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Ge, Fiona
Pietromonaco, Paula R
DeBuse, Casey J
et al.

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Concurrent and prospective associations between HPA axis activity and depression symptoms in newlywed women

Fiona Ge, M.S., **Paula R. Pietromonaco, Ph.D.**[*], **Casey J. DeBuse, Ph.D.**, **Sally I. Powers, Ed.D.**, and **Douglas A. Granger, Ph.D.**[1,2]

Department of Psychological and Brain Sciences, University of Massachusetts, Amherst, MA, 01003, USA

Abstract

We investigated the extent to which individual differences in activity of the hypothalamic pituitary adrenal axis (HPA) are associated with depressive symptoms among newlywed couples. Participants were 218 couples (M age 28.4 years; 94% White) who provided 5 saliva samples (later assayed for cortisol and DHEA-S) before and after participation in a discussion of a major area of disagreement in their relationship. Depressive symptoms were assessed initially, and approximately 19- and 37-months later. Results revealed an interactive effect suggesting that concordant levels of cortisol and DHEA-S (either both high or both low) were concurrently and prospectively associated with higher depression scores. Interestingly, this interactive effect was observed for wives only – not for husbands. These observations underscore contemporary theoretical assumptions that the expression of the association between HPA activity and depression is dependent on factors related to the interaction between characteristics of the person and features of the social environment, and moderated by co-occurring variation in endocrine milieu.

Keywords

Depression; Cortisol; Dehydroepiandrosterone-sulfate; Gender; Marital interactions

[*]Corresponding author at: Department of Psychological and Brain Sciences, 135 Hicks Way, Tobin Hall, University of Massachusetts, Amherst, MA 01003, USA. monaco@psych.umass.edu (D.A. Granger).

[1]Institute for Interdisciplinary Salivary Bioscience Research, University of California at Irvine, Irvine, CA, 92697, USA.

[2]Johns Hopkins University School of Nursing, Bloomberg School of Public Health, School of Medicine, Baltimore, MD 21218, USA.

Author contributions

Fiona Ge, Casey DeBuse, Paula Pietromonaco and Sally Powers developed the study concept. Paula Pietromonaco and Sally Powers created the study design. Fiona Ge and Casey DeBuse collected data and performed data analyses and interpretation under the supervision of Paula Pietromonaco. Fiona Ge, Paula Pietromonaco, Casey DeBuse, and Douglas Granger drafted the manuscript. All authors provided critical revisions, contributed to the interpretation of the data, and approved the final version of the manuscript for submission.

Disclosure statement

In the interest of full disclosure, DAG is Founder and Chief Scientific and Strategy Advisor at Salimetrics LLC and SalivaBio LLC and these relationships are managed by the policies of the committees on conflict of interest at Johns Hopkins University School of Medicine and the University of California, Irvine. No other author has conflicts to disclose.

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1. Depression symptoms, marital relationships, and HPA axis activity

Epidemiologic analyses in North America reveal that depression is among the most common mental health disorders, with the percent of adults who experience major depression during a one-year period reaching 4.8% in males and 8.2% in females (Center for Behavioral Health Statistics and Quality, 2015) and that the incidence/prevalence of impairing depressive symptoms is considerably more common (Rucci et al., 2003). Depression accounts for the heaviest burden of disability among mental and behavioral disorders worldwide (World Health Organization, 2013). Decades of research show reciprocal effects between interpersonal relationships and depressive symptoms—poor quality relationships impact the expression of depressive symptoms, and, not surprisingly, depressive symptoms affect the quality and maintenance of social relationships (Gotlib and Beach, 1995; Hammen, 1999; Teo et al., 2013). This link is particularly pronounced in the context of marriage where relationship quality between spouses can serve to attenuate or amplify depressive symptoms (Davila et al., 2003; Overbeek et al., 2006; Whisman, 2001), and elucidating the factors/forces which increase risks for depression has the potential to advance our understanding of the precursors and concomitants of significant social problems including interpartner violence (Ouellet-Morin et al., 2015), infidelity (Hall and Fincham, 2009), strained or abusive parent-child relationships (Davies et al., 2009), and separation or divorce (Ertel et al., 2011). In this study, we address this knowledge gap by exploring the degree to which individual differences in the activity of the hypothalamic-pituitary-adrenal (HPA) axis measured during marital conflict are related concurrently and over time to depression symptoms in newlywed husbands and wives.

1.1. Conceptual issues

Contemporary theorists propose that, to advance our understanding of depression, it is especially important to study factors that trigger the emergence, that maintain, or that exacerbate symptoms in context (Hammen, 1999; Sheets and Craighead, 2014). Here we focus on the social context of early marriage because, during this transitional phase, the quality of spousal interactions has the potential to serve as either a rarefaction or provocation ecology for depression (Frech and Williams, 2007). We assume that for some newlyweds the experience of marital problems is associated with increased risk, but others in the same circumstances will be resilient. Understanding what combination of factors and forces are related to those individual differences seems paramount. For instance, studies suggest that relationship or marital conflict, problems, strain or dissatisfaction in young couples and newlyweds is experienced differently by women and men, and may have different consequences for men and women's psychosocial adjustment (Beck et al., 2013; Kiecolt-Glaser and Newton, 2001; Powers et al., 2006).

Individual differences in the reactivity and regulation of environmentally sensitive physiological systems, like the HPA axis (estimated by cortisol, the primary HPA axis product), are considered to be among the physiological pathways through which life experience may be translated into differential emotional, cognitive, and physical health outcomes (Pietromonaco et al., 2013a,b; Pietromonaco and Powers, 2015; Weiner, 1992). The nature of the relationship between HPA axis activity and psychosocial adjustment is

perhaps best characterized as an inverted U-shape. The literature reveals evidence that risk for mental health and psychosocial problems is linked to both low and high levels of cortisol (Heim et al., 2000; Karb et al., 2012; Miller et al., 2007). However, with respect to depressive symptoms specifically, the literature directly linking salivary cortisol and depression (as a main, direct effect) has been somewhat inconsistent. One possibility raised by Granger and Kivlighan (2003) and others (Chen et al., 2015; Granger et al., 2007) is that across study inconsistency in findings linking cortisol to behavior may be at least in part due to a narrow operationalization of activity of the HPA axis. In response to adverse circumstances, the HPA axis secretes multiple products (e.g., dehydroepiandrosterone, epinephrine, norepinephrine), not just cortisol.

In the recent past, technical advances in salivary bioscience have enabled investigators to measure (non-invasively in saliva) variation in environmentally sensitive physiological systems, like the HPA axis (e.g., its primary product, cortisol), in social context. Whereas catecholamines have proven challenging to measure in oral fluid, dehydroepiandrosterone (DHEA) and its sulfated contemporary (DHEA-S), like cortisol, can be measured in saliva (Granger et al., 2012, 1999). Also like cortisol, DHEA(S)[3] is released from the adrenal gland in response to HPA axis activation. In contrast to the catabolic hormone cortisol, DHEA(S) is an androgenic/anabolic hormone. It has been theorized that higher DHEA(S) may counter depression because it regulates a number of processes that are neuroprotective and health-promoting (Maninger et al., 2009). As with cortisol, however, findings linking DHEA(S) levels and depression have also been inconsistent, with some studies linking depression to elevated basal or diurnal levels of DHEA(S) (Heuser et al., 1998; Takebayashi et al., 1998; Tollefson et al., 1990) but others linking depression to lower levels (Barrett-Connor et al., 1999; Michael et al., 2000; Morsink et al., 2007). These findings suggest that, similar to cortisol, DHEA(S) response patterns, may be important for understanding the link between DHEA(S) and depression symptoms.

The combined influence of both cortisol and DHEA(S) may be particularly important in connection with depressive symptoms. Although theorists have assumed that higher catabolic (e.g., cortisol) to anabolic (e.g., DHEA(S)) activity should be associated with greater depression (Maninger et al., 2009), findings present a complex, mixed picture (Maninger et al., 2009; Mocking et al., 2015). Some findings indicate that higher DHEA(S) but not cortisol is associated with depression (Assies et al., 2004); others indicate that lower DHEA(S) and not cortisol are associated with depression (Barrett-Connor et al., 1999); and others find that a higher ratio of cortisol to DHEA(S) is linked to depressive symptoms (Khanfer et al., 2011; Maninger et al., 2009). Most studies exploring combined effects have focused on the ratio of cortisol to DHEA(S). However, ratios are subject to statistical and interpretational problems (Chen et al., 2015; Sollberger and Ehlert, 2015). A more informative method for uncovering the combined roles of cortisol and DHEA(S) is to test for statistical interactions between cortisol and DHEA(S). An interactive approach to examining cortisol and DHEA(S) may clarify previous inconsistent findings by revealing that higher

[3]We use DHEA(S) when referring to both DHEA and DHEA-S, and DHEA-S to refer specifically to the sulfated form.

levels or lower levels of both DHEA(S) and cortisol are associated with higher levels of depressive symptoms.

1.2. Present study

In the current study, we examined the interactive effects of cortisol and DHEA-S during a session in which individuals' marital relationships and marital disagreements were salient. We tested whether the interaction between cortisol and DHEA-S would be associated with depressive symptoms both concurrently and over time. We further expected that the effects might be more pronounced for women because they may be more sensitive to and engaged in resolving challenges in their marital relationships and more susceptible to depression (Nolen-Hoeksema, 2001). In addition, in many prior studies, poorer marital functioning has been repeatedly found to be associated with depressive symptoms (Gotlib and Beach, 1995; Whisman, 2001). We therefore tested whether the interactive effects of cortisol and DHEA-S would hold even after controlling for the well-established link between marital functioning and depression. Finally, because past research has shown a link between metabolic syndrome and depressive symptoms (Goldbacher and Matthews, 2007; Pulkki-Raback et al., 2009), we also performed analyses controlling for individuals' body mass index (BMI).

2. Methods

2.1. Participants

The study began with 229 opposite-sex newlywed couples (458 individuals) who were recruited primarily through marriage license records in Western Massachusetts (for further details, see Beck et al., 2013). To be eligible to participate, we required that both members of the couple be between 18–50 years old, in their first marriage, married less than seven months, have no children, and that the wife not be pregnant at the time of the initial assessment session. We also required that they work daytime hours, and were not currently under a physician's care for an endocrine disorder (e.g., Cushing's or Addison's disease). Participants were mostly White (94%) and more than 45% had achieved a bachelor's degree. At Wave 1, the mean age of the husbands was 29.1 years (SD = 5.3) and the mean age of the wives was 27.7 years (SD = 4.8). Of the 229 couples, 218 couples' had complete data at Wave 1, 195 couples completed Wave 2, and 172 couples completed Wave 3. Details about criteria for exclusion from analyses and how many couples were lost at each wave and why appear in Table S1.

2.2. Procedure

Following recommendations by Granger et al. (2012), all laboratory assessments were conducted in the late afternoon or early evening and participants were asked not to eat within one hour, not to smoke or chew gum within 30 min, and not to drink alcohol within 12 h prior to arrival. All couples knew, prior to the lab session, that they would be discussing an area of disagreement in their relationship and that the discussion would be video-recorded. During the sessions, spouses first reviewed and completed consent forms and then separately completed a variety of questionnaires, including measures of symptoms of depression and relationship quality. Participants completed these two measures early in the session, prior to providing saliva samples and about 70 min prior to the discussion of an unresolved conflict

or disagreement in their relationship. Participants provided five whole unstimulated saliva samples using the passive drool technique (Granger et al., 2012). Samples were provided 30–45 min after participants arrived at the lab; 15 min after the experimenter provided a detailed description of the upcoming conflict discussion task; and at 10, 30 and 60 min after the conflict discussion. See Beck et al. (2013) for further details about the conflict discussion task and procedure.

2.3. Measures

2.3.1. Determination of salivary biomarkers—Saliva samples were collected and stored in a −80C freezer until the day of assay. All samples were assayed in duplicate for cortisol using a highly-sensitive enzyme immunoassay (Salimetrics, Carlsbad, CA). The test volume was 25 μL, the assay had a lower limit of sensitivity of 0.003 μg/dL, a standard curve range from 0.012 μg/dL to 3.0 μg/dL, with an average intra-assay coefficient of variation of 3.5%, and an average inter-assay coefficient of variation of 5.1%.

Samples were also assayed in duplicate for DHEA-S using a commercially available immunoassay without modifications to the manufacturer's recommended protocol (Salimetrics, Carlsbad, California). The assay used 100 μL of saliva per determination, had a lower limit of sensitivity of <43 pg/mL, standard curve range from 188.9 pg/mL to 15,300 pg/mL, an average intra-assay coefficient of variation of 7.3% and an inter-assay coefficient of variation of 7.6%. Following prior work (Laurent et al., 2016), we assessed the sulfated form (DHEA-S), which is more biologically active than DHEA.

2.3.2. Medications—Following Granger and colleagues (Granger et al., 2009), participants reported all medications taken in the 24 h prior to the session. Participants had access to a reference guide to assist them with recalling medication names. A trained research assistant categorized medications by type; participants received a "1" if they had used a particular class of medication and a "0" if they had not used it. Specific medications coded that were used by five or more participants were hormonal birth control (wives), corticosteroids, allergy medications, antidepressant or antianxiety medications, benzodiazepines, anti-inflammatory medications, analgesics, stimulants (mainly ADHD medications, wives), proton-pump inhibitors (husbands), and antihypertensive drugs (husbands).

2.3.3. Depressive symptoms—At each of three waves, depressive symptoms were assessed with the Inventory of Depressive Symptomatology—Self-Report (IDS-SR) (Rush et al., 2000). The IDS-SR was designed to assess all DSM-IV depressive symptoms, and it has been found to correlate highly with other standard measures of depression such as the Hamilton Rating Scale for Depression (r = 0.88) and Beck Depression Inventory (r = 0.93). The IDS-SR contains 28 scored items assessing both psychological (e.g., "I feel sad nearly all of the time") and somatic symptoms (e.g., "I sleep longer than 12 h in a 24-h period, including naps") of depression and is scored by summing the weights of the items. The possible range for scores on the IDS-SR is 0–84. Descriptive statistics of husbands and wives' depressive symptomology at each wave are summarized in Table 1. We focus here on the degree to which individuals evidenced lower or higher depressive symptoms (i.e., on a

continuous measure of depressive symptoms). For descriptive purposes, however, percentages of husbands and wives whose depressive symptoms fell above and below clinical cutoffs for no, mild, moderate, or severe depression (see Rush et al., 2000) across waves are summarized in Table S2 of the Supplementary material.

2.3.4. Marital quality—Marital quality was assessed with the Perceived Relationship Quality Components measure (Fletcher et al., 2000). Eighteen items (rated from 1 “not at all” to 7 “extremely”) assessed relationship satisfaction, commitment, intimacy, trust, passion and love. Ratings were averaged to form a composite score (for descriptive statistics, see Table 1).

2.3.5. Body mass index (BMI)—We calculated individuals’ BMI score at each wave from their self-reported height at Wave 1 and self-reported weight at each wave. Husbands’ average BMI score was 26.86 (SD = 5.84) at Wave 1, 26.71 (SD = 5.54) at Wave 2, and 27.33 (SD = 6.01) at Wave 3. Wives’ average BMI score at Wave 1 was 24.73 (SD = 5.24) at Wave 1, 25.85 (SD = 5.76) at Wave 2, and 26.08 (SD = 6.00) at Wave 3.

2.3.6. Data preparation and analytic strategy—Table 2 shows the means and standard deviations for the raw (untransformed) values for cortisol (ug/dL) and DHEA-S (pg/mL) for each sampling time point. Missing data in cortisol and DHEA-S values were handled using the multiple imputation module of the SPSS 20 software package (Schafer and Graham, 2002; West, 2001). The complete procedure for handling missing data in the present study appears in the Supplementary material.

2.3.6.1. Adjusting for medication use: Next, we removed variability in cortisol and DHEA-S scores that might be attributed to medications. We first regressed (separately for husbands and wives) cortisol or DHEA-S values from each saliva sampling point on any medications taken by five or more participants. Then, we trimmed medications that did not exhibit significant or marginal relationships with cortisol or DHEA-S from the models and fit them a second time. We again trimmed medications that did not exhibit significant or marginal relationships and fit the models a third time. Finally, we added together the intercept values (means) and the residuals obtained from fitting these final models.

2.3.6.2. Calculating area under the curve: We then used the resulting cortisol and DHEA-S scores to compute total area under the curve, or “ground” (AUCg), for the five lab samples (Pruessner et al., 2003). Prior to calculating the AUCg score across lab samples, we (a) converted DHEA-S values to the same units as cortisol (i.e., ug/dL), and (b) because both cortisol and DHEA-S values were positively skewed, we performed a square root transformation to normalize the data (Ayer et al., 2013; Sannes et al., 2013). (We also performed the main analyses using log transformed cortisol and DHEA-S values, and the results paralleled those using a square root transformation; see Table S5.) We focus on AUCg because our laboratory paradigm differs from standard stress paradigms such as the Trier, which generally elicit a peak cortisol response relative to baseline among most participants. In contrast, in our paradigm, individuals vary in the extent to which they show increased (or decreased) cortisol in response to anticipating the discussion, the discussion itself, and after the discussion. Although we could assess area under the curve reactivity

(AUCi; Pruessner et al., 2003), this index does not adequately capture reactivity in our paradigm because it assumes that there is a peak reactivity point relative to baseline and that increases in cortisol reflect stress in response to the task. In our paradigm, there is not an average pattern of reactivity (see Table 2); instead, reactivity not only varies across individuals but, just as both lower and higher cortisol responses can index altered HPA axis functioning, we find that both increases and decreases at points along the cortisol trajectory in our paradigm are associated with problematic relationship patterns (for details about individual differences in reactivity patterns in our paradigm, see Beck et al., 2013). We therefore focus on the overall level of cortisol and DHEA-S (AUCg), within the specific context of a lab session in which the marital relationship, functioning, and disagreement were salient.

2.3.6.3. Multilevel modeling: We analyzed the data using multilevel modeling techniques for repeated measures within dyads. We used the MIXED procedure in SPSS 20 to compute multilevel models. The data were structured in a person period pairwise format such that each row represented one couple member's data at each study wave. At the level of the fixed effects, the main effects of gender, time (wave of assessment), cortisol AUCg, DHEA-S AUCg, and possible interaction terms of interest were initially estimated in the model. Because the four-way interaction, the main effect of time, and all interactions with time were not significant, we dropped these terms in our final model to simplify interpretation. At the level of the random effects, husbands' and wives' mean depression symptoms across waves were modeled. Two types of interdependence were accounted for in the model: 1) depression symptoms across multiple waves were nested within person, and 2) couple members' depression symptoms were nested within dyad. Covariance matrices were modeled using the compound symmetry structure.

Gender was coded as 0 for wives and 1 for husbands. Time was coded as 0 for Wave 1 for all individuals. Because the exact timing of each wave varied slightly across couples (M = 19 months between Wave 1 and Wave 2; M = 37 months between Wave 1 and Wave 3), time was coded as the exact number of months after Wave 1 to Wave 2, and after Wave 1 to Wave 3. For example, if the couple came into the lab 19 months after Wave 1 for the second assessment and 37 months after Wave 1 for the third assessment, time was coded as 0 for Wave 1, 19 for Wave 2, and 37 for Wave 3 for the couple. Cortisol and DHEA-S AUCg were grand mean centered.

3. Results

The main analyses examined whether cortisol and DHEA-S levels interacted to predict symptoms of depression, particularly for wives. The estimates for the final model (Table 3) indicate that cortisol and DHEA-S did interact, b = 0.006, t = 3.36, p = 0.001, 95% CI [.003, 0.010] and this interaction was qualified by gender, b = −0.006, t = −2.70, p = 0.007, 95% CI [−0.010, −0.002]. Probing this three-way interaction revealed that the interaction between cortisol AUCg and DHEA-S AUCg was significant for wives, b = 0.006, t = 3.36, p = 0.001, 95% CI [.003, 0.010], but not for husbands, b = 0.000, t = 0.41, p = 0.684, 95% CI [−0.002, 0.003] (see Fig. 1). (To view the pattern at each wave of assessment, see Fig. S1.)

To further clarify the interaction pattern for wives, we conducted simple slope analyses with DHEA-S AUCg centered at 1 SD below and above the mean. When wives' DHEA-S AUCg was low, lower cortisol AUCg was associated with higher depressive symptoms, b = −0.163, t = −2.45, p = 0.014, 95% CI [−0.293, −0.033], whereas when wives' DHEA-S AUCg was high, higher cortisol AUCg was associated with higher depressive symptoms, b = 0.201, t = 2.43, p = 0.015, 95% CI [.039, 0.363].

To test whether these patterns held when controlling for marital quality, which is known to be associated with depressive symptoms, we repeated the analyses adjusting for marital quality as a time-varying covariate across three waves; the results paralleled those reported above (see Table 4). In addition, we repeated the analyses adjusting for additional important covariates – BMI and age – and again found parallel results (see Table S6).

4. Discussion

In the context of a structured laboratory task in which newlyweds discussed their marital relationship and disagreements, we found that wives whose levels of cortisol and DHEA-S were either both higher or both lower evidenced higher depression scores concurrently and approximately 19 and 37 months later. By contrast, there were no main or interactive effects between cortisol and DHEA-S and depressive symptoms for husbands. Importantly, the main findings held even after controlling for marital quality, medication use, age, and BMI. These observations underscore contemporary theoretical assumptions that the expression of the association between cortisol and depression is dependent on factors related to the interaction between characteristics of the person and features of the social environment, and moderated by co-occurring variation in the endocrine milieu (DHEA-S).

Our findings highlight the importance of the marital relationship as a context for examining links between HPA-axis activity and depressive symptoms. They are consistent with research on marriage (Kiecolt-Glaser and Newton, 2001) and dating relationships (Laurent et al., 2013; Powers et al., 2016) that has shown that physiological mechanisms and the quality of couples' interactions contribute to depression. One possibility raised here is that individual differences in biological sensitivity and the quality of couples' interactions have joint effects on the expression of depressive symptoms. The suggestion is that HPA responses may offer a pathway through which marital interactions contribute to later emotional health outcomes (Pietromonaco et al., 2013a; Pietromonaco and Powers, 2015). Given the nature of this study design, however, it is not possible to rule out an alternative possibility. That is, individuals who have higher levels of symptoms of depression, are more likely to express HPA axis activity when confronted with the challenges of discussing day-to-day marital issues and problems.

As noted above, the association between individual differences in cortisol and depression in the literature is not always clear cut. There are many possible explanations for the inconsistencies. Among them is the idea that we need a more comprehensive measurement strategy when we operationalize individual differences in HPA axis activity (Granger and Kivlighan, 2003). This study's observations are particularly noteworthy in this regard because they demonstrate that the association between cortisol and depression was not

revealed until levels of DHEA-S were also taken into account. The findings hint that prior research may have missed the opportunity to observe the expression of hormone-behavior associations because of the high degree of focus on cortisol as the sole index of HPA activity. Indeed, only when complementary measurements of the endocrine milieu were incorporated into the analytical plan did relationships with depression emerge. These findings underscore the value of examining cortisol levels together with other hormonal responses (Bauer et al., 2002; Laurent et al., 2016; Mehta and Josephs, 2010; Mendes et al., 2007) that may modulate the effects of cortisol on emotional and behavioral health outcomes.

It is also particularly noteworthy that these hormone-depression relationships were evident for wives but not husbands. Anticipating and engaging in discussions of relationship disagreements may be especially likely to impact women because the tasks are not only interpersonal but also evoke gender role norms suggesting that women should take a more active role in facilitating the discussion (Beck et al., 2013; Powers et al., 2006). As a result, such discussions are especially likely to reveal links between environmentally sensitive biological systems and depressive symptoms for women. In addition, the potential for women to be at greater risk of experiencing depressive symptoms as a result of relational difficulties (Nolen-Hoeksema, 2001) may have made it easier to detect associations between their physiological reactions occurring within a marital context and depressive symptoms in this study.

The current study has some limitations. As noted above, the present findings are correlational and therefore we cannot determine whether differences in HPA-axis functioning lead to depressive symptoms, whether depressive symptoms lead to differential physiological responses, or whether other related factors (e.g., prior trauma, concurrent stressors) may account for the link between the physiological responses and depressive symptoms. We analyzed the interactive effects of cortisol and DHEA-S only at Wave 1 of the study, and the effects may be larger than those observed here if these hormonal response patterns occur repeatedly and if their effects accrue over time. Granger and colleagues (Granger et al., 1999; Granger and Kivlighan, 2003) note that DHEA and DHEA-S are highly correlated in the circulation, but that DHEA-S is the more biologically active molecule. However, the serum-saliva association for DHEA is higher than that for DHEA-S (Granger et al., 1999) because when “-sulfate” is attached to DHEA the size of the molecule is large and it must pass from the circulation into oral fluid by ultra-filtration (through the junctions in the salivary gland acinar cells) rather than by passive diffusion. The ultrafiltration route by which DHEA-S moves from the circulation to oral fluid makes the measurement of DHEA-S in saliva more likely to be subject to the effects of salivary flow rate than is DHEA. Thus, there is a conundrum. Here, we made the decision to prioritize measuring DHEA-S over DHEA because it is the more biologically active species. Although this raises the possibility that some of the variation in DHEA-S is associated with salivary flow rate, this explanation is unlikely for the present findings because additional analyses indicated no association between salivary flow rate and DHEA-S in our sample. Finally, most of our participants were white, well-educated, and all were in opposite-sex couples; it will be important to determine whether the findings generalize to more diverse samples.

5. Conclusion

The current findings demonstrate the importance of taking into account the combined effects of cortisol and DHEA-S in predicting depressive symptoms, as well as the importance of taking into account the context when making such assessments (e.g., a relationship-relevant context). More generally, this work suggests the value of examining the connections between physiological responses and depression from a social ecologic point of view, that is, with an eye toward understanding how physiological indicators may act and interact with intrinsic individual differences in connection with depressive symptomatology. More generally, we note that while the integration of non-invasive, biological measures into behavioral research has increased, the interpretation of biobehavioral findings in relation to mental health and psychosocial adjustment outcomes is rarely straightforward. It is suggested here that the next phase of biosocial research needs to move beyond description and toward development of mid-level theories that will enable researchers to specify, test, and refine hypotheses of how biobehavioral processes interact with social-contextual factors to influence health and human development. These mid-level biosocial models will be necessary to determine whether individual differences in adrenocortical activity confer risk or resilience.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The source of funding for the research did not influence the study design, data collection, analyses, or the content of the manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.psyneuen.2016.07.217.

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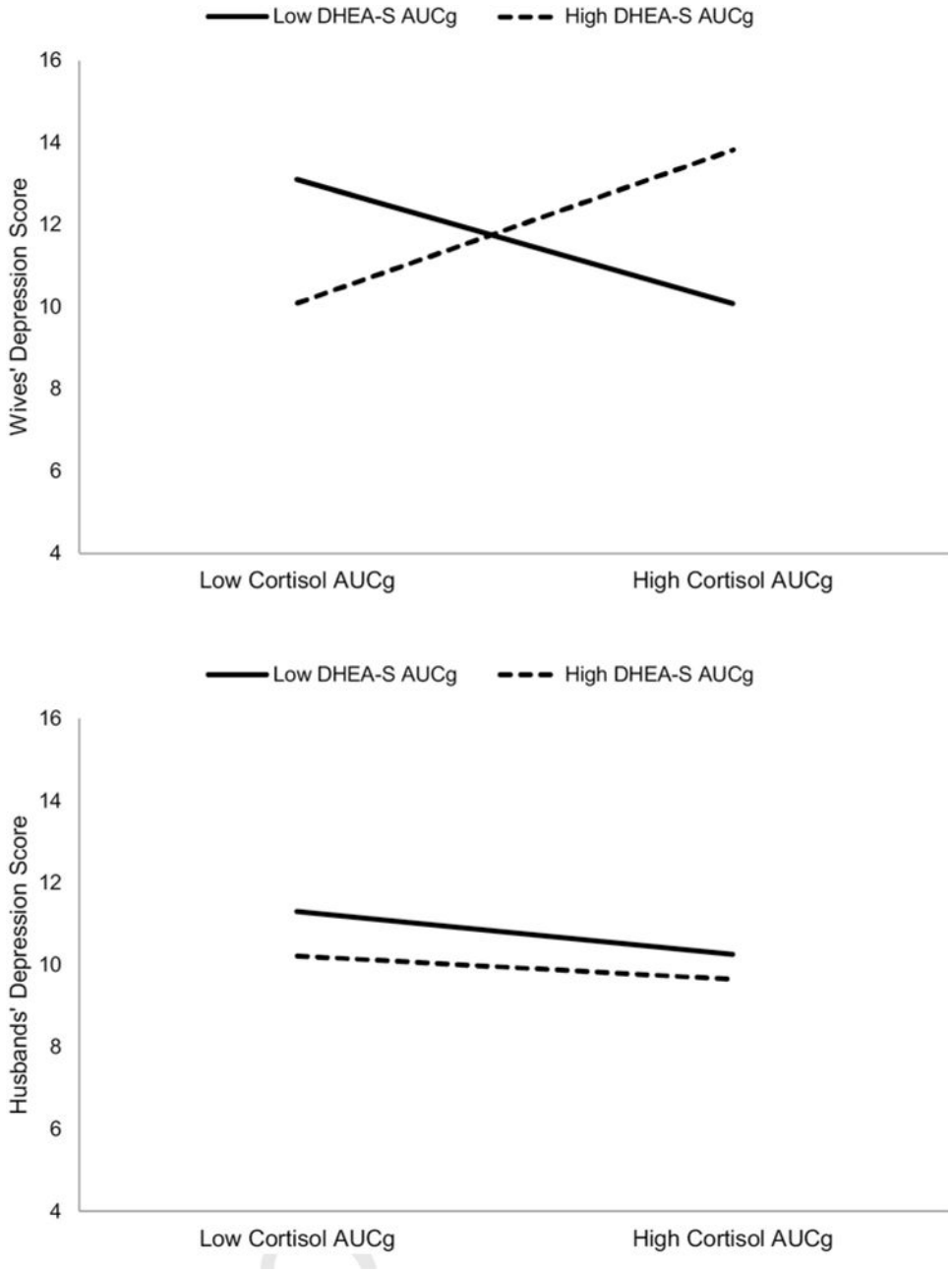

Fig. 1.

Depression scores (IDS-SR) by Cortisol (AUCg) and DHEA-S (AUCg) for wives (top panel) and husbands (bottom panel). DHEA-S is plotted at 1 SD below the mean (Low) and 1 SD above the mean (High).

Table 1

Means, Standard Deviations, and Reliabilities for Depression and Marital Quality across Waves for Husbands and Wives.

	M	*SD*	α
Depression			
Husbands			
Wave 1	10.17	6.02	0.92
Wave 2	10.09	6.62	0.81
Wave 3	10.42	6.87	0.92
Wives			
Wave 1	11.84	7.67	0.87
Wave 2	12.24	7.94	0.81
Wave 3	11.68	7.57	0.87
Marital Quality Husbands			
Wave 1	6.34	0.52	0.91
Wave 2	6.09	0.69	0.93
Wave 3	5.94	0.79	0.94
Wives			
Wave 1	6.38	0.52	0.91
Wave 2	6.18	0.65	0.92
Wave 3	6.07	0.78	0.95

Table 2

Means and Standard Deviations of Untransformed Cortisol (ug/dL) and DHEA-S (pg/mL) for Each Saliva Sample at Wave 1 for Husbands and Wives.

	Saliva Sample Time Points					
	Anticipatory Sample 1	**Anticipatory Sample 2**	**Conflict Discussion**	**Post-Discussion Sample 1**	**Post-Discussion Sample 2**	**Across the 5 Lab Samples – AUCg**
Cortisol (ug/dL)						
Husbands	0.11 (0.08)	0.08 (0.06)	0.07 (0.05)	0.06 (0.04)	0.05 (0.05)	31.56 (8.95)
Wives	0.10 (0.07)	0.09 (0.07)	0.07 (0.06)	0.07 (0.06)	0.06 (0.05)	32.31 (9.57)
DHEA-S (pg/mL)						
Husbands	6057.63 (4157.92)	5840.04 (4588.89)	5171.26 (4143.07)	5455.59 (4895.04)	5345.24 (4283.48)	85.27 (27.26)
Wives	3964.44 (4033.93)	3847.78 (4168.37)	3155.95 (3160.41)	3320.58 (3542.27)	3461.13 (3874.47)	64.53 (24.80)

Table 3

Final Estimation of the Predictors of Depressive Symptoms with Medications Removed from Cortisol and DHEA-S AUCg.

Full model				Reduced model		
Fixed Effects	**Unstandardized Estimate**	***t***	**95% CI of Unstandardized Estimate**	**Unstandardized Estimate**	***t***	**95% CI of Unstandardized Estimate**
Intercept	11.644	23.143***	[10.658, 12.630]	11.781	25.41***	[10.872, 12.690]
Time	0.009	0.72	[−0.015, 0.032]			
Cortisol	0.041	0.73	[−0.070, 0.152]	0.019	0.36	[−0.083, 0.121]
DHEA-S	0.002	0.13	[−0.030, 0.034]	0.006	0.41	[−0.023, 0.036]
Gender	−1.302	−1.89[a]	[−2.648, 0.044]	−1.418	−2.25*	[−2.654, −0.182]
Time × Cortisol	−0.001	−0.96	[−0.004, 0.001]			
Time × DHEA-S	0.000	0.65	[−0.001, 0.001]			
Time × Gender	−0.009	−0.56	[−0.042, 0.023]			
Cortisol × DHEA-S	0.006	2.89**	[0.002, 0.010]	0.006	3.36**	[0.003, 0.010]
Gender × Cortisol	−0.084	−1.03	[−0.243, 0.075]	−0.062	−0.83	[−0.208, 0.084]
Gender × DHEA-S	−0.008	−0.03	[−0.059, 0.043]	−0.020	−0.85	[−0.067, 0.027]
Time × Cortisol × Gender	0.001	0.63	[−0.003, 0.005]			
Time × DHEA-S × Gender	−0.001	−1.33	[−0.002, 0.000]			
Time × Cortisol × DHEA-S	0.000	0.42	[−0.000, 0.000]			
Gender × Cortisol × DHEA-S	−0.007	−2.86**	[−0.011, −0.002]	−0.006	−2.70**	[−0.010, −0.002]
Time × Gender × Cortisol × DHEA-S	0.000	1.33	[−0.000, 0.000]			

[a] $p < 0.10$.

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

Table 4

Final Estimation of the Predictors of Depressive Symptoms with Medications Removed from Cortisol and DHEA-S AUCg, Controlling for Marital Quality.

	Full model			Reduced model		
Fixed Effects	**Unstandardized Estimate**	***t***	**95% CI of Unstandardized Estimate**	**Unstandardized Estimate**	***t***	**95% CI of Unstandardized Estimate**
Intercept	27.648	14.01***	[23.782, 31.515]	26.376	14.88***	[22.901, 29.850]
Time	−0.013	−1.07	[−0.036, 0.011]			
Cortisol	0.044	0.80	[−0.063, 0.151]	0.003	0.67	[−0.065, 0.132]
DHEA-S	0.006	0.36	[−0.025, 0.037]	0.009	0.63	[−0.020, 0.038]
Gender	−1.536	−2.25*	[−2.872, −0.199]	−1.698	−2.71**	[−2.928, −0.469]
Time × Cortisol	−0.001	−0.45	[−0.003, 0.002]			
Time × DHEA-S	0.000	0.57	[−0.001, 0.001]			
Time × Gender	−0.013	−0.77	[−0.045, 0.020]			
Cortisol × DHEA-S	0.006	2.97**	[.002, 0.009]	0.006	3.19**	[.002, 0.009]
Gender × Cortisol	−0.074	−0.94	[−0.229, 0.081]	−0.055	−0.76	[−0.197, 0.087]
Gender × DHEA-S	−0.005	−0.20	[−0.055, 0.045]	−0.018	−0.77	[−0.064, 0.028]
Time × Cortisol × Gender	0.001	0.64	[−0.002, 0.005]			
Time × DHEA-S × Gender	−0.001	−1.33	[−0.002, 0.000]			
Time × Cortisol × DHEA-S	−0.000	−0.18	[−0.000, 0.000]			
Gender × Cortisol × DHEA-S	−0.006	−2.92**	[−0.011, −0.002]	−0.006	−2.74**	[−0.010, −0.002]
Time × Gender × Cortisol × DHEA-S	0.000	1.19	[−0.000, 0.000]			
Marital Quality	−2.502	−8.37***	[−3.087, −1.916]	−2.332	−8.52***	[−2.606, −2.058]

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.