the 32 participant families in the HC group included siblings, the data could not be handled as truly independent from one another, and thus multilevel modeling was utilized, with parent ID as the level 1 factor and child ID as the level 2 factor. Before testing the hypotheses, it was first determined which variables needed to be considered as covariates by performing backwards multilevel modeling entering all possible covariates that were not directly associated with a predictor variable of interest. These included child age, sex, and ethnicity; socioeconomic status; parent age, sex, and ethnicity; time of saliva collection; and whether parent hair was colored. Due to issues of statistical power, only the main effects of potential control variables were examined as potential variables to be added to the model. Based upon the results of this analysis, child age, child sex and parent ethnicity were included as control variables. The continuous variables used in the models testing the hypotheses, parent cortisol measures and child age, were centered before running the analyses. For all multilevel models, if the model did not converge due to boundary constraints, the random intercept was removed, allowing for convergence (Singer & Willett, 2003). Additionally, if a significant two-way interaction was found, follow-up simple effects analyses were run to determine the differences between groups. For a follow-up analysis of the corticosteroid exposed CS group, correlation of the unresidualized variables was used to identify the strength of relation between parent and child.

To test the prediction that parental cortisol levels correlates with child cortisol levels, several sets of multilevel models were run, one for each measure of parent

cortisol. Three models were run for each parent cortisol measure. In the first model, the predictor variables included child age, sex, parent ethnicity, group (cancer survivor or control), the parent cortisol measure of interest, and the interaction term between group and the parent cortisol measure of interest. The second and third models were run to determine the extent to which treatment severity and corticosteroid exposure might account for the effects related to the cancer experience. For the second model treatment severity and the interaction between treatment severity and parent cortisol were added as additional terms to the model. In the third and final model, instead of treatment severity, child corticosteroid exposure and the interaction between corticosteroid exposure and the parent cortisol measure were added as additional terms to the model.

Secondary Analyses. In order to comprehensively explore possible relationships between predictor and control variables as well as how they may interact to predict child HPA functioning, four backwards multilevel model analyses were performed, one for each parent cortisol measure. In these analyses all interaction terms between the predictor and control variables were entered. As these analyses capitalize on chance, particular attention was paid to simple and interaction effects that significantly predicted child cortisol concentrations within more than one analysis.

RESULTS

Participant Demographic Information

Intelligence, child age, child sex, parent ethnicity and socioeconomic status were examined to identify any systematic demographic differences between the healthy control and cancer survivor groups (Table 2). Children in the cancer survivor group were

significantly older than healthy controls, averaging 12 versus 10 years of age (t(83)=-2.598, p=.011). There were no other significant differences between groups.

Correlations of parent cortisol measures

Correlation was used to determine the relationship of how the four different measures of parent cortisol were related. Parent $CORT_{BASELINE}$ and $CORT_{POST\text{-}STRESS}$ measures were significantly correlated (Rs=.714, p=.000, N=64; Table 3) as were parent $CORT_{BASELINE}$ and $CORT_{NORM\_EVOKED}$ measures (Rs=-.585, p=.000, N=64; Table 3). No other significant correlations were found.

Interaction between parent cortisol and child experience of cancer

No main effect of cancer experience on child hair cortisol was found (F(1,55.73)=.14, p=.710). However, there were main effects of parent $CORT_{BASELINE}$ (F(1, 48.26)= 4.08, p=.049) and $CORT_{POST\text{-}STRESS}$ (F(1,49.01) =8.29, p=.006) on child $CORT_{HAIR}$. Specifically, as either measure of parent cortisol increased, child $CORT_{HAIR}$ also increased. When examining the relationship between cancer survivor group and parental $CORT_{BASELINE}$ there was a significant 2-way interaction (F(1, 46.23)=4.53, p=.039; Figure 2AB; Table 4) such that in the healthy control group parent cortisol was a significant positive predictor of child cortisol (F(1,24.24)=4.25, p=.050), while in the cancer survivor group no correlation was observed between parent $CORT_{BASELINE}$ and child $CORT_{HAIR}$ (F(1,24)=.149, p=.700). We found similar results were observed when examining the 2-way interaction between parental $CORT_{POST\text{-}STRESS}$ and child $CORT_{HAIR}$ (F(1,47.12)=8.99, p=.004; Figure 2AB; Table 5); child $CORT_{HAIR}$ was positively predicted by parent $CORT_{POST\text{-}STRESS}$ in the HC group (F(1,25.93)=9.12, p=.006), but not in the CS group (F(1,24)=.154, p=.699). No significant effects were found between either

parent $CORT_{NORM\_EVOKED}$ (interaction: F(1,56.81)=.026, p=.873; main effect: F(1,59.02)=.001, p=.970) or parent $CORT_{HAIR}$ (interaction F(1,68)=1.69, p=.198, main effect F(1,68)=1.13, p=.292) and child $CORT_{HAIR}$.

Interaction of Parent Cortisol Levels and Child Corticosteroid Exposure on Child Cortisol Levels

To determine what aspect of the cancer experience may be responsible for the the change in relationship between parent and child cortisol, treatment severity and child corticosteroid exposure were examined. No main effect of treatment severity was found (F(1,49.11)=.938, p=.338). Additionally, no significant interaction effects were observed between treatment severity and parent cortisol levels on child $CORT_{HAIR}$ ($CORT_{BASELINE}$ F(1,61.98)=.242, p=.624; $CORT_{POST\_STRESS}$ F(1, 62.35)=.136, p=.714; $CORT_{NORM\_EVOKED}$ F(1,56.81)=.026, p=.873; $CORT_{HAIR}$ F(1, 54.16)=.881, p=.352).

No significant main effect of corticosteroid exposure was found (F(1,55.81)=.078, p=.782). However there was a significant 2-way interaction between both parent $CORT_{BASELINE}$ and $CORT_{POST\_STRESS}$ levels and child corticosteroid exposure on child $CORT_{HAIR,}$ ($CORT_{BASELIINE}$: $F(1,61.02)=4.76$,p=.033, Table 6; $CORT_{POST\_STRESS}$: $F(1,68)=5.79$, p=.019, Table 7) was observed. Specifically, the cortisol levels of cancer survivors exposed to corticosteroids were negatively related to their parents' cortisol **(**$CORT_{BASELINE}$: F(1,5)=1.873, p=.229, Rs=-.592, n=11, p=.055; $CORT_{POST\_STRESS}$: F(1,5)=2.97, p=.145, Rs=-.633, n=11, p=.036; Figure 2CD), while the cortisol levels of cancer survivors not given corticosteroids, similar to healthy controls, were positively correlated to their parents' (Figure 2CD**;** $CORT_{BASELINE}$: F(1,40.46) =6.114, p=.018; $CORT_{POST\text{-}STRESS}$: F(1,41.66)=11.81, p=.001). We found no statistical difference

correlation between parent and child cortisol in the healthy control group versus the cancer survivor group not exposed to corticosteroids: parent $CORT_{BASELINE}$ ($F(1,39.54)=1.23$, $p=.274$) and $CORT_{POST\text{-}STRESS}$ ($F(1,40.546)=3.27$, $p=.078$) measures.

Interaction of Cancer Experience, Parental Ethnicity & Child Sex on Child Cortisol Levels

Through exploratory analyses, a 3-way interaction among cancer experience, parent ethnicity, and child sex on child $CORT_{HAIR}$ levels ($F(6,48.14)=2.998$, $p=.014$)). Specifically, females in the cancer survivor group had higher levels of cortisol compared to females in the healthy control group regardless of parent ethnicity, while male cancer survivors had cortisol levels lower than healthy controls if the parent was Hispanic or Non-Hispanic or White. Additionally, a significant 2-way interaction was found between child sex and parent ethnicity ($F(5,38.55)=5.31$, $p=.001$), such that female cortisol levels were generally the same regardless of parent ethnicity, while male cortisol levels were similar when parents were White or Hispanic but higher when parents were another ethnicity.

Discussion

The cancer experience was not found to affect the average cortisol levels of children but did modify the association between parent and child cortisol levels. Specifically, while parent and child cortisol levels were positively associated among healthy control families, this effect was not observed in cancer survivor families. Follow-up analyses revealed that the difference in this relationship was unrelated to the cancer experience itself, but confined to the subgroup of children who were treated with high levels of corticosteroids.

The finding that the experience of cancer alone did not significantly change child HPA function was surprising because other types of chronic stress, including maltreatment (Fisher et al., 2011) and chronic diseases such as HIV and wasting disorders (Zeitler et al., 1999), lead to HPA axis dysfunction. Thus, while pediatric cancer may affect child psychological outcomes (Ellenberg et al., 2009; Pelcovitz et al., 1998; Zeltzer et al., 2008), in the present study there is no evidence that the cancer experience alone affects child cortisol or the relationship between parent and child cortisol. More surprising, we did not find a main effect of high corticosteroid exposure. Other research examining the effects of high doses of corticosteroids has found that this exposure altered child HPA axis function (Gibbison, Angelini, & Lightman, 2013; Moisiadis & Matthews, 2014). While we did not find a difference in cortisol levels between pediatric cancer survivors and healthy controls, or related to cancer-related corticosteroid exposure, there may still be differences in these groups' HPA regulation (Gordijn et al., 2012) that were not reflected in long-term average cortisol levels expressed in children's hair. It is possible that these individuals have a bunted cortisol response to stress, which may be undetectable within hair. While the main effects of cancer experience and corticosteroid exposure did not show any changes in child cortisol within the current study we also examined HPA function by testing whether a consistently observed correlation was present within the sample. Specifically we examined if the consistently observed relationship of parent cortisol positively predicting child cortisol was still found after children experienced the chronic stress of cancer and the HPA axis perturbation of corticosteroid exposure. Indeed, the discordance between

parent and child cortisol in the corticosteroid treatment group suggests altered HPA axis regulation.

Parent and child cortisol levels have been shown to positively relate to one another from infancy (Stenius et al., 2008) until at least adolescence (Papp, Pendry, & Adam, 2009). This long lasting relationship between parent and child cortisol levels suggests that parental stress levels help to shape the maternal environment to which the child is exposed (Tang, Reeb-Sutherland, Romeo, & McEwen, 2014). Moreover, the maternal environment, along with other non-maternal factors, influence child HPA axis function and cortisol levels. Our results support this hypothesis, as for both healthy control children and children who experienced cancer but were not given steroids, we found a positive relationship between parent and child cortisol.

There are a number of possibly interrelated mechanisms as to how parent stress may affect child HPA axis function. These include: (a) parental stress leading to changes in parental behavior and then to child stress (Marceau, et al., 2013); (b) parental stress leading to epigenetic changes in the child that affect aspects of glucocorticoid function (Yehuda, et al., 2014); and (c) child HPA function being influenced directly by exposure to maternal stress hormones *in utero* (Reynolds, 2013), and during breastfeeding (Angelucci, Pataccchioli, Chierichetti, and Laureti, 1983), leading to similar responsiveness. Alternatively, child behavior may affect parental stress (Seltzer, et al., 2010), or parents and children may experience the same stressors due to the shared environment (Hunter, Minnis, & Wilson, 2011). Finally, shared genes (Kirschbaum, Wust, Faig, & Hellhammer, 1992) may affect parent and child HPA axis function. The current study was not designed to discriminate these alternative hypotheses. However,

prior research indicates that when children experience stress, the relationship between parent and child cortisol levels breaks down (Clearfield et al., 2014; Hibel et al., 2014), a finding that we re-examined in our study of pediatric cancer survivors.

We found that children exposed to high doses of corticosteroids had an inverse relationship between parent and child cortisol, such that if parents had low salivary baseline or post-stress cortisol levels, their children were more likely to have high hair cortisol. Without this exposure to a high dosage of corticosteroids, pediatric cancer survivors had cortisol levels positively related to their parents, statistically indistinguishable from the relationship observed among healthy control children. These findings imply that the cancer experience itself did little to change the long-term parent child cortisol relationship, and that high doses of exogenous corticosteroids are responsible for the changes in this relationship. The negative association found in the corticosteroid exposure group could be explained by interference in HPA axis regulation via negative feedback, a process that may be especially sensitive to perturbation in developing children. Exposure to high levels of endogenous or exogenous corticosteroids can alter HPA negative feedback loops by down regulation of glucocorticoid receptors in the hypothalamus (Barden, 2004) or alternatively by increased sensitivity or upregulation of these glucocorticoid receptors (Yehuda, 2003). These changes in negative feedback may result in increased susceptibility to distress and PTSD (Lesko, 1990; Pelocovitz et al., 1998; Zeltzer et al., 2008).

Our results imply that high dose corticosteroid exposure may have long-lasting impacts on child HPA axis function (Gibbison, Angelini, & Lightman, 2013; Moisiadis & Matthews, 2014). It is unknown whether this attenuation between parent and child HPA

function is damaging or beneficial to child functional outcomes. Yet, the limited functional outcome data for this study does indicate that the attenuation does not adversely impact child IQ. Prospective studies, may be able to answer this question by specifically assessing functional outcomes in children who show an attenuated relationship between their parents and their own cortisol levels. However since we are unsure what the long lasting impact of these steroid exposure might be, it is important to use these corticosteroid treatments with caution.

Limitations

This current presentation of the cancer experience and its effect upon child developmental outcomes is narrowly focused, as there are a number of other contextual factors, including treatment complications and child history before cancer diagnosis, that are not included but which may affect child HPA functioning. The results of this present study will need to be considered with these contextual factors in mind. Two of the limitations of this study are: 1) that there was a highly diverse group of participants (i.e., a broad range of cancer diagnoses), thus the experience of cancer was not uniform (e.g. treatment that varied in length and intensity), and 2) the study is limited by its cross sectional nature, thus shedding little light on causal factors. An additional limitation related to the sample size of this study is that siblings were included for more healthy controls than cancer survivor families. This may introduce discrepancies between the groups along with possible unequal variance. Additionally, there were unequal group sizes when examining factors not selected for during recruitment such as parental ethnicity and corticosteroid exposure. Unequal group sizes may decrease the robustness of the results. Conceptually there is ambiguity in interpreting the meaning of hair cortisol

levels, as this integrated measure does not allow one to distinguish individuals who have high baseline cortisol from those who have low baseline cortisol but experience frequent, strong stress responses. It was surprising that hair cortisol levels were not correlated with other parental measures of cortisol, as it has been previously shown that circulating and hair cortisol levels are modestly correlated (Xie et al., 2011). One explanation for this discrepancy may be that some parents used hair products that could have interfered with the assay. Additionally, most of the parents were mothers and we did not account for whether these women were taking oral contraceptives, which may affect HPA functioning (Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999; Roche, King, Cohoon, & Lovallo, 2013). Furthermore, unlike rodent studies (Tang et al., 2012), normalized evoked cortisol was not found to predict child cortisol; this may be due to variability in the baseline sample due to stress related to coming to a research laboratory. Some participants may have found coming to the University and being part of the study a stressor and therefore had high cortisol levels at the beginning of the study. Also, differences between groups' cortisol may have been present but undetectable. This could be due to variations in collection protocol due to multiple research assistants collecting data as well as the modest sample size for the corticosteroid exposed group. Lastly, when generalizing these results to other populations, we use caution, as this sample may have a lower SES than the typical American sample as this sample was taken from one of the lowest income states in the country and a minority-majority state.

Conclusions

The relationship between parent and child HPA function is significantly changed when children are given high doses of corticosteroids during cancer treatment. However,

children who were exposed to corticosteroids or who experienced the chronic stress of cancer had similar cortisol levels compared to healthy controls. Furthermore, the relationship between parent and child HPA function did not change as a result of the cancer treatment, but did change as a result of corticosteroid exposure. If the child was exposed to corticosteroids, this direct perturbation to the child's HPA axis attenuated the parent child cortisol relationship. This research may provide evidence that corticosteroids given to children as part of cancer treatment perturb the HPA axis, which is already vulnerable as the child experiences the multitude of stressors related to the cancer experience. These findings are significant because most children who are diagnosed with cancer survive (Institute of Medicine, 2003) but experience devastating late effects. At least some of these effects, particularly those related to psychological well-being, are known to interact with HPA function. When the effects of pediatric cancer treatment severity are examined, child corticosteroid exposure is frequently. Thus, some of the effects currently attributed to cancer may actually be related to corticosteroid exposure. More may aid in the development of more effective interventions for these children.

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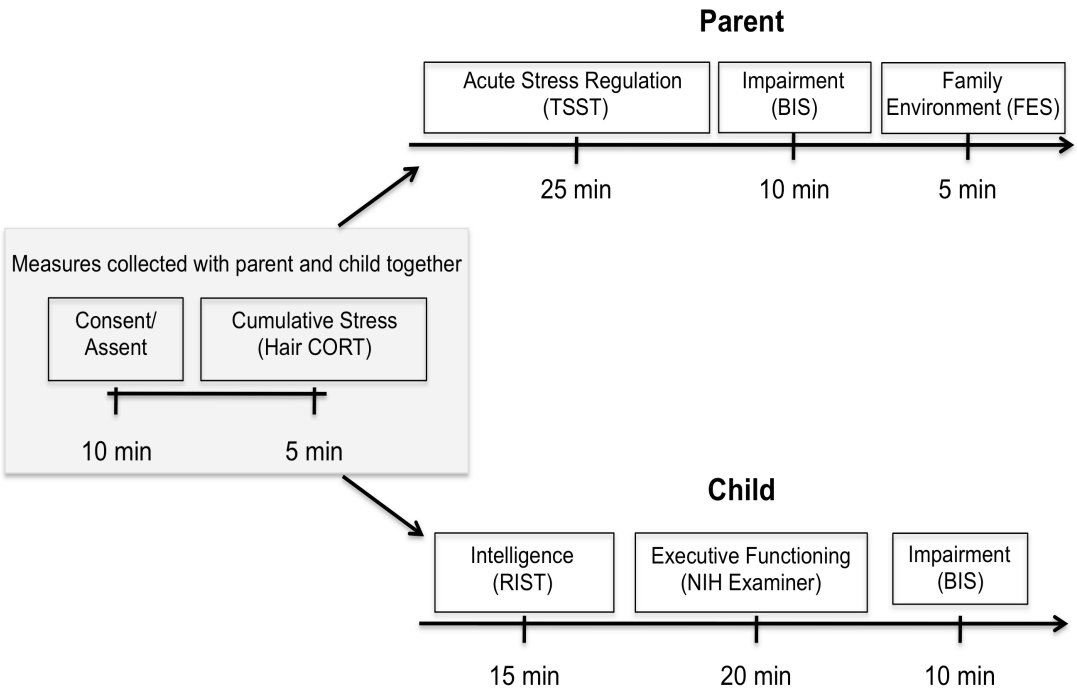
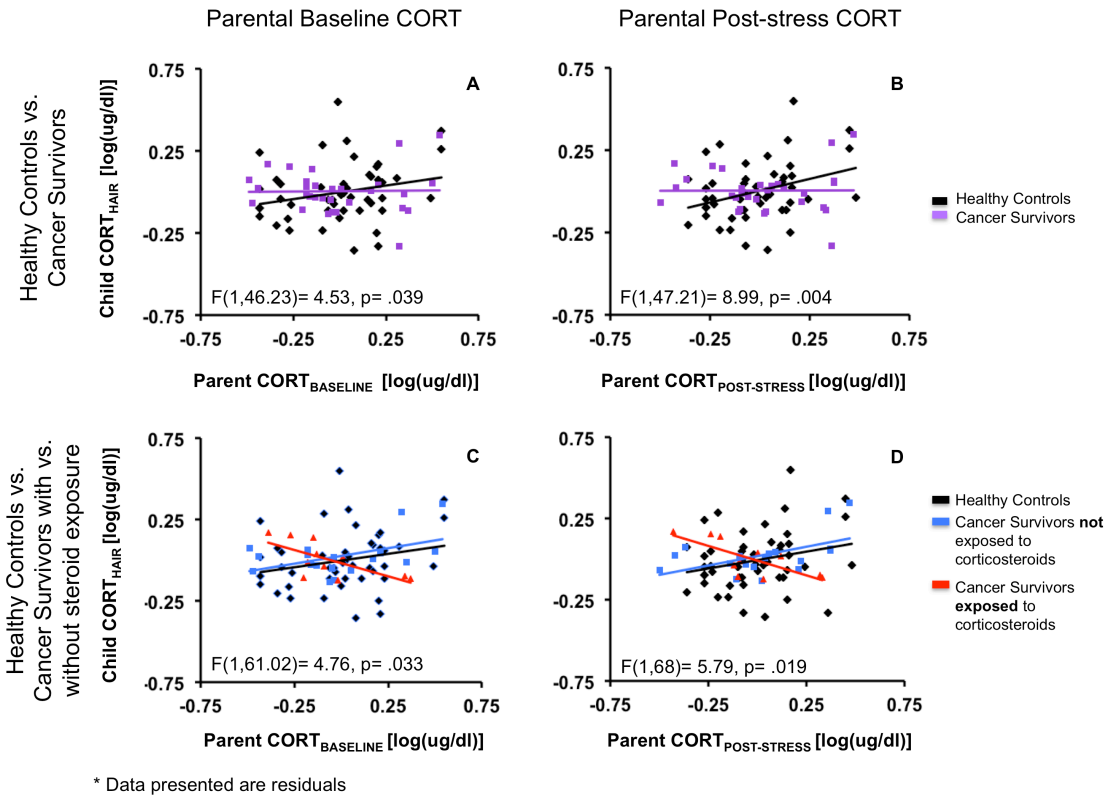
Figure 1



Experimental Timeline. Upon arrival to the laboratory, parent and child are first consented and then hair samples are taken from both individuals. Next, parent and child are separated. Parent is administered an amended version of the Trier Social Stressor Task (TSST) during which time two saliva samples are collected. After the TSST, parents are asked to respond to the Brief Impairment scale (BIS) rating their child's day-to-day impairment. Finally they are asked to fill out four subscales of the Family Environment Scale. Children are first administered the Reynolds Intellectual Screening Task (RIST) and are then their executive functioning is evaluated via the NIH Examiner. Lastly they are asked to respond to the child version of the Brief Impairment scale rating their own day-to-day impairment.

Figure 2



Interaction between parent saliva and child hair cortisol levels by child experience of cancer and interaction between child corticosteroid use and parent salivary cortisol on child hair cortisol. All data displayed above are residuals. For both parent baseline (A) and post-stress cortisol (B) for healthy controls (black line; n=49) there is a positive association between parent and child cortisol. However, for cancer survivors (purple line; n=29), this relationship is less positive. When examining how child corticosteroid use due to cancer treatment predicts the relationship between parent and child cortisol (C and D), those children given corticosteroids as part of cancer treatment (red line; n=11) have a negative association between parent baseline and post-stress and child hair cortisol levels, children who are cancer survivors unexposed to corticosteroids (blue line; n=18) have a relationship with parent cortisol similar to healthy controls (black line; n=49).

Table 1: Information regarding corticosteroid treatment for children given steroids as part of cancer treatment.

Participant ID	Diagnosis	Age at diagnosis/ testing	Protocol #	Steroid given	Total cumulative dosage of steroids (g/m^2)	Steps of treatment and dosage of steroids within each step
2	Precursor B cell acute lymphoblastic leukemia (ALL)	7/15	AALL0331	Dexamethasone	1.08	Induction (6mg/m^2/day X 28 days), Consolidation (none), Standard Interim maintenance (6 mg/m^2/ day X 5 days every 4 weeks for 2 cycles), Standard Delay intensification (10mg/m^2/day X 21 days), Maintenance (6mg/m^2/day X 5 days every 4 weeks for 6 cycles)
3	Precursor B cell acute lymphoblastic leukemia (ALL)	2/8	AALL0331	Dexamethasone	1.04	Induction (6mg/m^2/day X 28 days), Consolidation (none), Standard Interim maintenance (6 mg/m^2/day X 5 days every 4 weeks for 2 cycles), Standard Delay intensification (10mg/m^2/day X 21 days), Maintenance (6mg/m^2/day X 5 days every 4 weeks for 22 cycles)
4	LCH- Langerhans Cell Histiocytosis	1/7	LCH3	Prednisone	3	Induction (40mg/m^2/day X 28 days), Continuation (40mg/m^2/day X 5 days, every 3 weeks for 6 months)
5	Precursor B cell acute lymphoblastic leukemia (ALL)	2/9	AALL0331	Dexamethasone	1	Induction (6mg/m^2/day X 28 days), Consolidation (none), Standard Interim maintenance (6 mg/m^2/ day X 5 days every 4 weeks for 2 cycles), Standard Delay intensification (10mg/m^2/day X 21 days), Maintenance (6mg/m^2/day X 5 days every 4 weeks for 22 cycles)
15	Precursor B cell acute lymphoblastic leukemia (ALL)	3/7	AALL0331	Dexamethasone	.942	Induction (6mg/m^2/day X 28 days), Consolidation (none), Standard Interim maintenance (none), Standard Delay intensification (10mg/m^2/day X 21 days), Maintenance (6mg/m^2/day X 5 days every 4 weeks for 21 cycles)
40	Burkitt's, Non-Hodgkins lymphoma,	3/8	BCM	Prednisone	1.21	Reduction (60mg/m^2/day X 7days), Induction 1 (60mg/m^2/day X 5 days, taper off 3 day), Induction 2 (60mg/m^2/day X 5 days, taper off 3 days), Consolidation 1 (none), Consolidation 2 (none)
52	LCH- Langerhans histiocytosis	0/13	BCM	Dexamethasone	4.7	Induction (40mg/m^2/day X 28 days, taper over 2 weeks), Continuation (40mg/m^2/day X 5 days, every 3 weeks for 6 cycles), off treatment till 12/2003, Induction (40mg/m^2/day X28 days, taper over 2 weeks), Continuation (40mg/m^2/day X 5 days, every 3 weeks for 15 cycles)
54	Acute Myelogenous Leukemia	2/13	CCG 2891	Dexamethasone	.100	6mg/m^2/day X day 0-3 and day 10-13 for 2 courses
62	low risk ALL	3/10	AALL0331	Dexamethasone	1.32	Induction (6mg/m^2/day X 28 days), Consolidation (none), Standard Interim maintenance (none), Standard Delay intensification (10mg/m^2/day X 7 days, 2 cycles), Maintenance (6mg/m^2/day X 5 days every 4 weeks for 34 cycles)
68	Precursor B cell acute lymphoblastic leukemia (ALL)	12/18	AALL0232	Prednisone, switched to Dexamethasone for consolidation block 4	Dex: .0309 Prednisone: 1.6	Induction (60mg/m^2/day X 28 days), Consolidation block 1-3 (no steroids), block 4 (6mg/m^2/day X 5 days)
72	Precursor B acute lymphoblastic leukemia, standard risk high	1/9	AALL0331	Dexamethasone	.900	Induction (6mg/m^2/day X 28 days), Consolidation (none), Average Interim Maintenance 1 (none), Average Delay intensification 1 (10mg/m^2/day X 21 days), Average Interim Maintenance 2 (none), Average Delay Intensification 2 (10mg/m^2/day for 13 days), Maintenance (6mg/m^2/day X 5 days every 4 weeks for 16 cycles)
75	Precursor B acute lymphoblastic leukemia, standard risk high	2/10	AALL0331	Dexamethasone	1.44	Induction (6mg/m^2/day X 28 days), Consolidation (none), Average Interim Maintenance 1 (none), Average Delay intensification 1 (10mg/m^2/day X 21 days), Average Interim Maintenance 2 (none), Average Delay Intensification 2 (10mg/m^2/day for 21 days), Maintenance (6mg/m^2/day X 5 days every 4 weeks for 27 cycles)

Table 2: Child Demographic Information

	Healthy Control Children	Cancer Survivor Children
N	53	32
Age: M (SD) Range	10 (3) yrs. 5-17 yrs.	12 (4) yrs. 5-18 yrs.
Sex	28 male 25 female	17 male 15 female
Parent Ethnicity	12 White 32 Hispanic 2 Native American 2 African American 5 Other	14 White 14 Hispanic 3 Native American 1 Asian American
Socioeconomic Status: M (SD)	37.2 (10.6)	35.2 (10.9)
Intelligence: M (SD)	98.7 (13.6)	100.6 (13.2)

Table 3. Parent cortisol measures correlations

		$CORT_{BASELINE}$	$CORT_{POST\text{-}STRESS}$	$CORT_{NORM\_EVOKED}$	$CORT_{HAIR}$
$CORT_{BASELINE}$	Rs		.715***	-.585***	.056
	Sig		.000	.000	.667
	N		64	64	62
$CORT_{POST\text{-}STRESS}$	RS			-.014	.062
	Sig			.912	.633
	N			64	62
$CORT_{NORM\_EVOKED}$	RS				-.109
	Sig				.400
	N				62
$CORT_{HAIR}$	RS				
	Sig				
	N				

Table 4

Type III Tests of Fixed Effects for Parent $CORT_{BASELINE}$ X Cancer Experience

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	53.052	666.156	.000
group	1	55.725	.140	.710
Child sex	1	53.788	14.458	.000*
child age	1	68.566	2.867	.095
Parent ethnicity	2	54.411	2.193	.121
Parent $CORT_{BASELINE}$	**1**	**48.256**	**4.078**	**.049***
group * Parent $CORT_{BASELINE}$	**1**	**46.231**	**4.530**	**.039***

Estimates of Fixed Effects[a]

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	1.476403	.126668	58.581	11.656	.000	1.222904	1.729903
[group=control]	-.032171	.086047	55.725	-.374	.710	-.204564	.140221
[group=cancer survivor]	0[b]	0	.	.	.	.	.
[child sex=female]	-.256667	.067502	53.788	-3.802	.000	-.392012	-.121322
[child sex=male]	0[b]	0	.	.	.	.	.
child age	.016879	.009969	68.566	1.693	.095	-.003011	.036769
[parent ethnicity =.Hispanic]	-.154961	.120563	52.334	-1.285	.204	-.396852	.086929
[parent ethnicity =White]	-.272561	.131520	53.469	-2.072	.043	-.536302	-.008820
[parent ethnicity =Other]	0[b]	0	.	.	.	.	.
Parent $CORT_{BASELINE}$	**-.002143**	**.060304**	**59.869**	**-.036**	**.972**	**-.122774**	**.118488**
[group=control] * Parent $CORT_{BASELINE}$	**.184842**	**.086849**	**46.231**	**2.128**	**.039**	**.010048**	**.359636**
[group=cancer survivor] * **Parent $CORT_{BASELINE}$**	0[b]	0	.	.	.	.	.

a. Dependent Variable: child $CORT_{HAIR}$.

b. This parameter is set to zero because it is redundant.

Table 5

Type III Tests of Fixed Effects for Parent $CORT_{POST\text{-}STRESS}$ X Cancer Experience

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	51.033	760.315	.000
Child sex	1	56.678	16.847	.000*
Child age	1	68.839	5.283	.025*
Parent ethnicity	2	51.677	2.419	.099
group	1	55.093	.006	.939
Parent $CORT_{POST\_STRESS}$	**1**	**49.007**	**8.290**	**.006***
group * Parent $CORT_{POST\_STRESS}$	**1**	**47.209**	**8.994**	**.004***

Estimates of Fixed Effects[a]

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	1.468463	.119922	57.213	12.245	.000	1.228344	1.708583
[child sex=female]	-.272101	.066293	56.678	-4.105	.000	-.404867	-.139335
[child sex=male]	0[b]	0	.	.	.	.	.
child age	.022522	.009799	68.839	2.298	.025	.002973	.042072
[parent ethnicity =.Hispanic]	-.141227	.113351	49.665	-1.246	.219	-.368936	.086482
[parent ethnicity =White]	-.266426	.123815	50.936	-2.152	.036	-.515003	-.017849
[parent ethnicity =Other]	0[b]	0	.	.	.	.	.
[group=control]	-.006286	.081191	55.093	-.077	.939	-.168991	.156419
[group=cancer survivor]	0[b]	0	.	.	.	.	.
Parent $CORT_{POST\_STRESS}$	**-.003605**	**.052480**	**59.710**	**-.069**	**.945**	**-.108592**	**.101381**
[group=control] * Parent $CORT_{POST\_STRESS}$	**.239787**	**.079957**	**47.209**	**2.999**	**.004**	**.078953**	**.400621**
[group=cancer survivor] * **Parent $CORT_{POST\_STRESS}$**	0[b]	0	.	.	.	.	.

a. Dependent Variable: child $CORT_{HAIR}$.

b. This parameter is set to zero because it is redundant.

Table 6

Type III Tests of Fixed Effects for Parent $CORT_{BASELINE}$ X Corticosteroid Exposure

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	56.140	378.193	.000
Child sex	1	52.372	17.739	.000*
Child age	1	66.534	2.816	.098
Parent ethnicity	2	53.418	2.248	.116
group	1	56.199	.101	.752
Steroid group	1	60.548	.029	.865
Parent $CORT_{BASELINE}$	1	57.763	.119	.732
group * **Parent $CORT_{BASELINE}$**	1	47.190	1.440	.236
Steroid group*** Parent $CORT_{BASELINE}$**	**1**	**61.021**	**4.764**	**.033***

Estimates of Fixed Effects[a]

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	1.468656	.151823	58.312	9.673	.000	1.164784	1.772528
[child sex=female]	-.284906	.067645	52.372	-4.212	.000	-.420623	-.149188
[child sex=male]	0[b]	0	.	.	.	.	.
child age	.016831	.010029	66.534	1.678	.098	-.003190	.036852
[parent ethnicity =.Hispanic]	-.158586	.118216	51.409	1.342	.186	-.395868	.078696
[parent ethnicity =White]	-.273843	.130011	52.639	-2.106	.040	-.534654	-.013032
[parent ethnicity =Other]	0[b]	0	.	.	.	.	.
[group=control=0]	-.030949	.097503	56.199	-.317	.752	-.226255	.164357
[group=cancer survivor=1]	0[b]	0	.	.	.	.	.
[Steroid group=no exposure=0]	.021668	.127107	60.548	.170	.865	-.232536	.275871
[Steroid group=exposure=1]	0[b]	0	.	.	.	.	.
Parent $CORT_{BASELINE}$	-.227479	.119126	62.031	-1.910	.061	-.465607	.010649
[group=0] * **Parent $CORT_{BASELINE}$**	.110131	.091769	47.190	1.200	.236	-.074465	.294726
[group=1] * **Parent $CORT_{BASELINE}$**	0[b]	0	.	.	.	.	.
[ster_2grps=0] * Parent $CORT_{BASELINE}$	**.297806**	**.136436**	**61.021**	**2.183**	**.033**	**.024987**	**.570625**
[ster_2grps=1] * **Parent $CORT_{BASELINE}$**	0[b]	0	.	.	.	.	.

a. Dependent Variable: Child $CORT_{HAIR}$. b. This parameter is set to zero because it is redundant

Table 7

Type III Tests of Fixed Effects for Parent $CORT_{POST\text{-}STRESS}$ X Corticosteroid Exposure

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	68	495.297	.000
Child sex	1	68	17.230	.000*
child age	1	68	7.295	.009*
parent_ethnic_3groups	2	68	3.650	.031*
group	1	68	.195	.660
Steroid group	1	68	.092	.762
Parent $CORT_{POST\_STRESS}$	1	68	.102	.750
group * **Parent $CORT_{POST\_STRESS}$**	1	68	4.553	.036*
Steroid group * Parent $CORT_{POST\_STRESS}$	**1**	**68**	**5.787**	**.019***

Estimates of Fixed Effects[a]

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	1.482125	.142390	57.869	10.409	.000	1.197088	1.767163
[child sex=female]	-.301845	.065751	56.000	-4.591	.000	-.433559	-.170130
[child sex=male]	0[b]	0	.	.	.	.	.
child age	.022993	.009806	66.860	2.345	.022	.003419	.042567
[parent ethnicity =.Hispanic]	-.144775	.110045	49.548	-1.316	.194	-.365856	.076306
[parent ethnicity =White]	-.265049	.121274	50.776	-2.186	.033	-.508543	-.021555
[parent ethnicity =Other]	0[b]	0	.	.	.	.	.
[group=control=0]	.014255	.092057	56.760	.155	.877	-.170104	.198613
[group=cancer survivor=1]	0[b]	0	.	.	.	.	.
[steroid group= no exposure=0]	-.018636	.119805	61.764	-.156	.877	-.258142	.220869
[steroid group=exposure=1]	0[b]	0	.	.	.	.	.
Parent $CORT_{POST\_STRESS}$	**-.200416**	**.097029**	**68**	**-2.066**	**.043**	**-.394034**	**-.006799**
[group=0] * **Parent $CORT_{POST\_STRESS}$**	.164931	.077292	68	2.134	.036	.010698	.319164
[group=1] * **Parent $CORT_{POST\_STRESS}$**	0[b]	0	.	.	.	.	.
[ster_2grps=0] * **Parent $CORT_{POST\_STRESS}$**	.271489	.112859	68	2.406	.019	.046282	.496696
[ster_2grps=1] * **Parent $CORT_{POST\_STRESS}$**	0[b]	0	.	.	.	.	.

a. Dependent Variable: Child $CORT_{HAIR,}$ b. This parameter is set to zero because it is redundant.