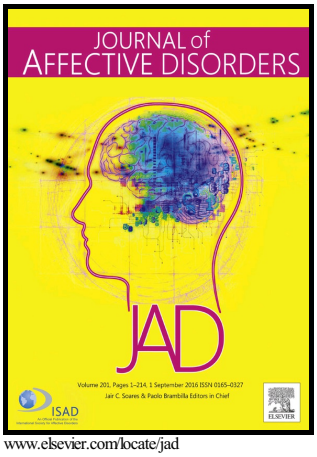


www.elsevier.com/locate/jad

Etiologic specificity of waking Cortisol: Links with maternal history of depression and anxiety in adolescent girls

Brandon L. Goldstein, Greg Perlman, Roman Kotov, Joan E. Broderick, Keke Liu, Camilo Ruggero, Daniel N. Klein

PII: S0165-0327(16)30553-5
DOI: http://dx.doi.org/10.1016/j.jad.2016.08.079
Reference: JAD8560

To appear in: *Journal of Affective Disorders*

Received date: 6 April 2016
Revised date: 28 July 2016
Accepted date: 24 August 2016

Cite this article as: Brandon L. Goldstein, Greg Perlman, Roman Kotov, Joan E Broderick, Keke Liu, Camilo Ruggero and Daniel N. Klein, Etiologic specificit of waking Cortisol: Links with maternal history of depression and anxiety i adolescent girls, *Journal of Affective Disorders* http://dx.doi.org/10.1016/j.jad.2016.08.079

Etiologic specificity of waking Cortisol: Links with maternal history of depression and anxiety in adolescent girls

Brandon L. Goldstein[a*], Greg Perlman[b], Roman Kotov[b], Joan E. Broderick[c], Keke Liu[d], Camilo Ruggero[d], Daniel N. Klein[a]

[a]Department of Psychology, Stony Brook University

[b]Department of Psychiatry, Stony Brook University

[c]Center for Economic and Social Research, University of Southern California

[d]Department of Psychology, University of North Texas

[*]Correspondence to: Brandon L. Goldstein, Department of Psychology, Stony Brook University, Stony Brook, NY 11794-2500. Tel.: +631 762 4530. E-mail: brandon.goldstein@stonybrook.edu

Abstract

Background

Many previous studies have indicated that individuals who are depressed or at risk for depression are characterized by increased levels of morning cortisol and a greater cortisol awakening response (CAR). However, despite the high comorbidity between depressive and anxiety disorders, fewer studies have examined whether these diurnal cortisol abnormalities are also characteristic of anxiety or risk for anxiety.

Methods

In the present study we examined cortisol in a community sample of 476 female adolescents and related it to maternal history of depression and/or anxiety disorders. Salivary cortisol was

collected at waking, 30 minutes post waking, and in the evening on three weekdays. Results: Contrary to prior results, offspring at risk for depression did not have increased morning cortisol or CAR. However, offspring at risk for anxiety disorders had elevated 30 minute cortisol and total cortisol produced throughout the day; this effect was primarily driven by offspring of mothers with panic disorder or agoraphobia. Additionally, levels of cortisol were highest among offspring of mothers with multiple anxiety diagnoses.

Limitations

The study is limited to female adolescents and maternal diagnostic history. Additionally, some diagnoses could not be examined as a result of too few cases (e.g. GAD).

Conclusions

Overall, these results underscore the importance of considering anxiety when examining the association of diurnal cortisol abnormalities with risk for psychopathology, as it may have influenced prior observations of elevated morning cortisol in depression.

Keywords

Cortisol; cortisol awakening response; depression; anxiety; maternal; offspring; vulnerability

Introduction

Response to stress is thought to play a major role in the etiology of depression (Brown, Bifulco, & Harris, 1987), which has led to a large literature examining associations of depression with salivary cortisol, an easily accessible index of the limbic-hypothalamic-pituitary-adrenal axis (LHPA), the primary biological stress system. Salivary cortisol has a diurnal pattern that is characterized by a sharp increase shortly after waking referred to as the cortisol awakening response (CAR; e.g. Fries, Dettenborn, & Kirschbaum, 2009; Wüst et al., 2000), followed by a decrease throughout the rest of the day. Several studies have found that depressed individuals exhibit increased morning salivary cortisol and an elevated CAR compared to healthy controls (e.g. Bhagwagar, Hafizi, & Cowen, 2005; Pruessner, Hellhammer, Pruessner, & Lupien, 2003; Vreeburg et al., 2009). Although there have been some conflicting reports (Huber, Issa, Schik, & Wolf, 2006; Stetler & Miller, 2005), a meta-analysis indicates that morning cortisol is elevated in depression (Stetler & Miller, 2011).

Morning cortisol and CAR have also been posited to serve as vulnerability markers for the subsequent development of depression. For example, studies of child, adolescent, and adult offspring of depressed mothers have exhibited increased morning cortisol and/or CAR relative to offspring of never depressed mothers (e.g. Dougherty, Klein, Olino, Dyson, & Rose, 2009; Dougherty et al., 2013; Foland-Ross, Kircanski, & Gotlib, 2014; Halligan, Herbert, Goodyer, & Murray, 2004; LeMoult, Chen, Foland-Ross, Burley, & Gotlib, 2015; Vreeburg, Hartman, et al., 2010). In addition, several studies have reported that increased morning cortisol and CAR predict the onset of depression (Adam et al., 2010; Goodyer, Herbert, Tamplin, & Altham, 2000; Harris et al., 2000; but see Carnegie et al., 2014 for negative findings).

Despite the well-established comorbidity between depression and anxiety, (e.g. Cummings, Caporino, & Kendall, 2014), less is known about the association of cortisol and CAR with common anxiety disorders such as specific phobia, social phobia, and panic/agoraphobia (posttraumatic stress disorder, no longer classified as an anxiety disorder, has been much better studied). A small, but growing body of research suggests that morning cortisol and CAR are also elevated in anxious individuals (e.g. Mantella, et al., 2008; Vreeburg, Zitman, et al., 2010). However, others find decreased morning cortisol in individuals with anxiety disorders (Hek et al., 2013). Unfortunately, most studies have either collapsed across all anxiety disorders or examined only a single anxiety disorder; hence, it is unclear whether particular forms of anxiety have differential associations with cortisol.

There are also fewer studies examining morning cortisol/CAR as a vulnerability marker of anxiety in offspring. However, similar to the literature on cortisol and risk for depression, a few studies have reported increased morning cortisol in offspring of mothers with anxiety disorders. Studies of 6-year old (Dougherty et al., 2013) and adult (Vreeburg, Hartman, et al., 2010) offspring of mothers with anxiety disorders found increased morning cortisol and CAR compared to controls, although one study found decreased CAR in adolescents as a function of maternal prenatal anxiety (O'Donnell, et al., 2013). In addition, there is recent evidence that increased CAR predicts the first onset of social anxiety disorder in young adults (Adam et al., 2014).

Thus, offspring and prospective studies suggest that increased morning cortisol/CAR may be a vulnerability marker for depression. A similar pattern of increased morning cortisol/CAR may also be a vulnerability factor for anxiety disorders, but the literature is limited. Additionally, most studies of salivary cortisol in individuals at risk for depression and anxiety compare

offspring of parents with and without only one of these disorders rather than look among anxiety disorders, and do not consider comorbidity. The only two studies to consider this question were in conflict, with one reporting that increased morning cortisol in offspring at risk for anxiety is largely explained by risk for depression (Vreeburg, Hartman et al., 2010), whereas the other found increased morning cortisol in offspring at risk for anxiety even after adjusting for maternal depression (Dougherty et al., 2013).

In the present study, a cohort of female adolescents provided salivary cortisol at waking, 30 minutes post waking, and in the evening. We examined whether offspring cortisol was differentially associated with maternal histories of anxiety and depression taking comorbidity into account as well as diagnoses in the offspring themselves.

Methods

Participants

A sample of 550 adolescent females with at least one available biological parent were recruited from Long Island, New York, to participate in the Adolescent Development of Emotions and Personality Traits (ADEPT) study. Details of the recruitment and inclusion criteria can be found elsewhere (Nelson et al., 2015). Briefly, girls in the sample were included if they were between ages 13.5-15.5, fluent in English such that they could independently read/understand questionnaire materials, and had at least one biological parent available for participation. While not the focus of the current study, this project was designed to identify predictors of the first onset of depression. Therefore, families were excluded if the adolescent was suspected of having met criteria for either depressive disorder or dysthymia based on a phone screen using the Patient Health Questionnaire (PHQ-9; Kroenke, Spitzer, & Williams,

2001) or in person diagnostic interview using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (K-SADS; Kaufman et al. 1997). Families were also excluded if the adolescent was suspected of having an intellectual disability.

We excluded participants if they did not complete at least one full day of saliva sampling that met quality standards described below (*N*=21), if the diagnostic interview was not conducted with the mother (*N*=39), or if the participant did not report information on puberty status (N=10). We also excluded offspring of mothers who were diagnosed with PTSD, GAD, and OCD, but no other diagnosis (*N* = 4) because there were too few cases to analyze as separate groups. Thus, the final analysis sample includes 476 adolescent offspring. Adolescents had an average age of 14.4 years of age (SD = .62) and were predominately white and non-Hispanic (*N* = 387, 81.3%). Most families had at least one parent who completed a 4-year college degree (*N* = 315, 66.2%). Pubertal development using the total Tanner pictures score (Morris & Udry, 1980) for this sample was an average of 7.76 (SD = 1.27) on a scale of 1-10 and suggesting that most girls were nearing completion of the development of secondary sex characteristics. Self-reported pubertal development on the Pubertal Development Scale (Petersen et al. 1988) averaged 12.93 (SD = 1.95) out of a possible 16 with the vast majority of girls (83.4%) having reached menarche (pubertal measures described in greater detail below). Most participants were not taking medication at the time of assessment; 12 reported taking medication for depression or anxiety, 13 reported taking medication for ADHD, and 37 reported taking allergy medication.

Maternal psychopathology

The Structured Clinical Interview for the DSM-IV (SCID; First et al. 1996) was used to assess parental psychopathology. Where applicable, dates of disorder onset and offset were

calculated for the mother's first episode and current episode. All interviews were conducted by trained research staff and supervised by experienced clinical psychologists (R. K., G. P., and D. K.). Inter-rater reliability was established using 25 SCID recordings and ranged from fair to excellent (kappa = .69-1.00 with the lowest for specific phobia and the highest for panic). While the SCID was completed with the participating parent regardless of gender, only 39 fathers completed the SCID (7% of the overall sample). We excluded these cases from the analysis sample as we would not have had sufficient power to examine effects of psychopathology differences by parent gender on offspring cortisol. Therefore, the present study only uses data concerning maternal diagnoses (final N = 476).

Maternal lifetime diagnoses included major depressive or dysthymic disorders (N = 101), panic disorder (N =44), agoraphobia (N =6), specific phobia (N = 92), social phobia (N = 84), GAD (N =16), PTSD (N = 18), and OCD (N = 6). Of 225 mothers with at least one diagnosis, 91 mothers (41.2%) had comorbid depression and anxiety. Of mothers with only a single depression or anxiety diagnosis, 46 had a depressive disorder, 10 had panic or agoraphobia, 39 specific phobia, 36 social phobia, and none had only GAD, PTSD, or OCD. Therefore, offspring with of mothers with a history of only GAD, PTSD, or OCD were excluded from analyses because of low caseness (defined as < 20 cases). However, to ensure that our results were not altered by excluding offspring of mothers with pure diagnoses of GAD, PTSD, and OCD, we repeated our analyses including these participants and found that the results did not change. In analyses, panic disorder and agoraphobia were collapsed (N = 50); however, results did not differ when using panic alone.

Based on evidence that timing of parental psychopathology can influence association with offspring cortisol (e.g., Halligan et al., 2004), we examined two aspects of the timing of

maternal diagnoses in relation to the offspring's cortisol assessment: 1) current diagnosis at time of saliva collection vs. remitted and 2) prenatal onset vs. postnatal onset. For the maternal diagnoses included in analyses diagnostic status was: 16 current and 85 remitted for depressive or dysthymic disorder, 44 and 48 for specific phobia, 27 and 57 for social phobia, and 9 and 41 for panic/agoraphobia. Timing of onset was: 70 after birth of the participant and 31 prior for depressive disorders, 17 and 71 for specific phobia (onset is unknown for four mothers), 5 and 76 for social phobia (unknown for three), and 17 and 32 for panic/agoraphobia (unknown for one).

Adolescent psychopathology

The Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime version (K-SADS; Kaufman et al. 1997) was used to assess psychopathology in the adolescent offspring typically within 1 week of cortisol sampling. The K-SADS interview was conducted individually with the participating offspring. All interviews were conducted by trained research staff and supervised by experienced clinical psychologists (R. K., G. P., and D. K.). The number of interviews that were double coded for reliability differed across diagnoses (N = 27-31) and reliability ranged from fair to excellent (Kappa = .51-.83; lowest for social phobia, highest for specific phobia).

Offspring lifetime diagnoses included depression not otherwise specified (N = 30), panic (N =3), specific phobia (N = 60), social phobia (N = 46), GAD (N =18), PTSD (N = 0), and OCD (N = 7). Of the 127 adolescents with diagnoses, 28 (22%) had multiple disorders. We examined bivariate associations with point-biserial correlations among offspring diagnoses and diurnal cortisol, finding that offspring diagnosed with social phobia had higher CAR (r = .10, p < .05) and AUC daily (r = .09, p < .05). No other diagnoses where significantly correlated with cortisol. To be conservative, we included offspring diagnoses of panic/agoraphobia, specific

phobia, social phobia, and depression NOS as covariates in multivariate models even though most offspring diagnoses did not demonstrate bivariate associations.

Pubertal development

Pubertal development was assessed using two self-report measures. The Pubertal Development Scale (PDS; Petersen et al. 1988) includes 5 items assessing body hair, skin changes, breast growth, and menarche. Items are rated on a 4-point scale ranging from 1 (not yet started) to 4 (seems complete), with the exception of menarche, which is rated as yes/no. A second measure assessed pubic hair and breast growth using pictorial representations of Tanner's 5 stages of development ranging from 1-5 (prepubertal to fully matured; Morris & Udry, 1980). The PDS and Tanner picture ratings were individually summed, z-scored, and the sum of two z-scores was used to yield a single measure of pubertal status. Lastly, self-reported height and weight were used to calculate body mass index (BMI).

Parenting

The Parental Bonding Instrument (PBI; Parker, Tupling & Brown, 1979) is a widely used self-report measure of two primary parenting dimensions, care (12 items) and overprotection (13 items). Participants were instructed to describe how much a phrase characterized their mother's behavior using a 5-point Likert scale ranging from 1 (Very like) to 5 (Very unlike). A typical question that characterizes the care scale is, "Enjoys talking things over with me," whereas a question from the overprotectiveness scale is, "Invades my privacy." The PBI exhibits strong test re-test reliability even over 10 years (.63 for care and .68 for overprotectiveness; Wilhelm & Parker, 1990). The internal consistency of PBI in the present sample was acceptable, with alphas of .89 for care and .79 for overprotectiveness.

Bullying

The Revised Peer Experiences Questionnaire (RPEQ; De Los Reyes & Prinstein, 2004; Prinstein, Boergers, & Vernberg, 2001) is a self-report measures designed to assess overt and indirect forms of peer victimization and bullying perpetration in adolescents. The current study used three scales: reputational victimization, relational victimization, and overt bullying. Items were answered using a 5-point Likert scale ranging from 1 (Never) to 5 (A few times a week). The construct validity of the RPEQ is supported by correlations with peer-reported victimization and exhibits test-retest reliability coefficients of .48-.52 over a 6 month interval (Prinstein, Boergers, & Vernberg, 2001). In the present sample, the internal consistency of the RPEQ was acceptable-good with alphas of .89 for reputational victimization, .82 for relational victimization, and .70 for the overt bullying scale.

Salivary cortisol

Families were given verbal and written instruction along with a cortisol collection kit. These kits included a standard kitchen timer; synthetic saliva-collection rolls placed inside of a MEMSCap^{TM} bottle that recorded time of each opening and thus saliva sampling; tubes (color coded according to sampling time) for each synthetic roll once the sample had been collected; and a paper diary to record the time of waking, when samples were collected, and any noteworthy events (e.g. eating/drinking, waking at an unusual time). Adolescents were told to place a synthetic roll in their mouth and to saturate it with saliva, then place rolls into the appropriate tube. Adolescents were instructed to provide three samples, immediately upon waking, 30 minutes after waking, and approximately 8:00 pm on three consecutive weekdays.

Sampling on weekdays was prioritized over sampling on the weekend such that some participants could provide two consecutive days and then a third non-consecutive weekday (e.g. Thursday, Friday, and then the following Monday). In rare instances, individuals collected a single day of samples on the weekend (N = 7). Lastly, families were asked not to sample cortisol within two weeks of starting the academic school year. A short video clip explaining the cortisol collection was posted online and viewing it was encouraged (SB ADEPT, 2012).

In addition to the adolescents' self-report of sampling times, families also were informed that the bottle with swabs contained a computer chip (MEMSCap^{TM}) that would create a time stamp whenever the bottle was opened, and that good agreement between time stamps and sampling times recorded in the diary would be reimbursed with a bonus $10 gift card. The MEMs sample time was prioritized over the self-reported time when determining sample collection time. The kitchen timer was used to help families ensure that they completed the 30-minute sample at the scheduled time. Families were contacted prior to starting collection to reiterate instructions and address any procedural questions. Staff continued to check-in with families throughout the collection process. Samples were returned via the US Postal Service and then frozen at -80°C until assayed using time-resolved immuno-assay with fluorescence detection (DELFIA). Duplicate assays were examined with average coefficient of variation (CV) where values greater than 12% for cortisol values greater than 5 nmol/L were reanalyzed. The average of the two assay values was used for analysis.

Salivary cortisol sample exclusion

Samples were excluded if the adolescent reported being sick or if the cortisol level was more than 3 SD above the mean for the cohort. Samples were also excluded if they fell outside the following time windows: waking samples taken more than 10 minutes after waking time, 30-

minute samples taken less than 15 or more than 45 minutes after waking, and evening samples taken before 16:00 hours or after 24:00 hours. Lastly, participants were only included in analyses if they had at least 1 day with all 3 samples meeting inclusion criteria.

Of the analysis sample, compliance with protocol was very high; 382 (80.3%) participants had 3 days with all 9 samples completed, another 77 (16.2%) had at least 2 days with all samples completed and only 17 (3.5%) had a single day with all samples completed. Excluding the participants with only one day of samples did not alter results.

Data analysis

Prior to conducting inferential statistics all individual cortisol samples were adjusted for sampling time since waking using regression. Next, we calculated CAR with respect to increase (the difference between the 30 minute and waking samples) and total daily cortisol throughout the day with respect to ground (AUCdaily; the area under the curve for the waking, 30 minute, and evening samples). We calculated mean waking, 30 minute, evening, CAR, and AUCdaily across all available days. To determine covariates to include in our models, we calculated correlations of these cortisol markers with offspring age, BMI, PDS composite, time of waking, offspring medication usage, parenting style, peer relationships, mother's marital status, and highest level of education by a parent as a proxy for socioeconomic status. Wake time was significantly correlated with the waking sample and CAR (r = .10 and r = -.15, ps < .05). Age was significantly correlated with CAR and AUCdaily (r = .11 and r = .10, ps < .05, respectively). PDS was significantly correlated with the evening sample, CAR, and of AUCdaily (r = .12; r = .10; and r =.09, ps < .05, respectively). In bivariate analyses, medication for mood problems (depression/anxiety) use was not significantly associated with cortisol, but a trend emerged for lower AUCdaily (r = -.09, p =.054). To be conservative, we repeated all analyses with

medication for mood problems as a covariate, but the results did not differ. Therefore, the final list of covariates included age, wake time, and PDS in all multivariate models.

First, we conducted t-tests to compare cortisol at waking, 30 minutes, evening, CAR, and AUCdaily in offspring of mothers with histories of depression, panic/agoraphobia, social phobia, or specific phobia to offspring of mothers without any internalizing history. We then conducted multiple linear regression analyses to explore unique variance in cortisol explained by each specific diagnosis, while using age, wake time, PDS, and offspring diagnoses of depressive or anxiety disorders as covariates. For example, in one model waking cortisol was the dependent variable and maternal history of specific phobia, panic/agoraphobia, social phobia, and depressive disorder were independent variables. We ran all analyses twice, once including and once excluding offspring of mothers with PTSD, GAD, or OCD but no other diagnoses of interest (N= 4). We also conducted analyses exploring the effect of the timing of maternal disorders on offspring cortisol. Specifically, we examined whether current vs. remitted diagnostic status as well as onset of maternal disorder before or after the child's birth was related to offspring cortisol. All data analyses were completed using SPSS version 21 (IBM).

Results

Individual maternal internalizing disorders

First, we conducted t-tests comparing offspring of mothers with each specific diagnosis to offspring without a maternal history of panic/agoraphobia, specific phobia, social phobia, or depression (see Table 1). Offspring with a maternal history of any of the disorders did not differ from offspring without a maternal history of those disorders on the waking sample. Although, offspring of mothers with social phobia had elevated cortisol at a trend level (t(333) =1.86, p = .07). However, for the 30 minute sample, offspring of mothers with panic or agoraphobia had

significantly higher cortisol than offspring of mothers without ($t(299) = 2.40$, $p < .02$). Similarly, for the 30 minute sample, offspring of mothers with social phobia had significantly higher cortisol than control offspring ($t(333) = 2.11$, $p < .05$). However, offspring of mothers with depression and specific phobia did not differ from offspring of mothers without internalizing disorders. For the evening sample, offspring of mothers with specific phobia showed a trend for higher cortisol levels ($t(341) = 1.75$, $p = .08$).

Offspring of mothers with internalizing disorders did not statistically differ on CAR compared to controls (Table 1). Specifically, offspring of mothers with panic/agoraphobia, $t(299) = 1.63$, $p > .05$; social phobia, $t(333) = 1.13$, $p > .05$; specific phobia, $t(341) = 1.13$, $p > .05$; and depressive disorders, $t(350) = .29$, $p > .05$, did not differ from control offspring.

Next, we compared AUCdaily in offspring of mothers with histories of specific internalizing disorders to offspring of mothers without a history of panic/agoraphobia, specific phobia, social phobia, or depression (see Figure 1). Offspring of mothers with panic/agoraphobia produced significantly more cortisol throughout the day than control offspring, $t(299) = 2.95$, $p < .005$. Similarly, offspring of mothers with social phobia produced significantly more cortisol throughout the day compared to offspring without, $t(333) = 2.65$, $p < .01$. Lastly, offspring of mothers with specific phobia showed a trend to produce more cortisol than offspring without, $t(341) = 1.88$, $p = .06$. However, AUCdaily for offspring of mothers with depression did not significantly differ from offspring of mothers without anxiety or depression, $t(350) = .48$, $p > .05$.

Unique effects of maternal diagnoses on offspring cortisol

Using multiple regression, we examined the unique effects of each maternal anxiety and depressive disorder on their offspring's 30-minute cortisol and AUCdaily, while controlling for

wake time, offspring age, pubertal status, and offspring psychopathology (see Table 2). The 30-minute cortisol and AUCdaily where selected, since the t-tests described above found associations with maternal psychopathology. When controlling for other maternal diagnoses, 30-minute cortisol and AUCdaily were significantly elevated in offspring of mothers with panic/agoraphobia. 30-minute cortisol was elevated at a trend level and AUCdaily was significantly elevated in offspring of mothers with social phobia.

Effects of multiple versus single anxiety diagnoses

Additionally, we examined whether offspring cortisol at 30 minutes post waking and AUCdaily varied as a function of number of maternal anxiety diagnoses as the previous analyses suggest that anxiety, but not depression are associated with elevated cortisol. Using multiple regression we entered a count of the total number of maternal anxiety diagnoses, age, wake time, pubertal status, and a count variable of offspring anxiety diagnoses as predictors. 303 offspring did not have a maternal history of anxiety disorders, 128 offspring had a mother with one anxiety diagnosis, 37 offspring had a maternal history of two anxiety diagnosis, and 8 offspring had three (the most possible). We found a significant linear effect for the number of maternal anxiety diagnoses, such that offspring of mothers with more anxiety disorders had greater cortisol 30 minutes post waking, $\beta = .12$, $p < .05$; and greater AUCdaily, $\beta = .15$, $p < .001$. We also tested a model with a quadratic term, however the squared term was not significant for either cortisol 30 minutes post waking, $\beta = -.12$, $p > .05$ or greater AUCdaily, $\beta = -.04$, $p > .05$.

Effect of timing of maternal diagnosis

Finally, we examined effect of the timing of maternal diagnosis on offspring cortisol in two ways. First, ANCOVA models examined whether current vs. remitted disorder status influenced each cortisol marker, while controlling for age, wake time, and pubertal status (Table

3). These analyses were limited to mothers with a current or past episode of the disorder; mothers with no history of the disorder were not included. Effects of both maternal social phobia and depression were both non-significant in these models. Effects of maternal specific phobia were all non-significant except for the evening sample ($F(1, 87) = 4.69$, $p < .05$), such that offspring of mothers with remitted specific phobia had higher cortisol than offspring of mothers with current specific phobia. Effects of panic/agoraphobia were all non-significant except for the CAR, ($F(1, 45) = 4.54$, $p < .05$, such that offspring of mothers with remitted panic/agoraphobia had a higher CAR than those with current panic/agoraphobia. However, this result should be interpreted with caution as only 9 mothers had a current diagnosis.

We used a similar ANCOVA approach to explore the effect of maternal diagnostic onset prior vs. after the child's birth using offspring age, wake time, and pubertal status as covariates (see Table 4). None of the models for specific phobia, social phobia, panic/agoraphobia, or depression produced significant differences, indicating that cortisol in offspring of mothers with onsets prior to the child's birth did not significantly differ from cortisol in offspring of mothers with onsets after the child's birth.

Discussion

In the current study, we explored the patterns of salivary cortisol in female adolescents of mothers with and without common internalizing disorders. In bivariate analyses, we found that offspring with a maternal history of either panic/agoraphobia or social phobia had significantly higher cortisol levels at 30 minutes post waking to offspring of mothers without panic/agoraphobia, specific phobia, social phobia, or depression. Offspring of mothers with histories of panic/agoraphobia and social phobia also exhibited higher total cortisol throughout the day compared to control offspring. Furthermore, a similar pattern of results was evident in

offspring of mothers with panic/agoraphobia even after adjusting for the other maternal anxiety and depressive disorders, offspring age, wake time, pubertal status, and offspring psychopathology. However, the effect of maternal history of social phobia on AUCdaily remained significant, but the effect on 30 minute cortisol was no longer significant when including covariates. We also observed a linear relationship with the number of maternal anxiety diagnoses, such that 30-minute cortisol and total daily cortisol levels were greater in offspring of mothers with more anxiety diagnoses. Finally, we found a few instance in which timing of maternal psychopathology influenced offspring cortisol, but this did not appear to explain elevated cortisol seen in maternal history of either panic/agoraphobia or social phobia.

There have been relatively few studies examining diurnal salivary cortisol in individuals with or at risk for anxiety disorders, and no studies have compared diurnal cortisol across risk for several different anxiety disorders. Yet, our findings are consistent with reports of increased cortisol in individuals at risk for panic and/or agoraphobia and social phobia. For instance, Vreeburg, Hartman et al. (2010) found that adult offspring of parents with panic disorder exhibited elevated CAR. In addition, Adam (2014) reported that increased CAR predicted the subsequent onset of social phobia. However, there are few studies that have examined these association and require replication is needed.

Our results suggest that increased 30 minute and total cortisol throughout the day may be risk markers for the more severe anxiety disorders. Specifically, panic/agoraphobia and social phobia are more pervasive and impairing than specific phobia (Alonso et al., 2004; Greenberg et al., 1999). We also found that increased cortisol at 30 minutes and total cortisol over the course of the day were linearly associated with the number of maternal anxiety diagnoses. This suggests that the offspring with the highest loading of maternal anxiety (those most likely to develop

anxiety themselves) are also at the greatest risk for having the most elevated cortisol, and raises the possibility that elevated cortisol may play a role in the mediating effect of familial vulnerability on the later development of anxiety disorder.

In contrast, offspring of mothers with a history of depression did not exhibit elevated cortisol levels. This conflicts with previous studies which typically find increased cortisol in offspring of depressed parents (e.g. Dougherty, Klein, Olino, Dyson, & Rose, 2009; Foland-Ross, Kircanski, & Gotlib, 2014; LeMoult, Chen, Foland-Ross, Burley, & Gotlib, 2015; Vreeburg, Hartman, et al., 2010). However, most of these studies used depressed parents who received treatment in mental health care facilities (which often possess greater comorbidity) or had recurrent or melancholic forms of depression, and our sample did not select for severe depression. Additionally, our sample expressly excluded adolescents with past depression, and previous studies of depressed parents indicate that offspring of depressed parents often have an earlier onset of depression than offspring of healthy controls (Keller, et al., 1986; Weissman, Warner, Wickramaratne, Moreau, & Olfson, 1997). Therefore, our sample of offspring of depressed mothers may have been relatively more resilient or less severely afflicted by depression. Alternatively, the absence of an effect for depressive disorders in our sample might reflect a file-drawer problem in literature on the salivary cortisol risk for depression.

However, it is also possible that maternal comorbidity, and specifically anxiety disorders that are not typically included in basal cortisol studies such as panic/agoraphobia and social phobia, may account for inconsistent findings. Previous studies reporting on links between maternal depression history and cortisol may not have fully accounted for the presence of these comorbid anxiety diagnoses in mothers. Our analyses suggest that future studies examining

offspring of depressed mothers should explore maternal comorbid anxiety disorders and include offspring of mothers with anxiety only to tease apart the effects of depression and anxiety risk.

The links between maternal psychopathology and offspring cortisol may be mediated by genetic influences (e.g. Goldstein & Klein, 2014). However, there is also evidence indicating that maternal depression and anxiety may affect offspring cortisol through a number of environmental pathways. Maternal depression is associated with high levels of stress (e.g. Hammen, 2005), and mothers who experience high levels of stress early in a child's life have offspring with elevated levels of cortisol (e.g. Essex, Klein, Cho, & Kalin, 2002). In addition, depressed mothers may be more withdrawn in their parenting, which has been shown to increase offspring cortisol levels (Murray, Halligan, Goodyer, & Herbert, 2010). Similarly, lower marital quality, which is common in individuals with depression and anxiety (e.g. Aseltine & Kessler, 1993; McLeod, 1994) has been associated with higher waking cortisol in offspring (Pendry & Adam, 2007). Thus, environmental stress and related psychosocial factors may account for our findings. Our exploration of timing of maternal depression suggested that current specific phobia and panic/agoraphobia had no effect or lowered cortisol.

In addition to examining offspring of parents with multiple specific internalizing disorders, strengths of this study include a large sample, obtaining three days of salivary cortisol samples, electronically monitoring the times that samples were collected, and very high sampling compliance with 80.3% of subjects providing three days of quality samples. However, the study also has several limitations. First, we were unable to look at effects of paternal history of psychopathology, since very few fathers were assessed. Second, we were unable to closely examine each type of anxiety diagnosis such as GAD. Third, the offspring sample was comprised entirely of female adolescents, so the effects may not generalize to males or offspring of other

ages. Fourth, although we examined several aspects of the timing of maternal psychopathology, we did not directly assess the timing of episodes of maternal disorders during specific periods of offspring postnatal development, which may be distinctly sensitive to stress and influence cortisol (Halligan, Herbert, Goodyer, & Murray, 2004). Finally, only a subset of offspring at risk for depression or anxiety by virtue of maternal disorder will ultimately develop internalizing psychopathologies; long-term follow-up is necessary to determine whether elevated cortisol in high-risk offspring predicts onset.

In conclusion, the present study fills a gap in the literature by examining diurnal salivary cortisol in offspring at risk for anxiety, in addition to depressive disorders. We found that offspring of parents with histories of social phobia and panic/agoraphobia exhibited increased cortisol, but contrary to previous findings, offspring of parents with histories of depression did not have increased cortisol. It is conceivable that some previous findings linking increased cortisol to risk for depression are a result of unexamined comorbidity. Thus, this study highlights the importance of assessing and examining a variety of forms of psychopathology when evaluating cortisol as a risk marker.

References

Adam, E. K., Doane, L. D., Zinbarg, R. E., Mineka, S., Craske, M. G., & Griffith, J. W. (2010). Prospective prediction of major depressive disorder from cortisol awakening responses in adolescence. *Psychoneuroendocrinology*, *35*(6), 921–31. http://dx.doi.org/10.1016/j.psyneuen.2009.12.007

Adam, E. K., Vrshek-Schallhorn, S., Kendall, A. D., Mineka, S., Zinbarg, R. E., & Craske, M. G. (2014). Prospective associations between the cortisol awakening response and first onsets of

anxiety disorders over a six-year follow-up – 2013 Curt Richter Award Winner. *Psychoneuroendocrinology*, *44*(0), 47–59. http://dx.doi.org/10.1016/j.psyneuen.2014.02.014

Alonso, J., Angermeyer, M. C., Bernert, S., Bruffaerts, R., Brugha, T. S., Bryson, H., … Kessler, R. C. (2004). Disability and quality of life impact of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatrica Scandinavica*, *109*(109), 38–46. http://doi.org/10.1111/j.1600-0047.2004.00329.x

Aseltine Jr, R. H., & Kessler, R. C. (1993). Marital disruption and depression in a community sample. *Journal of Health and Social Behavior*, 237-251.

Bhagwagar, Z., Hafizi, S., & Cowen, P. J. (2005). Increased salivary cortisol after waking in depression. *Psychopharmacology*, 182(1), 54-57. http://dx.doi.org/10.1007/s00213-005-0062-z

Brown, G. W., Bifulco, A., & Harris, T. O. (1987). Life events, vulnerability and onset of depression: some refinements. *The British Journal of Psychiatry*, *150*(1), 30–42. http://doi.org/10.1192/bjp.150.1.30

Cummings, C. M., Caporino, N. E., & Kendall, P. C. (2014). Comorbidity of anxiety and depression in children and adolescents: 20 years after. *Psychological Bulletin*, *140*(3), 816–845. http://dx.doi.org/10.1037/a0034733

De Los Reyes, A., & Prinstein, M. J. (2004). Applying depression-distortion hypotheses to the assessment of peer victimization in adolescents. *Journal of Clinical Child and Adolescent Psychology*, *33*(2), 325–335. http://dx.doi.org/ 10.1207/s15374424jccp3302_14

Dougherty, L. R., Klein, D. N., Olino, T. M., Dyson, M., & Rose, S. (2009). Increased waking salivary cortisol and depression risk in preschoolers: The role of maternal history of melancholic depression and early child temperament. *Journal of Child Psychology and Psychiatry*, *50*(12), 1495-1503. http://dx.doi.org/10.1111/j.1469-7610.2009.02116.x

Dougherty, L. R., Smith, V. C., Olino, T. M., Dyson, M. W., Bufferd, S. J., Rose, S. A., & Klein, D. N. (2013). Maternal psychopathology and early child temperament predict young children's salivary cortisol 3 years later. *Journal of Abnormal Child Psychology, 41*(4), 531-542. http://dx.doi.org/10.1007/s10802-012-9703-y

Essex, M. J., Klein, M. H., Cho, E., & Kalin, N. H. (2002). Maternal stress beginning in infancy may sensitize children to later stress exposure: effects on cortisol and behavior. *Biological psychiatry*, *52*(8), 776-784. http://dx.doi.org/10.1016/S0006-3223(02)01553-6

Fries, E., Dettenborn, L., & Kirschbaum, C. (2009). The cortisol awakening response (CAR): facts and future directions. *International Journal of Psychophysiology*, *72*(1), 67–73. http://dx.doi.org/10.1016/j.ijpsycho.2008.03.014

Foland-Ross, L. C., Kircanski, K., & Gotlib, I. H. (2014). Coping with having a depressed mother: The role of stress and coping in hypothalamic–pituitary–adrenal axis dysfunction in girls at familial risk for major depression. *Development and Psychopathology*, *26*(4pt2), 1401–1409. http://dx.doi.org/10.1017/S0954579414001102

Greenberg, P. E., Sisitsky, T., Kessler, R. C., Finkelstein, S. N., Berndt, E. R., Davidson, J. R. T., … Fyer, A. J. (1999). The Economic Burden of Anxiety Disorders in the 1990s. *Journal of Clinical Psychiatry*, *60* (7), 427–435. http://doi.org/10.4088/JCP.v60n0702

Goldstein, B. L., & Klein, D. N. (2014). A review of selected candidate endophenotypes for depression. *Clinical Psychology Review*. http://doi.org/10.1016/j.cpr.2014.06.003

Goodyer, I.M., Herbert, J., Tamplin, A., & Altham, P.M.E. (2000). Recent life events, cortisol, dehydroepiandrosterone and the onset of major depression in high-risk adolescents. *British Journal of Psychiatry, 177*, 499-504. http://dx.doi.org/10.1192/bjp.177.6.499

Halligan, S. L., Herbert, J., Goodyer, I. M., & Murray, L. (2004). Exposure to postnatal depression predicts elevated cortisol in adolescent offspring. *Biological Psychiatry*, *55*(4), 376–381. http://doi.org/10.1016/j.biopsych.2003.09.013

Hammen, C. (2005). Stress and depression. *Annual Review of Clinical Psychology*, *1*, 293–319. http://doi.org/10.1146/annurev.clinpsy.1.102803.143938

Harris, T.O., Borsanyi, S., Messari, K., Stanford, K., Cleary, S.E., Shiers, H.M., et al. (2000). Morning cortisol as a risk factor for subsequent major depressive disorder in adult women. *British Journal of Psychiatry, 180,* 24-28. http://dx.doi.org/10.1192/bjp.177.6.505

Hek, K., Direk, N., Newson, R. S., Hofman, A., Hoogendijk, W. J. G., Mulder, C. L., & Tiemeier, H. (2013). Anxiety disorders and salivary cortisol levels in older adults: a population-based study. *Psychoneuroendocrinology*, *38*(2), 300–305. http://dx.doi.org/10.1016/j.psyneuen.2012.06.006

Huber, T. J., Issa, K., Schik, G., & Wolf, O. T. (2006). The cortisol awakening response is blunted in psychotherapy inpatients suffering from depression. *Psychoneuroendocrinology*, *31*(7), 900–904. http://dx.doi.org/10.1016/j.psyneuen.2006.03.005

Kroenke, K., Spitzer, R. L., & Williams, J. B. W. (2001). The phq-9. *Journal of General Internal Medicine*, *16*(9), 606–613. http://doi.org/10.1046/j.1525-1497.2001.016009606.x

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., … Ryan, N. (1997). Schedule for affective disorders and schizophrenia for school-age children present and lifetime version (K-SADS-PL): Initial reliability and validity data. *Journal of the American*

Academy of Child and Adolescent Psychiatry, 36, 980-988. http://dx.doi.org/10.1097/00004583-199707000-00021

Keller, M. B., Beardslee, W. R., Dorer, D. J., Lavori, P. W., Samuelson, H., & Klerman, G. R. (1986). Impact of severity and chronicity of parental affective illness on adaptive functioning and psychopathology in children. *Archives of General Psychiatry*, *43*(10), 930-937. http://dx.doi.org/10.1001/archpsyc.1986.01800100020004

Lenze, E. J., Mantella, R. C., Shi, P., Goate, A. M., Nowotny, P., Butters, M. A., … Rollman, B. L. (2011). Elevated cortisol in older adults with generalized anxiety disorder is reduced by treatment: a placebo-controlled evaluation of escitalopram. *The American Journal of Geriatric Psychiatry*, *19*(5), 482–490.http://dx.doi.org/10.1097/JGP.0b013e3181ec806c

LeMoult, J., Chen, M. C., Foland-Ross, L. C., Burley, H. W., & Gotlib, I. H. (2015). Concordance of mother–daughter diurnal cortisol production: Understanding the intergenerational transmission of risk for depression. *Biological Psychology*, *108*, 98–104. http://dx.doi.org/10.1016/j.biopsycho.2015.03.019

Mantella, R. C., Butters, M. A., Amico, J. A., Mazumdar, S., Rollman, B. L., Begley, A. E., … Lenze, E. J. (2008). Salivary cortisol is associated with diagnosis and severity of late-life generalized anxiety disorder. *Psychoneuroendocrinology*, *33*(6), 773–781. http://dx.doi.org/10.1016/j.psyneuen.2008.03.002

Marshall, W. A., & Tanner, J. M. (1969). Variations in pattern of pubertal changes in girls. *Archives of Disease in Childhood*, *44*, 291-303.

Meewisse, M. L., Reitsma, J. B., De Vries, G.J., Gersons, B. P. R., & Olff, M. (2007). Cortisol and post-traumatic stress disorder in adults. *The British Journal of Psychiatry*, *191*(5), 387–392. http://dx.doi.org/10.1192/bjp.bp.106.024877

McFarlane, A. C., Barton, C. A., Yehuda, R., & Wittert, G. (2011). Cortisol response to acute trauma and risk of posttraumatic stress disorder. *Psychoneuroendocrinology*, *36*(5), 720–727. http://dx.doi.org/10.1016/j.psyneuen.2010.10.007

McLeod, J. D. (1994). Anxiety disorders and marital quality. *Journal of Abnormal Psychology*, *103*(4), 767–776. http://doi.org/10.1037/0021-843X.103.4.767

Michael, A., Jenaway, A., Paykel, E. S., & Herbert, J. (2000). Altered salivary dehydroepiandrosterone levels in major depression in adults. *Biological Psychiatry*, *48*(10), 989–995. http://dx.doi.org/10.1016/S0006-3223(00)00955-0.

Morris, N. M., & Udry, J. R. (1980). Validation of a self-administered instrument to assess stage of adolescent development. *Journal of Youth and Adolescence*, *9*(3), 271–280. http://doi.org/10.1007/BF02088471

Murray, L., Halligan, S. L., Goodyer, I., & Herbert, J. (2010). Disturbances in early parenting of depressed mothers and cortisol secretion in offspring: a preliminary study. *Journal of Affective Disorders*, *122*(3), 218-223.

Nelson, B. D., Perlman, G., Hajcak, G., Klein, D. N., & Kotov, R. (2015). Familial risk for distress and fear disorders and emotional reactivity in adolescence: An event-related potential investigation. *Psychological Medicine*, *45*(12), 2545-2556.

Neylan, T. C., Brunet, A., Pole, N., Best, S. R., Metzler, T. J., Yehuda, R., & Marmar, C. R. (2005). PTSD symptoms predict waking salivary cortisol levels in police officers. *Psychoneuroendocrinology*, *30*(4), 373–381. http://dx.doi.org/10.1016/j.psyneuen.2004.10.005

O'Donnell, K. J., Glover, V., Jenkins, J., Browne, D., Ben-Shlomo, Y., Golding, J., & O'Connor, T. G. (2013). Prenatal maternal mood is associated with altered diurnal cortisol in

adolescence. *Psychoneuroendocrinology*, *38*(9), 1630-1638. http://dx.doi.org/10.1016/j.psyneuen.2013.01.008

Parker, G., Tupling, H., & Brown, L. B. (1979). A parental bonding instrument. *British Journal of Medical Psychology*, *52*(1), 1–10. http://dx.doi.org/10.1111/j.2044-8341.1979.tb02487.x

Pendry, P., & Adam, E. K. (2007). Associations between parents' marital functioning, maternal parenting quality, maternal emotion and child cortisol levels. *International Journal of Behavioral Development*, *31*(3), 218-231. http://dx.doi.org/10.1177/0165025407074634

Petersen, A. C., Crockett, L., Richards, M., & Boxer, A. (1988). A self-report measure of pubertal status: Reliability, validity, and initial norms. *Journal of Youth and Adolescence*, *17*, 117-133. http://dx.doi.org/10.1007/BF01537962

Prinstein, M. J., Boergers, J., & Vernberg, E. M. (2001). Overt and relational aggression in adolescents: Social-psychological adjustment of aggressors and victims. *Journal of Clinical Child Psychology*, *30*(4), 479–491. http://dx.doi.org/10.1207/S15374424JCCP3004_05

Pruessner, M., Hellhammer, D. H., Pruessner, J. C., & Lupien, S. J. (2003). Self-reported depressive symptoms and stress levels in healthy young men: associations with the cortisol response to awakening. *Psychosomatic Medicine*, *65*(1), 92–99.

SB ADEPT (2012, July 25). *ADEPT: Instructional Cortisol Collection Video*. Retrieved from https://www.youtube.com/watch?v=ffWhIM6agNk

Stetler, C., & Miller, G. E. (2011). Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. *Psychosomatic Medicine, 73*(2), 114–126. http://dx.doi.org/10.1097/PSY.0b013e31820ad12b

Van Veen, J. F., van Vliet, I. M., DeRijk, R. H., van Pelt, J., Mertens, B., & Zitman, F. G. (2008). Elevated alpha-amylase but not cortisol in generalized social anxiety disorder.

Psychoneuroendocrinology, *33*(10), 1313–1321. http://dx.doi.org/10.1016/j.psyneuen.2008.07.004

Vreeburg, S. A., Hoogendijk, W. G., van Pelt, J., DeRijk, R. H., Verhagen, J. C. M., van Dyck, R., … Penninx, B. W. J. H. (2009). Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: Results from a large cohort study. *Archives of General Psychiatry*, *66*(6), 617–626. http://dx.doi.org/10.1001/archgenpsychiatry.2009.50

Vreeburg, S. A., Hartman, C. A., Hoogendijk, W. J. G., van Dyck, R., Zitman, F. G., Ormel, J., & Penninx, B. W. J. H. (2010). Parental history of depression or anxiety and the cortisol awakening response. *The British Journal of Psychiatry*, *197*(3), 180–185. http://dx.doi.org/10.1192/bjp.bp.109.076869

Vreeburg, S. A., Zitman, F. G., van Pelt, J., DeRijk, R. H., Verhagen, J. C. M., van Dyck, R., … Penninx, B. W. J. H. (2010). Salivary cortisol levels in persons with and without different anxiety disorders. *Psychosomatic Medicine*, *72*(4), 340–347. http://dx.doi.org/10.1097/PSY.0b013e3181d2f0c8

Vrshek-Schallhorn, S., Doane, L. D., Mineka, S., Zinbarg, R. E., Craske, M. G., & Adam, E. K. (2013). The cortisol awakening response predicts major depression: predictive stability over a 4-year follow-up and effect of depression history. *Psychological Medicine*, *43*(03), 483–493. http://dx.doi.org/10.1017/S0033291712001213

Weissman, M. M., Warner, V., Wickramaratne, P., Moreau, D., & Olfson, M. (1997). Offspring of depressed parents: 10 years later. *Archives of General Psychiatry*, *54*(10), 932–940. http://doi.org/10.1001/archpsyc.1997.01830220054009

Wessa, M., Rohleder, N., Kirschbaum, C., & Flor, H. (2006). Altered cortisol awakening response in posttraumatic stress disorder. *Psychoneuroendocrinology*, *31*(2), 209–215. http://dx.doi.org/10.1016/j.psyneuen.2005.06.010

Wilhelm, K., & Parker, G. (1990). Reliability of the parental bonding instrument and intimate bond measure scales. *Australian and New Zealand Journal of Psychiatry*, *24*(2), 199–202. http://dx.doi.org /10.3109/00048679009077683

Wüst, S., Wolf, J., Hellhammer, D. H., Federenko, I., Schommer, N., & Kirschbaum, C. (2000). The cortisol awakening response - normal values and confounds. *Noise and Health*, *2*(7), 79-88.

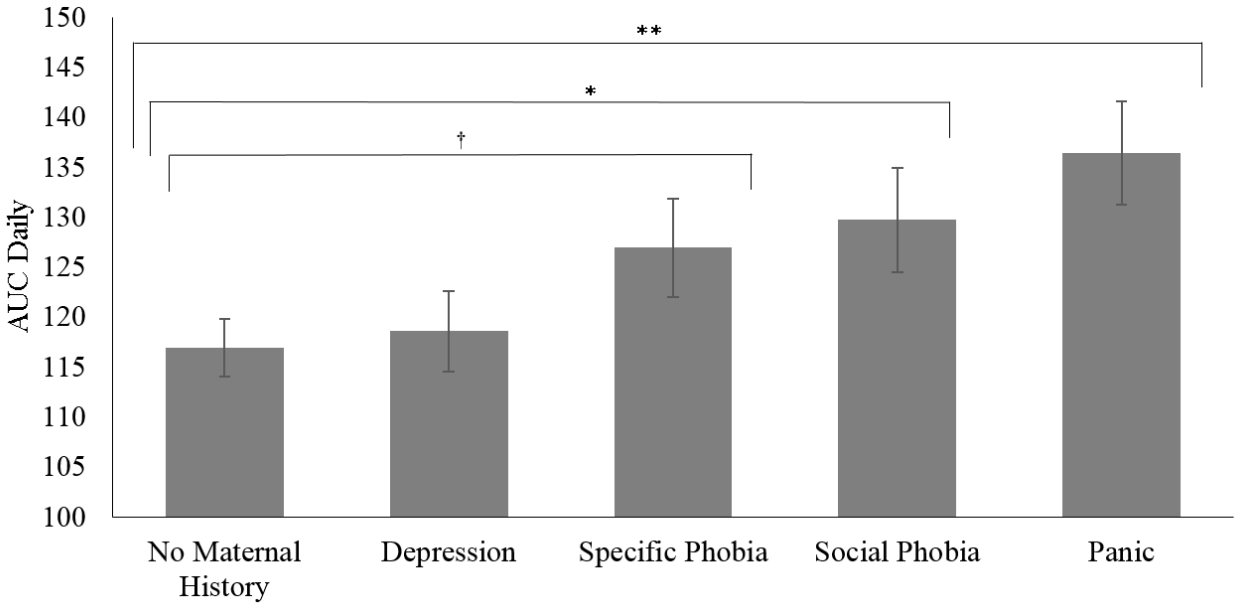
Yehuda, R. (1997). Sensitization of the hypothalamic-pituitary-adrenal axis in posttraumatic stress disorder. *Annals of the New York Academy of Sciences*, *821*(1), 57–75. http://dx.doi.org/10.1111/j.1749-6632.1997.tb48269.x

Yehuda, R., Engel, S. M., Brand, S. R., Seckl, J., Marcus, S. M., & Berkowitz, G. S. (2005). Transgenerational effects of posttraumatic stress disorder in babies of mothers exposed to the World Trade Center attacks during pregnancy. *The Journal of Clinical Endocrinology & Metabolism*, *90*(7), 4115–4118. http://dx.doi.org/ 10.1210/jc.2005-0550

Yehuda, R., Golier, J. A., & Kaufman, S. (2005). Circadian rhythm of salivary cortisol in Holocaust survivors with and without PTSD. *American Journal of Psychiatry*, *162*(5), 998–1000. http://dx.doi.org/10.1176/appi.ajp.162.5.998

Figures

Figure 1. *Daily cortisol area under the curve by maternal history of internalizing diagnoses.*



Note. † significant at $p < .10$; * significant at $p < .01$; ** significant at $p < .005$

Tables

Table 1. *Cortisol in offspring of mothers with specific internalizing disorders*

		No Maternal Hx Internalizing (N =251)	Maternal Specific Phobia (N= 92)	Maternal Social Phobia (N= 84)	Maternal Panic or Agoraphobia (N= 50)	Maternal Depression (N= 101)
Waking	M	7.25	7.49	8.07	8.12	7.30
	(SD)	3.56	3.39	3.40	3.46	3.78
	d	-	0.06	0.23	0.25	0.02
	p	-	0.58	0.07	0.11	0.90
30 Minute	M	15.01	16.00	16.66	17.26	14.90
	(SD)	6.08	6.15	6.42	5.25	5.27

	d	-	0.16	0.26	0.38	-0.02
	p	-	0.18	0.04	0.02	0.87
Evening	M	1.72	2.10	2.07	2.07	1.99
	(SD)	1.63	2.18	2.34	2.61	2.20
	d	-	0.21	0.20	0.19	0.15
	p	-	0.08	0.12	0.21	0.21
CAR	M	7.77	8.53	8.58	9.13	7.57
	(SD)	5.48	5.83	6.32	5.02	5.82
	d	-	0.14	0.14	0.25	-0.03
	p	-	0.26	0.26	0.10	0.78

Note. Means, standard deviations, effect sizes, and p-values for cortisol samples (controlled for time since waking and then averaged across all available samples for that time point) in offspring without maternal internalizing history compared to offspring of mothers with common internalizing diagnoses. The p-values are based on independent samples t-tests comparing cortisol levels in offspring of mothers with a diagnosis compared to healthy controls. N = 476

Table 2. *Regressions of offspring cortisol and unique effects of specific maternal diagnoses*

	30 Minute			AUCdaily		
Maternal Diagnosis	*β*	*t*	*p*	*β*	*t*	*p*
Specific Phobia	.01	.26	.80	.05	1.09	.28
Social Phobia	.09	1.87	.06	1.03	2.19	.03
Panic or Agoraphobia	.11	2.30	.02	.11	2.40	.02
Depression	-.07	-1.53	.13	-.05	-1.09	.28

Covariates include offspring age, wake time, pubertal status, and offspring diagnoses including specific phobia, social phobia, panic/agoraphobia, and depression NOS.

Table 3. *ANCOVAs of current vs. remitted maternal diagnostic histories by disorder type.*

	Specific Phobia					
	Current *N*=44		Past *N*=48			
	Mean	SD	Mean	SD	*F*	*p*
Waking	7.82	3.59	7.19	3.20	1.47	0.23
30 minute	17.04	6.02	15.05	6.18	2.71	0.10
Evening	1.57	1.08	2.58	2.77	5.74	0.02
CAR	9.24	5.62	7.88	6.00	1.04	0.31
AUCDaily	129.82	46.79	123.83	46.50	0.51	0.48
	Social Phobia					
	Current *N*=27		Past *N*=57		*F*	*p*
Waking	8.50	3.42	7.87	3.41	0.72	0.40
30 minute	17.47	5.87	16.27	6.69	0.58	0.45
Evening	1.90	1.40	2.16	2.69	0.25	0.62
CAR	8.98	6.07	8.39	6.48	0.11	0.74
AUCDaily	135.55	48.18	129.70	47.19	0.27	0.61
	Panic/Agoraphobia					
	Current *N*=9		Past *N*=41		*F*	*p*
Waking	9.63	4.44	7.79	3.18	1.49	0.23
30 minute	15.71	6.56	17.60	4.95	1.40	0.24
Evening	3.50	5.34	1.76	1.44	2.46	0.12
CAR	6.08	7.07	9.80	4.28	4.54	0.04
AUCDaily	133.85	31.40	136.93	36.98	0.27	0.61
	Depression					
	Current *N*=16		Past *N*=85		*F*	*p*
Waking	7.99	4.86	7.17	3.56	0.51	0.48

30 minute	13.28	6.78	15.20	4.93	1.98	0.16
Evening	2.80	4.03	1.83	1.65	2.47	0.12
CAR	5.26	6.38	8.01	5.65	3.07	0.08
AUCDaily	114.43	48.57	119.47	37.47	0.32	0.57

Table 4. *ANCOVAs of maternal diagnostic onsets prior vs. after the birth of their child by disorder type.*

	Specific Phobia					
	After child Born *N*=17		Before Child was born *N*= 71			
	Mean	SD	Mean	SD	*F*	*p*
Waking	7.07	3.22	7.52	3.50	0.11	0.75
30 minute	17.02	6.65	15.63	6.17	0.81	0.37
Evening	2.07	1.62	2.09	2.34	0.00	0.95
CAR	9.98	5.43	8.13	6.00	1.33	0.25
AUCDaily	133.67	48.65	123.82	46.66	0.72	0.40
	Social Phobia					
	After child Born *N*=5		Before Child was born *N*= 76		*F*	*p*
Waking	9.04	3.18	7.97	3.48	0.21	0.65
30 minute	18.11	6.07	16.36	6.50	0.44	0.51
Evening	1.36	1.00	2.11	2.42	0.34	0.56
CAR	9.10	5.16	8.38	6.48	0.20	0.66
AUCDaily	134.08	44.32	129.77	47.61	0.09	0.76
	Panic/Agoraphobia					
	After child Born *N*=17		Before Child was born *N*= 32		*F*	*p*
Waking	7.98	3.73	8.15	3.42	0.10	0.76
30 minute	16.15	4.94	17.82	5.47	1.08	0.30
Evening	2.20	3.94	2.06	1.63	<0.01	1.00
CAR	8.20	6.66	9.64	4.02	0.68	0.41
AUCDaily	129.13	29.31	140.31	39.15	1.22	0.27
	Depression					
	After child Born *N*=70		Before Child was born *N*=31		*F*	*p*
Waking	7.67	4.08	6.49	2.90	2.08	0.15

30 minute	14.92	5.50	14.84	4.82	0.00	0.97
Evening	2.03	2.49	1.89	1.37	0.04	0.84
CAR	7.24	6.17	8.33	4.96	0.91	0.34
AUCDaily	119.08	40.26	117.77	37.32	<0.01	0.99

Highlights

- Offspring at risk for anxiety disorders had higher cortisol 30 minutes post waking
- Offspring at risk for anxiety disorders had higher cortisol throughout the day
- The anxiety effect was primarily driven by maternal history of panic/agoraphobia
- Offspring of mothers with more anxiety diagnoses had the highest cortisol
- Maternal depression history was not associated with offspring cortisol