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Early trauma moderates the link between familial risk for depression and post-stress DHEA/cortisol ratios in adolescents

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ABSTRACT

Background: One proposed mechanism for familial transmission of depression risk is impaired ability to regulate stress. While much of this work has focused on the stress hormone cortisol, there is evidence that the neuroprotective hormone dehydroepiandrosterone (DHEA) may play a critical role in stress regulation and that the ratios of DHEA to cortisol may provide meaningful information about individual differences in stress processing. In this study, we examined DHEA and DHEA/cortisol ratios among teens at low and high risk for depression.

Methods: Participants included 101 youth (12-16-year-old; 50 female) including 53 with a family history of depression (High Risk for depression). Adolescents and their parents completed diagnostic interviews, the Childhood Trauma Questionnaire and the Childhood Depression Inventory. Saliva samples were collected at multiple time points before and after adolescents underwent the Trier Social Stress Test. Cortisol and DHEA ratios were examined at baseline and 35 min post-stress initiation.

Results: High risk (HR) and low risk (LR) participants did not differ on DHEA/cortisol ratios. However, childhood trauma moderated the relationship between risk group and DHEA/cortisol ratios, where at high levels of trauma, HR participants had significantly higher ratios than LR participants.

Conclusion: Our findings suggest that higher DHEA/cortisol ratios may not be indicative of greater protection against risk for depression as previously conceptualized. In the context of early trauma, higher DHEA/cortisol ratios may reflect a blunting of the HPA-axis that is not observed when examining cortisol levels alone. This study has implications for our conceptualization of DHEA/cortisol ratios as an indicator of risk for psychopathology.

1. Introduction

Adolescents with a family history of depression are more likely to experience stressful life events and develop depression than their low-risk peers (Goodman et al., 2011; Weissman et al., 2016). Thus, atypical stress regulation in high-risk teens may be a potential mechanism for the intergenerational transmission of risk. Stress regulation research has focused primarily on hypothalamic-pituitary-adrenal-axis (HPA axis) functioning and its end product, cortisol, given their established role in stress processing (Tsigos and Chrousos, 2002). However, there is evidence that the hormone dehydroepiandrosterone (DHEA) plays a critical role in stress regulation (Ruttle et al., 2015) and that the ratio of DHEA to cortisol (DHEA/cortisol ratios) provides unique information about stress regulation beyond what can be learned from either hormone alone (Kamin and Kertes, 2016). Yet, little is known about DHEA/cortisol ratio profiles in children at familial risk for depression and whether atypical ratio profiles reflect a potential mechanism of risk.

Researchers have extensively studied atypical HPA axis functioning in youth depression. For example, cortisol hypersecretion in youth predicts depression diagnosis (Lopez-Duran et al., 2015), onset (Adam et al., 2010; Vrshek-Schallhorn et al., 2013), and course (Rao et al., 2010). Not surprising, dysregulation of HPA axis functioning has been proposed as a likely mechanism that explains intergenerational transmission of depression risk. For example, exposure to maternal postnatal depression predicts greater cortisol levels in adolescent offspring (Halligan et al., 2004). Likewise, hypersecretion of the cortisol awakening response (Mannie et al., 2007) as well as a failure to suppress cortisol secretion after a dexamethasone test (Holsboer et al., 1995) have been found in healthy young people who have a family history of depression.

However, links between HPA-axis and youth depression are equivocal and likely influenced by age (Hankin et al., 2010), gender (Lopez-Duran et al., 2015), history of trauma (Harkness et al., 2011; Wessa et al., 2006), and comorbidities (Oquendo et al., 2003). Another

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potential contributor to such variability is the hormone dehydroepiandrosterone (DHEA), an androgen that is also released from the adrenal gland in response to stress (Ogino et al., 2016). DHEA is thought to be neuroprotective in that it mitigates the effects of excessive cortisol (Kalimi et al., 1994) and facilitates HPA axis regulation via direct action on corticoid receptors (Maninger et al., 2008). Indirectly, it may protect by modulating emotion regulation neurocircuitry (Sripada et al., 2013). Clinically, DHEA supplementation has been shown to decrease depression symptoms in a number of trials in adults (Rabkin et al., 2006; Schmidt et al., 2005; Wolkowitz et al., 1997). Thus, higher levels of DHEA may increase the HPA-axis's capacity for regulation and provide protection against potential negative effects of stress, thus reducing the risk for stress-related disorders.

Nonetheless, the literature on DHEA and mental health is highly contradictory. For example, some studies have found increased DHEA levels in depressed groups (Heuser et al., 1998) while others found lower levels (Goodyer et al., 1996). Likewise, high levels of DHEA have been found in adults with post-traumatic stress disorder (PTSD; Rasmusson et al., 2004; Spivak et al., 2000), while others have found lower levels of DHEA in PTSD patients (Kanter et al., 2001), or report no group differences (Bremner et al., 2007). This variability is not surprising given DHEA is a stress-induced hormone and thus "high" levels may be indicative of greater stress exposure. Thus, whether "high" levels of DHEA reflect a protective or risk status depends on the context in which DHEA levels are measured and their relative availability to compensate for the level of stress exposure experienced by an individual.

Given the coordinated release of DHEA and cortisol in response to stress and their partially opposite effects, the ratio of DHEA to cortisol may reflect the relative availability of DHEA to protect against the potentially harmful effects of excessive cortisol. Thus, lower DHEA/cortisol ratios would indicate a less adaptive (risk) profile. In fact, lower DHEA/cortisol ratios have been found to predict persistent depression in adolescents (Goodyer et al., 2003; Herbert et al., 1996), current, but not remitted, depression in adults (Michael 2000) as well as worse prognosis for depression in adults (Markopoulou et al., 2009). Lower DHEA/cortisol ratios have also been found in adolescents at high risk for depression on the basis of early symptomatology (Goodyer et al., 2003). However, it is unknown whether similar low ratios are found in youth at familial risk as it would be expected if low availability of DHEA is a mechanism of risk in this population.

Nonetheless, trauma exposure can have a significant effect on HPA axis functioning in ways that may alter the functional meaning of DHEA/cortisol ratios. Considering the impact of early trauma is especially important in the study of teens at high risk for depression given that these teens are exposed to greater levels of stress than their low-risk peers (Bouma et al., 2008). Despite evidence of cortisol hypersecretion being associated with depression, the opposite is true for trauma-related psychopathology such that lower cortisol levels are often found in the context of childhood trauma exposure in adults (Carpenter et al., 2007) and in PTSD in adults (Wessa et al., 2006). Thus, the impact of trauma may artificially create high DHEA/cortisol ratios that are actually reflecting the blunting of the cortisol response as opposed to high availability of DHEA (see Van Voorhees et al., 2014).

The current study investigated differences in DHEA/cortisol ratios between youth at high and low risk for depression and whether these differences were moderated by a history of trauma. We hypothesized that these high-risk adolescents would show lower DHEA/cortisol ratios than their low-risk peers, which would be indicative of a less protective endocrine profile. However, we also hypothesized that the protective profiles associated with low risk status would be stronger in teens without a history of trauma. This study contributes to our understanding of mechanisms of risk and provides more nuanced information about the impact of trauma history in the relationship between neuroendocrine functioning and familial risk for depression.

2. Methods

2.1. Participants

Participants included 101 adolescents, aged 12–16 years old (Mean age = 13.96 years), who were recruited from southeast Michigan through flyers placed in public spaces and advertisement on a university health website. About half of the participants had a parent with a history of depression (n = 54). The remaining participants did not have a parental history of depression (n = 47). Inclusion criteria for this study were: age 12–16 years old, having the ability to read and speak English, and one parent with or without a history of depression who was also interested in participating. Exclusion criteria included: adolescent or parent history of psychosis and adolescent diagnosis of Autism, Down's syndrome, or significant neurological or medical conditions (e.g. cancer, endocrine disorder, cerebral palsy). Participants identified their race as White (75.3%), African American (4.95%), Native American (0.99%), Latino/Hispanic (2.97%), or Biracial/Other (15.84%). A majority of the adolescents came from households where both parents were married (72.3%).

2.2. Procedure

Adolescents and their parents participated in a single laboratory visit at the University of Michigan Department of Psychology, conducted between 1400 h and 1800 h, lasting approximately 4 h. The current study comes from a larger study of adolescents at risk for depression. Adolescent participants and their parents provided consent/assent to participate, completed self-report questionnaires, and participated in clinical interviews. The adolescent also completed a well-established social evaluative stress task, the Trier Social Stress Test (TSST; Het et al., 2009). We used a version of the TSST modified for children and adolescents that has been shown to elicit cortisol response in adolescents (Ellenbogen and Hodgins, 2009). In this version, the speech portion of the task is a speech on why they would be a good class president. Saliva samples were collected before, during, and after the task at multiple time points to assay for cortisol and DHEA levels. After completing the TSST, the teens watched a neutral movie to relax and were then debriefed and made aware of the purpose of the task. The larger study included a randomization of the participants to either spend the first 10 min of recovery in the presence of their parent or not in the presence of their parent. Randomization status was included as a covariate on all analyses, but was not of central importance for the hypotheses tested in this article.

Informed consent and assent was obtained from all individual participants and their parents in this study. This study was approved by the University of Michigan Institutional Review Board. Participants were compensated with a $50 gift card for their participation.

2.3. Measures

2.3.1. Demographic and lab visit questionnaire

Participants completed a demographic and lab information questionnaire which included questions about age, gender (male or female), religious affiliation, family structure, parental education, employment and income, birth complications and developmental milestones, questions about utilization of mental and physical health services, medication use (including birth control use), and what time the teen awoke that morning and when they last ate.

2.3.2. Pubertal status

We used the *Pubertal Development Scale* (PDS; Petersen et al., 1988) to determine pubertal status. This is a non-invasive, 9-question self-report questionnaire about the development and status of physical manifestations of puberty such as hair growth, growth spurts, and menarche. Scores were summed based on the gender of the participant

and provided placement into five categories of pubertal development: Prepubertal, Early Pubertal, Midpubertal, Late Pubertal, and Post-pubertal. The PDS has been shown to be reliable (median alpha = 0.77) and correlated with interview ratings of pubertal development (median correlation = 0.70; Petersen et al., 1988).

2.3.3. Current depression symptoms

Adolescent participants and their parents reported on adolescent current depression symptoms through completion of the *Children's Depression Inventory* Self and Parent report versions (CDI; Kovacs, 2011). The current study used the self-report version which has 27 items. The CDI is a commonly used measure of adolescent depression and has been shown to be have acceptable reliability and validity (Smucker et al., 1986).

2.3.4. Childhood trauma exposure

Adolescent participants completed the *Childhood Trauma Questionnaire* (CTQ; Bernstein et al., 2003). The CTQ is a 28 item self-report questionnaire which assesses overall trauma exposure. Items on the questionnaire include different types of abuse and neglect, including items such as, "When I was growing up, people in my family called me things like stupid, lazy, or ugly" and" When I was growing up, I was punished with a belt, board, cord, or other hard object." Additionally, reverse coded items about positive experiences are also included. Adolescents were asked about their perception of each item occurring during their childhood and the scale ranges from 1 (Never true) to 5 (Very often true). Items on the measure were summed with possible scores ranging from 25-125. Three of the items are not included in the total score as they are a measure of minimization. This questionnaire has been shown to be a valid and sensitive tool to measure childhood trauma exposure in adolescent psychiatric populations (Bernstein et al., 1997)

2.3.5. Parent diagnostic interview

In order to assess for parental history of depression, trained clinicians conducted the *Structured Clinical Interview for DSM-5 Axis I Disorders* (SCID-5; First et al., 2015) with the parent. This semi-structured interview includes probes and anchor points for symptoms and diagnosis of DSM-5 disorder criteria. This interview provided verification that the parent has met criteria of major depression in the past or currently allowing us to place participants into the High Risk (HR; parental depression was present) and Low Risk (LR; parental depression absent) groups. The interview was conducted by graduate students in clinical psychology who were extensively trained by the Principal Investigator of the study. The Principal Investigator also leads the clinical diagnostic training for the doctoral program in clinical psychology at the University of Michigan. All cases were reviewed by the study clinical staff and the PI, and diagnoses were derived using the best estimate procedures via clinical consensus (Maziade et al., 1992).

2.3.6. Cortisol and DHEA sampling

Saliva samples were collected via passive drool from adolescent participants using a standard salivette. Adolescents in the study were instructed not to eat or drink anything but water one hour prior to the appointment. All appointments took place at the same time during the day to control for glucose interference and diurnal changes in salivary cortisol. Saliva was collected from the adolescents immediately after the informed consent/assent procedure. Participants then completed questionnaires and rested for 40 min to facilitate adaptation to the laboratory environment before completing the TSST. Saliva was collected right before the TSST, directly after the TSST and then at 10-minute intervals until 65 min post-stress initiation. Cortisol was assayed from saliva at all time points, while DHEA was assayed at time points 0 min, 35 min, and 45 min. Samples were stored frozen and assayed for cortisol and DHEA within six months of collection using a commercial enzyme immunoassay kit (Salimetrics). All samples from each participant were assayed in the same batch to minimize interassay variability. Interassay and intraassay variability coefficients for cortisol were 7.61% and 5.83%, respectively. Interassay and intraassay variability coefficients for DHEA were 8.05% and 6.88%, respectively.

2.4. Analyses

DHEA to cortisol ratios were calculated by dividing the raw DHEA values by raw cortisol values at any given time point. These ratios were then logarithmically transformed to provide a normal distribution for analyses. We chose to examine DHEA/cortisol ratios at baseline and at 35 min post-stress initiation. The 35 min sample was selected as a reflection of peak ratios as this time was closest to the overall average peak levels for the sample (most participants peaked between 25 and 35 min) given that we only had DHEA levels for baseline, 35 min, and 45 min after the stress. Because our interest was in ratios at the peak of cortisol exposure, and not in the changes in ratios over time, baseline ratios levels were not included as a control when examining peak ratios (35 min) so as not to unnecessarily constrain the variance in the model. For analyses using DHEA levels alone, the values were Winsorized at 5% to reduce the effect of extreme values on our outcomes. Related predictors (e.g. Risk group and trauma) were examined for excessive collinearity and all variance inflation factors were low. Regression analyses were performed using general linear model regression in SAS statistical software (PROC GLM). We ran the models with and without covariates.

3. Results

3.1. Sample characteristics

The high risk and low risk participants did not differ in gender, $\chi^2(1) = 1.70$, $p = 0.19$, age, $t(99) = -0.43$, $p = 0.67$, pubertal status, $t(99) = -0.93$, $p = 0.35$, or time from when they awoke in the morning to the start of the lab visit, $t(99) = -1.09$, $p = 0.28$. The groups did,

Table 1
Demographic Differences in Sample.

	High Familial Risk	Low Familial Risk	Difference
Count	$n = 54$	$n = 47$	
Gender	Girls = 30 Boys = 24	Girls = 20 Boys = 27	χ^2 (1) = 1.7, $p = 0.2$
Age	$M = 13.9$, $SD = 1.3$	$M = 14.0$, $SD = 1.3$	t (99) = -0.4, $p = 0.7$
Pubertal Development Stage (PDS)	$M = 2.5$, $SD = 0.6$	$M = 2.6$, $SD = 0.6$	t (99) = -0.9, $p = 0.4$
Time from Wakening (hours)	$M = 5.7$, $SD = 1.5$	$M = 6.0$, $SD = 1.6$	t (99) = -1.1 $p = 0.3$
Trauma Exposure (CTQ)	$M = 36.1$, $SD = 7.2$	$M = 32.4$, SD = 5.8	t (99) = 2.0, $p = 0.05$*
DHEA/cortisol ratio at 35 min.	$M = 6.8$, $SD = 0.7$	$M = 6.5$, $SD = 1.0$	t (99) = 1.6, $p = 0.1$
DHEA/cortisol ratio at 0 min.	$M = 6.9$, $SD = 0.7$	$M = 6.9$, $SD = 1.0$	t (99) = -0.2, $p = 0.9$

** $p < .01$, * $p < .05$.

Table 2
Mixed Models examining the Effect of Group on DHEA/cortisol Ratios at Baseline (0 min) and Post-stress (35 min).

Parameter	Group	Beta	Std. Error	df	*t*	Sig.
Baseline						
Intercept		6.94	0.12	99	56.23	< .001**
Group	*High Risk*	−0.03	0.17	99	−0.16	0.88
	Low Risk	0	–	–	–	–
35 min						
Intercept		6.53	1.22	99	53.12	< 0.001**
Group	*High Risk*	0.26	0.17	99	1.57	0.12
	Low Risk	0	–	–	–	–

** $p < .01$, * $p < .05$.

however, differ in mean levels of trauma exposure, with the high risk group reporting greater total trauma exposure, $t(99) = 2.0$, $p = 0.05$. See Table 1 for details. The models below were conducted with and without these covariates but only models without covariates are described below for parsimony except for cases where the inclusion of covariates alter the results, in which case both models are presented.

3.2. Risk group differences in DHEA, cortisol, and DHEA/cortisol ratios

We examined whether familial risk for depression (HR vs. LR) impacted DHEA/cortisol ratios at baseline and 35 min post-stress initiation using separate mixed linear models. Contrary to our hypothesis, the high risk and low risk groups did not differ on levels of DHEA/cortisol ratios at baseline, b = -0.03, t = -0.16, p = 0.88, or 35 min post-stress initiation, b = 0.26, t = 1.57, p = 0.12. Interestingly, in the model examining post-stress initiation (at time 35 min), there was a trend, albeit not significant, in the opposite direction than predicted, with high risk adolescents having greater DHEA/cortisol levels than their low risk peers (see Table 2). When looking at DHEA levels alone, the groups (HR vs. LR) did not differ on levels of DHEA alone at baseline, b = 6.61, t = 0.42, p = 0.66, or 35 min post-stress initiation, b = 4.83, t = 0.29, p = 0.77. Additionally, they did not differ in cortisol levels alone at baseline, b = -0.05, t = -0.47, p = 0.64, or 35 min post-stress initiation, b = -0.09, t = -1.05, p = 0.29.

3.3. Trauma exposure as moderator of the relationship between group, DHEA, cortisol, and DHEA/cortisol ratios

We examined early trauma exposure as a potential moderator of the link between familial risk and DHEA/cortisol ratios. No such moderation was observed at baseline, Trauma x Group b = 0.04, t = 1.5, p = 0.14. However, trauma exposure moderated the link between familial risk and ratios at 35 min post-stress, Trauma x Group b = 0.06, t = 2.29, p = 0.02. Specifically, at average levels of trauma exposure, the effect of familial risk on ratios at 35 min remained non-significant, High Risk b = 0.22, t = 1.37, p = 0.17. However, as trauma levels increased, group differences in DHEA/cortisol ratios at 35 min began to emerge. We ran regions of significance analysis for probing interaction effects using the Johnson-Neyman technique (see Preacher et al., 2006) and found that the group difference effect becomes significant when CTQ ≥ 33.99, which represents 0.32 standard deviations above the CTQ mean M = 31.83, SD = 6.70 (See Fig. 1). Those at high risk for depression and greater than 0.32 SD above the mean levels of trauma had significantly higher DHEA/cortisol ratios than their low risk peers at the same level of trauma, High Risk b = 0.62, t = 2.51, p = 0.01. Notably, in the context of trauma exposure, this difference in DHEA/cortisol ratios in high risk vs. low-risk participants was the opposite of what we hypothesized. See Table 3 for details. The moderation effect of trauma remains when controlling for all covariates, except that it becomes trend level when controlling for age (Trauma x Group b = 0.05, t = 1.90, p = 0.06) raising the possibility that the observed effect is due

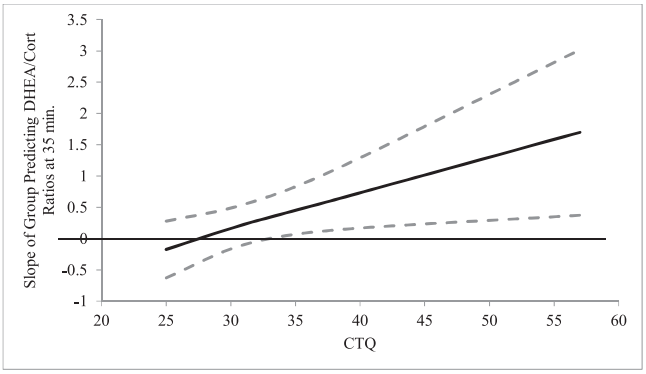

Fig. 1. Regions of Significance: Trauma Exposure Moderates DHEA/cortisol ratios at 35 min post-stress initiation in High and Low Risk Adolescents. The slope of the group differences predicting DHEA/cortisol ratios becomes significant at CTQ 33.99, which is 0.032 SD above the mean.

Table 3
Mixed Models examining Trauma Exposure as Moderator on the Relationship between Risk Group status and DHEA/cortisol Ratios at Baseline (0 min) and Post-stress (35 min).

Parameter	Group	Beta	Std. Error	df	*t*	Sig.
Baseline						
Intercept		6.92	0.12	97	55.59	< 0.001**
CTQ		−0.01	0.02	97	−0.42	0.67
		0	–	–	–	–
Group	*High Risk*	−0.05	0.17	97	−0.31	0.76
	Low Risk	0	–	–	–	–
CTQ*Group	*High Risk*	0.04	0.03	97	1.5	0.14
	Low Risk	0	–	–	–	–
35 min						
Intercept		6.51	0.12	97	53.79	< 0.001**
CTQ		−0.01	0.02	97	−0.63	0.53
Group	*High Risk*	0.22	0.16	97	1.37	0.17
	Low Risk	0	–	–	–	–
CTQ*Group	*High Risk*	0.06	0.03	97	2.29	0.02*
	Low Risk	0	–	–	–	–

Note: Total Trauma Scores (CTQ) centered at Mean.
** $p < .01$.
* $p < .05$.

to age differences in either trauma or group risk status. However, there were no group difference in age, $t(99)$ = -0.43, p = 0.67, and age was not correlated with trauma, r = 0.09, p = 0.36. Nonetheless, we tested whether age moderated the association between group and ratios. In this model, age did not significantly interact with group status, b = -0.07, t = -0.62, p = 0.54, suggesting that our original finding was not due to age differences in trauma levels.

We also examined early trauma exposure as a potential moderator of the link between familial risk and DHEA levels alone and found that trauma exposure did not moderate this relationship at baseline, b = 0.51, t = 0.19, p = 0.85, or 35 min post-stress initiation, b = -1.33, t = -0.46, p = 0.65. Additionally, trauma exposure did not moderate the relationship between familial risk and cortisol levels alone at baseline, b = -0.02, t = -1.23, p = 0.22, or 35 min post-stress initiation, b = -0.02, t = -1.28, p = 0.20, suggesting that this finding is unique to the ratios themselves.

3.4. Secondary analyses

3.4.1. Important covariates as potential moderators

We conducted additional analyses to test whether important covariates moderated the relationship between risk status and post-stress DHEA/cortisol ratios, which could explain our trauma moderation finding. Using separate linear mixed models, we found that age, b =

-0.07, t = -0.62, p = 0.54 (also reported above), gender b = -0.16, t = -0.47, p = 0.64, pubertal status b = -0.49, t = -1.75, p = 0.08, or time from awakening to the task b = 0.07, t = 0.62, p = 0.54, did not moderate the relationship between risk status and post-stress (35 min) DHEA/cortisol ratios. Additionally, current self-reported depressive symptoms did not moderate the post-stress DHEA/cortisol ratio and familial risk association, b = -0.01, t = -0.52, p = 0.61.

4. Discussion

In this study, we examined the relationship between adolescent familial risk for depression and DHEA/cortisol ratios during a laboratory-based stress task. We hypothesized that low-risk adolescents would have higher DHEA/cortisol ratios as high ratios were expected to be indicative of a more protective profile (Goodyer et al., 1998). However, we did not find a group difference in DHEA/cortisol ratios before or after the TSST. In contrast, group differences emerged when considering childhood trauma exposure. As total trauma exposure increased, high-risk adolescents exhibited greater DHEA/cortisol ratios than the low-risk adolescents, likely a function of blunting of the HPA axis response to stress in the trauma-exposed high risk group. This study sheds light on trauma history as an important moderator of risk in high-risk adolescents and furthers our understanding of how trauma exposure may impact the relationship between risk for depression and stress regulation.

Contrary to our main hypothesis, we did not find any differences between high and low-risk participants in DHEA/cortisol ratios at baseline or 35 min after stress. High ratios have traditionally been conceptualized as "protective". For example, lower diurnal DHEA/cortisol ratios were found in adolescent participants with persistent major depressive disorder (Goodyer, I. M., Herbert, J., & Tamplin, 2003) and decreased DHEA/cortisol ratios have been shown to be associated with current depressive symptoms in adults (Gallagher and Young, 2002). In contrast, we found a trend for high-risk individuals showing greater ratios than their low-risk peers, indicating that high ratios may not always reflect a protective profile. Ratios fluctuate as a function of the relative levels of DHEA and cortisol. High ratios, therefore, can reflect either high DHEA availability or relatively low cortisol for the level of DHEA response. In fact, there is evidence of blunted cortisol reactivity to stress tasks among depressed adults with trauma history (Oquendo et al., 2003). Thus, we examined whether early trauma moderated the risk-ratios link.

We found that childhood trauma exposure moderated the relationship between group status and DHEA/cortisol ratios at 35 min post-stress initiation but not at baseline. Our model suggests that at no trauma exposure (i.e., CTQ centered at zero), there were no group differences in DHEA/cortisol ratios. However, at high levels of trauma, high-risk teens showed greater DHEA/cortisol ratios than their low-risk peers. Thus, high familial risk in the context of high early childhood trauma is associated with greater DHEA/cortisol ratios in response to an in-lab stressor. This finding is consistent with the trauma exposure literature in adults, specifically, that early life trauma exposure and PTSD are associated with blunted cortisol reactivity (Yehuda and Seckl, 2011). Likewise, DHEA levels and DHEA/cortisol ratios are higher in veterans with PTSD (Yehuda et al., 2006). Additionally, our finding is supported by recent work finding higher hair DHEA/cortisol ratios in trauma exposed adolescents (Schindler et al., 2019) as well as higher plasma DHEA/cortisol ratios in adult PTSD patients with childhood trauma exposure (Kellner et al., 2010). However, among adult patients with depressive and anxiety disorders, there were no group differences in DHEA/cortisol ratios between the trauma and no trauma exposed groups, suggesting that clinical status may add complexity to the DHEA-trauma link (Kellner et al., 2018). All in all, it is likely that the high ratios observed in the trauma-exposed high-risk adolescents are due to blunting of the cortisol response and/or an upregulation of the DHEA response. The question remains, however, as to why this trauma-induced effect was found in the high risk group only, which could suggest a unique mechanism of risk that impacts youth at familial risk for depression.

Our initial conceptualization of DHEA/cortisol ratios was predicated on cortisol variability being a proxy of the stress response, and DHEA variability being a measure of the corresponding neuroprotective and down-regulatory response. However, our findings highlight a potential different conceptualization of DHEA/cortisol ratios in some contexts, where high ratios may reflect blunted stress-related cortisol release but intact DHEA output. In response to stress-induced ACTH signals, cortisol and DHEA are released by the *zona fasciculata* and *zona reticularis* of the adrenal, respectively. Reduced sensitivity of the *zona fasciculata* would result in low cortisol release in response to ACTH. Yet, if the *zona reticularis* have normal sensitivity, the DHEA response would be in line with the intensity of the stressor (as reflected in the ACTH input) and thus atypically high DHEA/cortisol ratios would result. Thus, high-risk adolescents might react to early trauma with a down-regulation of the adrenal response to ACTH in the *zona fasciculata*. There is an extensive literature examining the adaptive biological downregulation of cortisol responses to protect the organism from the toxic effects of excess cortisol with much of this literature focusing on adaptations at the glucocorticoid receptor level (Herman et al., 2012). We speculate that such adaptation may also occur at the level of the *zona fasciculata* by reducing the adrenal sensitivity to ACTH. It is possible that there is not a similar drive to downregulate the DHEA response in the *zona reticularis* given no known toxic effects of excess DHEA. This may be the case given that intact or even increased DHEA levels have been associated with resilient children who have been exposed to maltreatment (Cicchetti and Rogosch, 2007). In fact, by not downregulating DHEA release in the *zona reticularis*, the system would further adapt by having greater availability of the neuroprotective effects of DHEA. Therefore, the decoupling of the cortisol and DHEA response among those exposed to trauma would lead to higher DHEA/cortisol ratios reflecting intact DHEA but blunted cortisol response to ACTH. Notably, this blunting was not captured by cortisol levels alone given that trauma exposure did not moderate the association between risk status and cortisol levels at 35 min after the TSST. This is not surprising given that low cortisol reflects other processes beyond blunting of the HPA axis, such as a failure to activate the axis because individuals simply did not find the task threatening and thus stressful. Thus, DHEA/cortisol ratios may reflect a unique process within the HPA axis that is not observed when examining cortisol levels alone.

Finally, our findings are in line with previous studies showing higher DHEA levels and lower cortisol levels in women with PTSD, which were highest among women with comorbid PTSD and MDD (Gill et al., 2008). While PTSD symptomatology in either adolescents or their parents was not a focus of this study, high ratios in those exposed to early trauma may be a biomarker of risk for PTSD in this high-risk for depression group. In fact, children of depressed parents are at greater risk for many forms of psychopathology, including PTSD (Morris et al., 2012). Thus, while we aimed to capture a mechanism of risk for depression, it is possible that the high ratios observed in the familial risk trauma exposed sample are instead a marker for risk for PTSD.

Our findings should be interpreted in the context of some limitations. First, our sample was relatively homogenous and well-educated which may impact the generalizability to other more diverse samples. Additionally, it should be noted that our sample reported relatively low levels of trauma. Future work should look to replicate our findings in larger more diverse and nationally representative samples as well as samples with a greater range of trauma exposure levels. Additionally, the cross-sectional nature of the data did not allow us to determine which of our high and low-risk kids go on to develop psychopathology. One final limitation is that while we collected cortisol values at several time points, we did not collect DHEA at all of the same time points. This did not allow us to model a curve of the DHEA response and therefore limited our ability to look at DHEA/cortisol ratio changes over time.

In conclusion, we found DHEA/cortisol ratio group differences between high and low risk for depression adolescents only in the context of greater childhood trauma exposure and these differences were in the opposite direction than initially hypothesized. In our sample, the high-risk teens with a history of trauma displayed elevated DHEA/cortisol ratios. This finding highlights the importance of considering key factors, such as trauma history, when examining HPA functioning in children of depressed parents. Additionally, given that the stress-induced profile of greater DHEA/cortisol ratios was only present in the high risk adolescents, this suggests a trauma response in this group that may signify a unique mechanism of risk. Additionally, our study provides evidence that DHEA/cortisol ratios provide unique information not obtained from DHEA or cortisol levels alone that may reflect a unique downregulation of the adrenal to early stress among youth at familial risk for depression. Future research should focus on understanding how the adrenal gland is responding to ACTH signals as well as understanding how high ratios may differentially predict the onset of stress related disorders in children with and without a history of trauma.

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Declaration of Competing Interest

None.

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