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# Life stress influences the relationship between sex hormone fluctuation and affective symptoms in peripubertal female adolescents

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## Abstract

Female adolescents have a greatly increased risk of depression starting at puberty, which continues throughout the reproductive lifespan. Sex hormone fluctuation has been highlighted as a key proximal precipitating factor in the development of mood disorders tied to reproductive events; however, hormone-induced affective state change is poorly understood in the pubertal transition. The present study investigated the impact of recent stressful life events on the relationship between sex hormone change and affective symptoms in peripubertal female participants. 35 peripubertal participants (ages 11–14, premenarchal, or within 1 year of menarche) completed an assessment of stressful life events and provided weekly salivary hormone collections (estrone, testosterone, dehydroepiandrosterone (DHEA)) and mood assessments for eight weeks. Linear mixed models tested whether stressful life events provided a context in which within-person changes in hormones predicted weekly affective symptoms. Results indicated that exposure to stressful life events proximal to the pubertal transition influenced the directional effects of hormone change on affective symptoms. Specifically, greater affective symptoms were associated with increases in hormones in a high stress context and decreases in hormones in a low stress context. These findings provide support for stress-related hormone sensitivity as a diathesis for precipitating affective symptoms in the presence of pronounced peripubertal hormone flux.

### Keywords

puberty; female; depression; sex hormones; stress

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# 1 INTRODUCTION

The pubertal transition (peripuberty) is characterized by nearly a 3-fold greater risk of a depressive disorder in female adolescents (SAMHSA, 2020). Among other factors, this increased risk may be a result of simultaneous increases in sex hormone fluctuations and interpersonal stressors in female adolescents (Balzer et al. 2015). The sex disparity first emerges at mid-puberty (Tanner stage 3 or 4) and continues throughout the female reproductive lifespan, suggesting a role of ovarian hormone fluctuations in vulnerability to psychopathology (Angold, 1993; Angold et al., 1999; Schiller et al., 2016). An abnormal neurobiological sensitivity to normal reproductive hormone flux can trigger affective symptoms in hormone-sensitive individuals. Furthermore, stress exposure interferes with the maturation of neurodevelopmental trajectories (Walker et al., 2004) and can predict who is at risk for developing reproductive mood disorders (Bromberger et al., 2011; Namavar Jahromi et al., 2011). However, the biological mechanisms by which life stress exposure interacts with the peripubertal reproductive endocrine environment to promote depression risk are poorly understood. The present study examines how within-person deviations in sex hormones may predict depressive symptoms in peripubertal female adolescents, particularly in the context of recent stressful life events.

## 1.1 Mechanisms of depression risk during the pubertal transition

**Reproductive hormone environment—**The pubertal transition is accompanied by extensive changes in ovarian and adrenal hormones (Andersen et al. 2022; Apter 1980; Apter et al. 1989), heightened interpersonal stress exposure and a critical window in which neurodevelopmental trajectories are established (Blakemore, 2008). Adrenarche, increased activity of the hypothalamic-pituitary-adrenal (HPA) axis, initiates the developmental hormone cascade with the production of androgens, including dehydroepiandrosterone (DHEA). This is followed by reactivation of the hypothalamic-pituitary-gonadal (HPG) axis (i.e., gonadarche) and stimulation of sex steroid production, for example estradiol (E2), estrone (E1), and testosterone (T). Moreover, not only absolute concentrations but also the degree of hormone fluctuation increases with the onset of the first menstrual cycle (menarche)(Andersen et al. 2022; Janfaza et al. 2006). The first gynecological year (first year after menarche) is characterized by frequent anovulatory (up to 66%) and irregular cycles that further increase exposure to hormone fluctuation (Carlson & Shaw, 2019; Gunn et al., 2018). This dramatic reproductive endocrine instability may contribute to the abrupt emergence of affective illness during the pubertal transition in female adolescents (Angold, 1993; Patton et al., 2008).

Given the significant regulatory effect of sex hormones on mood and behavior, women are more likely to experience affective dysregulation during reproductive transition events characterized by significant hormonal flux, including premenstrual, postpartum, and perimenopausal periods (Balzer et al. 2015; Schiller et al. 2016). Hormone manipulation studies simulating reproductive transition events indicate that a vulnerability to normal changes in sex hormones, rather than the absolute level, precipitate the emergence of depressive symptoms in women with a history of reproductive hormone-related mood impairment (Bloch et al. 2000; Gordon et al. 2015, 2016; Schmidt et al. 1998,

2017). Accordingly, fluctuations in sex hormones such as estrogens (e.g., estradiol, estrone), progesterone and its derivatives, and testosterone have been shown to trigger the development of affective symptoms in a subset of hormone-sensitive individuals across the lifespan (premenstrual: Schmidt et al. 1998; perinatally: (Bloch et al., 2000); perimenopausal: (Sander et al., 2021; Schmidt et al., 2015); in males: (Schmidt et al., 2004). We recently demonstrated that a large proportion of peripubertal female adolescents showed mood sensitivity to sex hormone flux. Specifically, 57% of participants exhibited increased dysphoric mood with weekly changes (i.e., increase, decrease or large change in either direction from the previous week) in estrone and 37% of participants were mood sensitive to weekly changes in testosterone (Andersen et al. 2022). Our previous findings suggest that peripubertal female adolescents' mood sensitivity to sex-hormone flux can be categorized into four different hormone sensitivity profiles: 1) insensitive (no increase in mood symptoms with weekly change in hormone); 2) withdrawal sensitive (increased mood symptom severity with *decreases* in hormone change from the previous week); 3) increase sensitive (increased mood severity with *increased* hormone change); and 4) change sensitive (increased mood severity with large changes in hormone, regardless of direction) (Andersen et al. 2022). The identification of these different hormone sensitivity profiles highlights the importance of assessing within-person hormone variability in determining mood and hormone relationships.

**Life stress exposure and HPA axis dysfunction—**Along with profound physical developmental changes, the pubertal transition is characterized by elevated life stress exposure (Spear, 2009). The impact of life stress is especially relevant during critical developmental windows characterized by dramatic neurodevelopment, including childhood and adolescence (Blakemore, 2008). Exposure to life stress during these early developmental periods has been shown to modify biological stress response systems (i.e., HPA axis), and is associated with sustained alterations in brain function, behavior and cognition (Lupien et al., 2009). As such, dysregulation of the HPA axis can have long-term consequences and increase the risk for psychological disorders (De Carvalho Tofoli et al., 2011). The deleterious effect of stress may be even more pronounced for adolescents who experience earlier pubertal maturation relative to their peers (i.e., early pubertal timing)(Hamlat et al., 2014). African American or Black and Latino/Latina adolescents, youth from lower socioeconomic contexts (James-Todd et al., 2010), and those exposed to early life adversity (Colich & McLaughlin, 2022) are disproportionately more likely to experience early pubertal timing (Colich and McLaughlin 2022). Therefore, social context and diversity may converge with the unique reproductive endocrine features of puberty to promote greater risk of psychopathology during the pubertal transition (Mendle et al., 2019).

Although null findings exist (Meadows et al., 2006), a number of studies report increased stress exposure for female compared to male adolescents (Ge et al., 1994, 2001). This applies particularly to interpersonal stress (Hankin et al., 2007), possibly due to social gender roles (McLeod & Kessler, 1990; Turner et al., 1995). Female adolescents also experience increased rates of severe stressful life events, including physical and sexual abuse, which also contributes to long-term modifications in stress reactivity (LeMoult et al., 2015, 2020). Exposure to stressful life events is strongly associated with an increased risk

of affective disorders, including depression (Hammen, 2005; Monroe & Reid, 2008; Paykel, 2003). The association of stress exposure and depression has been shown to be stronger in female adolescents compared to male adolescents (Ge et al., 1994; Shih et al., 2006). Further, stressful life events proximal to reproductive transition events have been shown to be strong predictors of the emergence of reproductive mood disorders (Bromberger et al., 2011). As such, in initially euthymic perimenopausal women, the number of recent stressful life events in combination with greater estradiol variability over the menopause transition predicted the emergence of depression (Gordon et al. 2016). However, this relationship between hormone fluctuation and affective state change is poorly understood during the pubertal transition, which shares many parallels with the menopause transition and is similarly characterized by substantial reproductive hormone flux and heightened life stress.

### 1.2 Aims of the current study

The present study employed a longitudinal, dimensional approach to examine within-person relationships between life stress, weekly changes in sex hormones (estrone, testosterone, DHEA) and affective state change in peripubertal female adolescents. The present study tests a novel diathesis-stress model of adolescent depression in which we propose that life stress modifies the brain's sensitivity to hormone fluctuation and precipitates vulnerability (i.e., a diathesis) to depressive symptoms in the presence of normal peripubertal hormone flux (i.e., an acute hormonal stressor). The rationale for examining stress-related hormone sensitivity as a diathesis for affective symptoms is twofold. First, sensitivity to hormonal flux during specific reproductive events has been shown to trigger affective symptoms in women who are more susceptible to stress and, second, sex hormones are powerful neuroregulators of frontal and limbic neural networks (Ottowitz et al., 2008) and the HPA stress axis, each of which is implicated in depression (Pandya et al., 2012). Specifically, the present analysis examines recent life stress as a moderator of the relationship between weekly hormone deviations and specific affective symptom constructs (e.g., interpersonal depressive symptoms, low positive affect, somatic symptoms) (Figure 1). The initial investigation of peripubertal hormone and mood relationships was restricted to general dysphoric mood and did not examine hormone-induced changes in distinct symptom domains (i.e., anxiety, irritability, etc.). This additional decomposition of affective symptoms is warranted given that previously reported hormone-related mood disturbances are symptom and hormone specific (Eisenlohr-Moul et al. 2016; Schiller et al. 2022; Schmidt et al. 1998). Consistent with hormone-mood relationships observed in other female reproductive transitions (i.e., premenstrual phase, perimenopause), weekly deviations in hormones (estrone, testosterone, DHEA) in the context of high life stress were expected to be associated with greater depressive symptoms and distress.

## 2. METHODS

### 2.1. Participants

35 participants assigned female at birth, between the ages of 11 and 14, and who were undergoing a healthy pubertal transition were recruited from the local community using flyers, mass emails to university staff and students, word-of-mouth, and online posts on middle school parent sites. The protocol was approved by the local Institutional Review

Board and was conducted in accordance with the Declaration of Helsinki. Parents provided written consent and adolescent participants provided written assent to be involved in the study. Participants received a $150.00 Visa gift card for full compliance.

## 2.2 Procedure

The study was conducted between 2018 and 2020, and consisted of three phases, including 1) screening, 2) enrollment, and 3) weekly hormone and mood measurements, described in more detail below and in Andersen et al. (2022). Participants included in the present analysis were a subsample of a larger study ($n$=52) who all had weekly (vs. daily) mood assessments and morning (vs. afternoon) salivary hormone collections. The present analysis with this subsample ($n$=35) permitted the investigation of life stress and its effect on hormone-related changes in distinct symptom constructs of depression with refined collection parameters.

**2.2.1 Screening—**Parents of interested participants completed an online screening form to assess eligibility. Participants were recruited based on parental and self-reported pubertal stage (Tanner Stage 3 or 4, breast development and pubic hair growth started, but not complete - as assessed by the Pubertal Development Scale (PDS) at screening and enrollment) and were premenarchal or within one-year post-menarche. Non-English speakers and participants with psychotic or bipolar disorders, active suicidal ideation, or severe symptoms that would interfere with participation were excluded. To obtain a wide range and adequate variance of depressive symptoms, current self-reported clinical diagnoses of depression or anxiety were permitted if no suicidal ideation, and no symptoms of psychosis or mania were reported at enrollment. Participants did not use hormonal agents or contraceptives, or mood-altering medications (e.g., antidepressants). If eligible, the screening was followed by a phone call with the parent to discuss the specifics of the study procedure and confirm eligibility before scheduling the enrollment session.

**2.2.2 Enrollment—**At enrollment, participants and their parents completed questionnaires assessing personal and family medical history, including self-reported clinical diagnoses, demographic characteristics, mood, stressful life events, and pubertal stage. An abbreviated Structured Clinical Interview for DSM-V (SCID) was administered to screen for psychosis symptoms or bipolar disorder. Height and weight measurements were collected to calculate age-corrected BMI according to Centers for Disease Control and Prevention guidelines, as BMI consistently increases with pubertal maturation (Bini et al., 2000). Parental reports of highest educational attainment and total household income were collected and assessed as indicators of socioeconomic status. Participants and their parents were instructed on best practices for collecting saliva samples and were given clearly labeled collection vials.

**2.2.3 Weekly hormone and mood assessments—**Following the enrollment session, participants completed eight consecutive weeks of saliva and mood assessments. Using the unstimulated passive drool technique, participants provided 3mL of saliva into cryovials immediately upon awakening to capture the expected peak hormone levels for 8 consecutive weeks (Hucklebridge et al., 2005; Janfaza et al., 2006; Kuzawa et al., 2016). To prevent contamination and dilution, participants were instructed not to visit the dentist

within two days before the next collection, refrain from drinking (water included) and brushing their teeth thirty minutes prior to their collection, and refrain from eating one hour before the collection. Saliva samples were immediately placed in the participant's home freezer before being transferred to a −80°C laboratory freezer every 1–3 weeks. Weekly compliance checks were completed along with the surveys to determine if there were any changes in activity level, diet, sleep, or medication use prior to the saliva collection.

## 2.3 Measures

**2.3.1 Enrollment assessments—**Pubertal Development was self-reported using a combination of the Pubertal Development Scale *(PDS;* Petersen et al., 1988) and Tanner line staging, in which participants selected line drawings of breast development and pubic hair growth that best matched their own (Taylor et al., 2001). Line drawings corresponded to Tanner stage criteria, with 1 indicating no development ("breasts are flat"; "no hair") and 5 indicating complete development ("only the nipple sticks out beyond the breast"; "hair has spread over the thighs"). Participants rated menarche status, height or growth spurt, breast development, pubic hair growth and appearance of acne on the PDS using a 4-point scale ranging from 1) no development/no menses, 2) barely begun, 3) definitely underway, to 4) completed/menses. The PDS score was calculated as the mean of the five responses. The category PDS score corresponds to the sum of the items pertaining to pubic hair growth, breast development and menarche status, as described previously (Carskadon & Acebo, 1993). Category scores range from 3- prepubertal to 12 post-pubertal. PDS and tanner line staging scores were averaged for breast development and pubic hair growth. Self-reported PDS for female breast and pubic hair development has shown excellent agreement with a physical examination (85% within 1 Tanner stage) (Schmitz et al., 2004) and good reliability (Cronbach's alpha for PDS in the present sample was 0.70).

Recent Stressful Life Events were assessed using a modified version of the Coddington Life Events Scale (CLES) (Coddington, 1972). Participants were asked to indicate whether or not they had experienced any of the 25 stressful experiences listed in the measure in the past year by checking 'yes' or 'no' for each item. Samples items include "death of a family member," "end of romantic relationship," "serious personal injury/illness," "change in acceptance by peers," "move or change in residence," and "parents' divorce." A total score was calculated from the aggregated number of stressful life events that the participant reported. The number of stressful life events (continuous) was standardized using a z-score.

Mood and Feelings Questionnaire *(MFQ;* Costello and Angold 1988) is a 33-item self-report inventory to assess adolescent depressive symptoms. Participants rate how they have been feeling or acting over the past 2 weeks by indicating whether each statement is not true (0), somewhat true (1) or mostly true (2) for them. The total score reflects the sum of the 33 items and ranges from 0 to 68, with larger scores reflecting greater depressive symptoms. Cronbach's alpha for MFQ in the present sample was 0.96.

**2.3.2 Weekly mood assessments—**The Center for Epidemiological Studies Depression Scale for Children (CES-DC) is a 20- item assessment for child and adolescent depressive symptoms (Roberts et al., 1990). Items are scored 0 (not at all) to 3 (a lot) with

4 items reverse coded for a range between 0–60. Cronbach's alpha for all 20 items in the present sample was 0.95. Previous studies on reproductive mood disorders have reported that the psychological relevance of hormone change may be specific to certain symptom domains (Eisenlohr-Moul et al., 2016; Gordon et al., 2019). As such, the current study employed a dimensional approach to elucidate specific mood and hormone relationships. To refine the investigation of depressive symptom domains, four predefined subscales were computed (reviewed in Shafer, 2006), including interpersonal (2 items, α (present sample)=.862), low positive affect (4 items, α (present sample)= .852), depressed affect (7 items, α (present sample)=.932) and somatic symptoms (7 items, α (present sample) =.855).

The Perceived Stress Scale (for children) is a 10-item self-report assessment to evaluate perceived coping and distress associated with stressful situations (Cohen et al., 1983). Items are rated on a 5-point Likert scale from 0 (never) to 4 (very often). Summary scores were calculated after reversing 4 items. Higher scores represent higher subjective stress. Consistent with previous reports, two factors were confirmed in the current sample: a positive-worded factor associated with perceived coping and a negative-worded factor indexing perceived distress (Ezzati et al., 2014; Hewitt et al., 1992) both of which have been found to predict depression symptoms. Correlations among scale items ranged from r=.210 to r=.742, with Cronbach's α=.896 for all 10 items, α=.780 for the coping factor, and α=.889 for the distress factor.

Weekly Subjective Stress Rating. Each week, participants were asked to indicate whether they experienced "any problems" over the last week by checking a box next to relevant items or filling in their own response. The seven items included in the list were: 1) performed poorly on an exam or assignment, 2) received a bad report card, 3) felt overbooked with extracurricular activities, 4) got in a fight with a friend(s), 5) didn't get along with parents, 6) experienced bullying, 7) didn't get along with siblings, and 8) other. They were also asked to enter the most stressful event that happened each week and how stressed it made them feel on a sliding bar from 1 (not very stressful) to 10 (extremely stressful).

### 2.4 Salivary hormone collection and analysis

Salivary samples were assayed at ZRT Laboratory (Beaverton, OR) using liquid chromatography-tandem mass spectrometry (LC-MS/MS) to achieve the most sensitive and accurate quantification of salivary hormones. Average inter-assay precision was 7.27% for estrone, 9.77% for testosterone, and 7.03% for DHEA, with the average intra-assay coefficients of variance as follows: 9.47% for estrone, 4.20% for testosterone, and 7.27% for DHEA. Minimum detection limits were 0.4 pg/mL for estrone, 3.2 pg/mL for testosterone, and 17.1 pg/mL for DHEA. Measurements that fell below assay sensitivity were assigned a value that was one-half the limit of detection. Estrone was selected over estradiol (E2) for the present analyses because estrone rises before E2 during the pubertal transition (Biro et al., 2014) allowing for easier detection, and has been shown to be highly correlated with E2 in previous reports (r=0.80, $p$<.0001) (Andersen et al., 2022). Lower concentrations of E2 are expected in peripubertal females – especially premenarche (Janfaza et al., 2006).

### 2.5 Analytic Plan

**2.5.1 Data coding and preparation—**Analyses were performed in SAS On Demand for Academics. Hormone measurements were centered within-person (CWP) to extract within-person hormone variance (i.e., [hormone level at this sample] – [participant's average hormone level across all samples]). As such, greater values of hormone CWP reflect increased levels relative to a participant's individual mean (Eisenlohr-Moul et al., 2015).

**2.5.2 Weekly hormone and mood relationships—**Separate multilevel models were performed to predict each affective symptom outcome (CES-DC-depressed, CES-DC-interpersonal, CES-DC-low positive affect, CES-DC-somatic, PSS-coping, PSS-distress) from weekly deviations from an individual's average hormone level (DHEA, testosterone, estrone), number of stressful life events (SLE, sample standardized), and all associated interactions. "Week" was specified as a repeated statement to account for serial correlation of weekly hormone and mood assessments, and a random slope within-person was applied with a variance component structure. Null multilevel models (without predictors) were used to calculate the intraclass correlation coefficient (ICC) for each predictor and outcome variable (see Table 1). Given the small sample size, restricted maximum likelihood estimation (REML) was implemented to account for potential biases in random-effect variances and the Kenward-Roger correction was used to address biases in standard error estimation (McNeish & Matta, 2018). Age, race, parental education (as a proxy for socioeconomic status) and BMI did not significantly contribute to the models and were therefore excluded from final analyses.

The effect of stress was further probed by calculating the simple slopes of hormone (CWP) at various levels of stress for each combination of symptom and hormone pair. The simple slopes were calculated from three levels of SLE: mean SLE = 5.029, mean SLE + standard deviation (sd) = 7.578, and mean SLE − sd = 2.479.

**2.5.3 Power Analysis—**With 35 participants that completed CES-DC ratings and hormone collections, the current study had 86% power with $\alpha$=0.05 to detect small effects ($f$=0.15) of within-person weekly hormone and mood associations (8 repeated measures with 0.50 correlation).

## 3 RESULTS

### 3.1 Descriptive information

Demographic and sample characteristics are presented in Table 1. 35 participants (mean age =12.48, SD=1.01) provided weekly mood ratings and salivary hormone samples. The majority of participants identified as White (74.3%), with 11.4% identifying as multiracial, 11.4% as Hispanic/Latino or Spanish, and 2.9% Black. Participants' parents were highly educated (graduated or postgraduate) and were affluent middle to upper class, representative of the local community. Participants were self-reported mid-puberty (PDS category score: mean = 8.33, SD = 2.30), with 51.4% (18/35) of the sample pre-menarche and 48.6% (17/35) of participants post-menarche within one year. Pictorial rating of breast (mean = 3.23, SD = 0.69) and pubic hair development (mean = 2.94, SD = 0.87) subjectively

confirmed peripubertal status. One participant identified as male. Pubertal status, BMI, MFQ, number of stressful life events and average estrone, testosterone and DHEA levels did not differ by race or ethnicity, nor were these variables associated with parental education (as a proxy for socioeconomic status). Pubertal status was correlated with BMI ($r_S$=.484, $p$=.004), and associated with greater estrone ($r_S$=.535, $p$=.001), testosterone ($r_S$=.477, $p$=.004) and DHEA ($r_S$=.398, $p$=.018) levels.

The frequency of stressful life events ranged from 2 to 11 events, with an average of 5.03 (SD = 2.55). As expected, there was a wide range of depressive symptom severity reported on the mood and feelings questionnaire, ranging from 0 to 53 (mean=14.43, SD=13.31, a score of 29 or above is considered clinically significant (Burleson Daviss et al., 2006)), with increased symptom severity associated with a greater number of stressful life events ($r_S$=.385, $p$=.022). Further, more stressful life events were related to higher DHEA levels ($r_S$=.380, p=.024). The most frequently experienced weekly stress was associated with academic performance (26.84%), followed by conflicts with parents (16.67%) and “other” (16.67%). Descriptions of “other” included being excluded from a sleepover, feeling jealous, not getting enough sleep, getting braces, a sick pet, etc. There were no major life events reported during the 8-week collection period.

Study adherence was high, with only 13 weekly surveys missed (4.6%, 267/280) and 5 saliva samples missed (1.8%, 275/280) across all participants. Estrone and testosterone were below the limit of detection in 4% (E1:12/275; T:10/275) of the samples, and DHEA was undetectable in 2% (6/275) of the samples collected.

### 3.2 Intraclass correlations of repeated hormones and outcomes

Intraclass correlations indicated that the majority of the variance in symptoms could be attributed to stable between-person differences (trait-like; ICCs between 0.58 and 0.77). Variability in estrone was primarily at the within-person level (ICC=0.36), whereas 64% of testosterone and 54% of DHEA variance was trait-like (Table 1).

### 3.3 Interactive effects of stressful life events and hormone change on symptoms

Results of models examining the moderating role of stressful life events on the association between within-person deviations in hormones (CWP) and symptom expression for all outcomes are reported in Table 2. *P*-values presented in Table 2 are FDR corrected and Cohen’s $f^2$ was calculated for mixed-effects models using recommendations proposed by Selya et al. 2012.

#### 3.3.1 Stressful life events and within-person weekly hormone deviations

**Estrone.:** Stressful life events interacted with estrone CWP to predict somatic ($F(1,230)=6.32$, $p$=.013), interpersonal ($F(1,230)=6.78$, $p$=.01), and depressed affect ($F(1,230)=5.62$, $p$=.019) symptoms. Specifically, within-person elevations of estrone predicted greater somatic ($t(230.2) = 2.67$, $p$=0.008) and interpersonal ($t(230.1) = 2.31$, $p$=0.022) symptoms in the context of high stress (SLE+sd), and lower-than-usual estrone predicted greater depressed affect ($t(230.1) = -2.14$, $p$=0.033) at low stress (SLE-sd).

**Testosterone.:** Within-person deviations in testosterone interacted with stressful life events to predict somatic (F(1,230)=9.16, $p$=.003), depressed affect (F(1,230)=11.81, $p$=.001), and perceived distress (F(1,230)=15.74, $p$<.001) symptoms. Probing the impact of stress revealed differential effects of within-person deviations in testosterone on somatic symptoms and perceived distress, with higher-than-usual testosterone predicting greater symptoms at high stress (somatic: $t$(230.2) = 2.65, $p$=0.009; distress: $t$(230.2) = 3.04, $p$=0.003), and lower-than-usual testosterone predicting greater symptoms at low stress (somatic: $t$(230.1) = −2.11, $p$=0.036; distress: $t$(230.2) = −3.12, $p$=0.002) (Figure 2b, 2c). Additionally, low ($t$(230.1) = −4.05, $p$<0.001) to average ($t$(230.1) = −2.72, $p$=0.007) stress was associated with greater depressed affect following lower-than-usual testosterone.

**DHEA.:** DHEA CWP interacted with stressful life events to predict somatic (F(1,230)=8.88, $p$=.003), low positive affect (F(1,230)=5.05, $p$=.026), depressed affect (F(1,230)=7.90, $p$=.005), interpersonal symptoms (F(1,230)=6.75, $p$=.010), and perceived distress (F(1,230)=6.02, $p$=.015). A similar pattern of stress-hormone interactions was found for DHEA, with higher-than-usual DHEA predicting greater depressed affect symptoms at high stress ($t$(230.3) = 2.04, $p$=0.042), and lower-than-usual DHEA predicting greater symptoms at low stress ($t$(230.1) = −1.98, $p$=0.049) (Figure 2a). At high stress, within-person elevations in DHEA predicted increased symptom ratings for low positive affect ($t$(230.3) = 2.31, $p$=0.022), interpersonal symptoms ($t$(230.3) = 3.00, $p$=0.003), perceived distress ($t$(230.5) = 2.84, $p$=0.005), and somatic symptoms ($t$(230.3) = 4.43, $p$<0.001; average: $t$(230.1) = 2.83, $p$=0.005).

# 4. DISCUSSION

## 4.1 Summary of results

The present study used a dimensional approach with weekly measures of sex hormones and depressive symptom ratings to determine the role of recent stressful life events in modifying the relationship between hormone flux and depressive symptoms in peripubertal females. Weekly hormone (estrone, testosterone, and DHEA) deviations predicted differential changes in key constructs of adolescent depression and perceived stress. Results indicated that stress exposure provides a context that unmasks directional effects of hormone flux on affect state change in peripubertal females. Specifically, a consistent pattern emerged with within-person elevations in hormones predicting greater affective symptoms in high stress and decreases in hormones predicting greater symptom severity in low stress contexts. Stress-related hormone effects on affective symptoms appear to be hormone-specific. Namely, DHEA interacted with stressful life events to broadly impact symptom expression, whereas estrone and testosterone had more restricted effects on affective symptoms. The present study supports a diathesis-stress model of adolescent depression in which exposure to life stress proximal to the pubertal transition modifies vulnerable neural networks, making them more sensitive to normal peripubertal hormone flux, which in turn, promotes the emergence of adolescent mood dysregulation and affective illness.

### 4.2 DHEA deviations predicted a range of depressive symptoms

DHEA interacted with stressful life events to predict all symptom outcomes except perceived coping ability, and higher levels of DHEA were associated with a greater number of stressful life events. DHEA and cortisol are both products of the HPA stress axis that begin to rise with adrenarche and progressively increase during the pubertal transition, and exert opposing physiological actions (Kamin & Kertes, 2017). Because of DHEA's reported antagonistic effects on glucocorticoids (i.e., cortisol), the preferential production of DHEA over cortisol is thought to buffer against stress-related mood impairment (Karishma & Herbert, 2002). At low stress, elevated DHEA in the present study predicted less severe symptom ratings, particularly depressed affect. This is consistent with previous reports that DHEA has antidepressant-like effects, with administration of DHEA improving depressive symptoms by over 50% in patients with midlife-onset depression (Schmidt et al., 2005). More recently, DHEA administration was found to reduce amygdala and hippocampus engagement and enhance limbic connectivity during an emotion regulation paradigm, which in turn, was associated with improved negative effect (Sripada et al., 2013). However, at high stress in the present analyses, higher-than-usual DHEA predicted greater symptom expression, including somatic and interpersonal symptoms, depressed and low positive affect, and perceived distress. The greater symptom expression with DHEA elevations in the high stress context resembles the higher DHEA levels in response to acute stress (Dutheil et al., 2021), also observed among adolescents with affective symptoms (Shirtcliff et al., 2007). Given DHEA's antiglucocorticoid properties, DHEA may be protective against the deleterious effects of cortisol during the pubertal transition, which is characterized by heightened stress exposure (Flinn et al. 2011). DHEA relative to other hormones, including cortisol, could be investigated in future studies to advance our understanding of stress-related mood sensitivity to peripubertal DHEA changes.

### 4.3 Estrone deviations predicted depressed affect, somatic and interpersonal symptoms of depression

The interaction of estrone and stressful life events predicted somatic symptoms, depressed affect, and interpersonal depression symptoms. When probing the effects of different levels of stress, estrone surges were associated with increased interpersonal and somatic symptoms at high stress and decreased depressed affect at low stress. The relevance of estrogen fluctuations and interpersonal symptoms has also been reported in the menopausal transition (Gordon et al. 2016), similarly characterized by substantial ovarian hormone flux and heightened stress exposure. In fact, estradiol variability was found to predict greater sensitivity to rejection during psychosocial stress in perimenopausal women. Moreover, in women who had experienced a greater number of recent stressful life events, rejection sensitivity predicted the emergence of depression symptoms one year later (Gordon et al. 2016). Importantly, rejection sensitivity is a proximal risk factor for clinical depression and transdiagnostic factor shared across psychopathologies (Kupferberg, Bicks, and Hasler 2016; Owens et al. 2018; Slavich and Irwin 2014, Slavich et al. 2010). The results of the present study further support the pathophysiologic relevance of estrogens, specifically estrone, in the interpersonal symptoms of depression, and for the first time, demonstrated a relationship between estrone change and increased interpersonal depressive symptoms

during the pubertal transition. The specificity of symptoms highlights the importance of conducting dimensional, symptom-specific research.

### 4.4 Divergent effect of testosterone-related affect dysregulation in the context of stress

The stress context created a divergence in testosterone-related affective symptoms, particularly for somatic symptoms and perceived distress. Participants exhibited increased symptoms with lower-than-usual testosterone levels at low stress, yet testosterone elevations were associated with increased symptoms at high stress. The role of testosterone in depression has been investigated particularly in regard to pharmacological use (with testosterone treatment showing antidepressant effects) and primarily in male samples (Zarrouf et al., 2009). In adolescents, and especially female adolescents, the relationship between depression and testosterone is understudied. One previous longitudinal study investigated 630 female participants annually through adolescence for up to seven years (Copeland et al., 2019). Higher serum testosterone concentrations predicted diagnoses of depressive disorders significantly, even after controlling for factors such as pubertal status or age. Moreover, testosterone has been shown to have puberty-unique influences on neurofunction and neuroarchitecture in brain regions associated with the development of affective disorders (Bramen et al., 2012). We recently demonstrated that a significant proportion of female adolescents showed meaningful associations between fluctuations of testosterone and mood (Andersen et al. 2022). The results reported here take these investigations one step further and highlight the essential role of stressful life events on the testosterone-mood relationship. However, the biological mechanisms contributing to the interaction of life stress and mood sensitivity to testosterone flux have yet to be identified. Research on other sex steroids, such as progesterone, suggest that dysregulated receptor functioning can cause hormone sensitivity and HPA axis dysregulation in some individuals (as reviewed for progesterone by Gordon et al. 2015). Future research could explore this as a potential mechanism underlying sensitivity to testosterone flux.

### 4.5 The impact of stressful life events on hormone-induced affective symptoms

The results not only support the interaction of sex hormones and mood in the pubertal transition, but they also suggest that life stress exposure has an essential moderating effect on this interaction. One theory suggests that this moderation is biologically underpinned by dysregulation of the HPA axis. Early and chronic life stress can alter HPA axis functioning with long-term effects on mental health (Ho & King, 2021). These HPA axis alterations have been specifically demonstrated for severe forms of life stress in the form of trauma exposure (Steudte-Schmiedgen et al., 2016) and for life stress experienced early in life, which is especially relevant to adolescents (Young et al., 2021). The pubertal transition is a unique window of vulnerability to the impact of stress-related mood impairment and contributes to differential stress responses following early life stress (Flannery et al., 2017; King et al., 2017; Nelson & Gabard-Durnam, 2020; Sisk & Gee, 2022). The HPA and HPG axes interact on various levels to regulate sex steroids, and in turn, sex steroids modulate HPA function (Oyola & Handa, 2017). Changes in HPA activity during adolescence [possibly through estrogen modifications of the GABAergic system in the amygdala (Walker et al., 2004)] may contribute to hormonal sensitivity and precipitate depressive symptoms in susceptible individuals. Results from the present study suggest that experiencing a greater

number of stressful life events proximal to the pubertal transition can modify hormone-mood relationships. However, the positive relationship between stressful life events and depressive symptoms at enrollment in the present study suggest that greater depressive symptoms at enrollment could have influenced the report of stressful life events, particularly stressful events that are more subjective (e.g., change in acceptance by peers). Consequently, it remains unclear whether the type or severity of stressor within the context of baseline depressive symptoms differentially impacts hormone-related mood dysregulation.

In summary, early life stress, via modifications of developing neural circuitry, may give rise to hormone sensitivity, thus enhancing vulnerability for affective symptoms in the context of normal peripubertal hormone fluctuations. Stress related alterations of HPA functioning and the strong interaction of HPA and HPG axes may underlie the relationship between sex hormone fluctuation and mood. However, the neurophysiological mechanisms supporting this relationship are poorly understood and remains a promising pursuit of future research.

### 4.6 Limitations

Despite the strengths of the longitudinal, dimensional approach employed in the current study, there are several limitations to address. While serum hormone measurement is typically preferred to saliva methods because of its greater detection sensitivity, salivary hormone collections offer a non-invasive alternative with superior feasibility and compliance in adolescent participants. Given the current study's objective to determine the relationship between hormone change and mood does not require the ability to detect the absolute lowest hormone level, the trade-off between ultra-low sensitivity and feasibility is appropriate. To account for potential confounds in saliva hormone measurement (time of day, food and water intake, etc.), we provided participants and their parents with detailed instructions and required sample collection to occur first thing upon awakening. Furthermore, steroid concentrations measured in saliva provide integrative information on free, unbound estradiol and testosterone and thereby measure the biologically active component of the hormone (Gao et al., 2015; Yasuda et al., 2008). The present study is also limited by the observation interval, which occurred weekly, and the relatively small sample size to examine moderation effects. While weekly observations may be sufficient to demonstrate how hormone flux can influence depressive symptoms from week to week (Gordon et al. 2016, 2020; Lozza-Fiacco et al. 2022), daily measures may more precisely asses hormone flux and should be considered in future studies.

For the same reasons that make the pubertal transition a critical developmental window for examining the impact of hormones on mental illness trajectories, the peripubertal endocrine environment is associated with unique study design challenges. It is difficult to study specific hormones of interest, particularly progesterone and its metabolites, because of the limited sensitivity of the available analysis methods for the relatively low levels expected during the first gynecological year. While valuable guidelines exist for determining ovulation status and cycle phasing in adult participants (Schmalenberger et al., 2021), these recommendations have only limited utility for identifying menstrual cycle phase and ovulation status in peripubertal participants, in which anovulatory and irregular cycles are common (Carlson and Shaw 2019; Sharma, Deuja, and Saha 2016). Typical hormone

thresholds (i.e., progesterone rise, LH peak) for determining cycle phase in adults are not applicable because of overall lower peripubertal hormone concentrations, and counting methods are not relevant when shorter luteal phases are expected (Carlson and Shaw 2019; Sun et al. 2019). Currently, there are no clear guidelines for determining ovulation status and cycle phasing during the first gynecological year, and thus, the impact of the menstrual cycle on hormone-mood relationships during the pubertal transition remains an important area of investigation.

### 4.7 Future Directions

Future research is needed to examine the neurobiological mechanisms underlying the relationship between hormone change, stress and depressive symptoms. Because sex hormones (e.g., estradiol, testosterone) influence the regulation of the HPA stress system and the abundance of sex hormone receptors in limbic brain regions engaged during emotion, the probability exists that the HPA stress response may mediate the hormone-mood relationship. Moreover, the biological mechanisms supporting the relationship between psychopathology and sex-hormones (i.e., DHEA and testosterone) and their fluctuation are poorly understood – not only in adolescents but across the female reproductive lifespan and should be a focus of future studies to close these existing research gaps.

The results from the present study confirm and further highlight the need to include stress exposure in studies linking sex hormones and affective symptoms. As shown in trauma research (Forbes et al., 2013; López-Martínez et al., 2018), not only the absolute number of stressful life events, but also the type of stressor is a promising factor to investigate (McLaughlin et al., 2021). Results also highlight the importance of using a dimensional approach. Limiting the investigation to total depression symptom scores could dilute or mask significant effects only apparent on the symptom level. Accordingly, we recommend future studies similarly employ a dimensional and symptom-specific approach to investigate key constructs of depression in adolescents. This dimensional approach will also allow more specific exploration of the neurobiological mechanisms underlying the etiology of affective illness. Finally, the current results provide a foundation for understanding the impact of life stress on hormone-mood relationships in a low-risk sample reflecting the socioeconomic, racial and ethnic composition of the local community. A larger and more diverse sample of adolescents could, for instance, be employed to elucidate unique psychosocial and neuroendocrine features of the pubertal transition experienced by participants who identify differently from their sex assigned at birth. Including a wide range of depressive symptoms was not only important to achieve adequate variability, but it also allowed for greater generalizability of a developmental window in which elevated stress and depression are common. That said, the diathesis model tested in the present analyses could inform future investigations of the biological, social, environmental, and cultural factors that converge to make the pubertal transition a unique window of vulnerability for psychopathology.

### 4.8 Conclusion

The present study contributes to our understanding of peripubertal hormone-mood relationships by demonstrating that life stress differentially impacts hormone-related changes in distinct symptom constructs of depression. This study reveals how life stress

predisposes sensitivity to hormone fluctuation in peripubertal female adolescents, ultimately resulting in depressive symptoms in response to normative hormone flux. Results indicated that sensitivity to within-person deviations in DHEA, testosterone and estrone predict affective symptoms, and that mood-sensitivity to weekly hormone deviations is stress context specific. Given the role of sex hormones in regulating neural networks involved in cognitive and emotional processing, the combination of increased sex hormones and their variability during the pubertal transition and more frequent stress exposure may promote heightened emotional reactivity and arousal and thus, promote greater risk for psychopathology. The impact of stressful life events on the unique peripubertal neuroendocrine environment should continue to be investigated to inform advancements in the early detection and intervention of affective illness.

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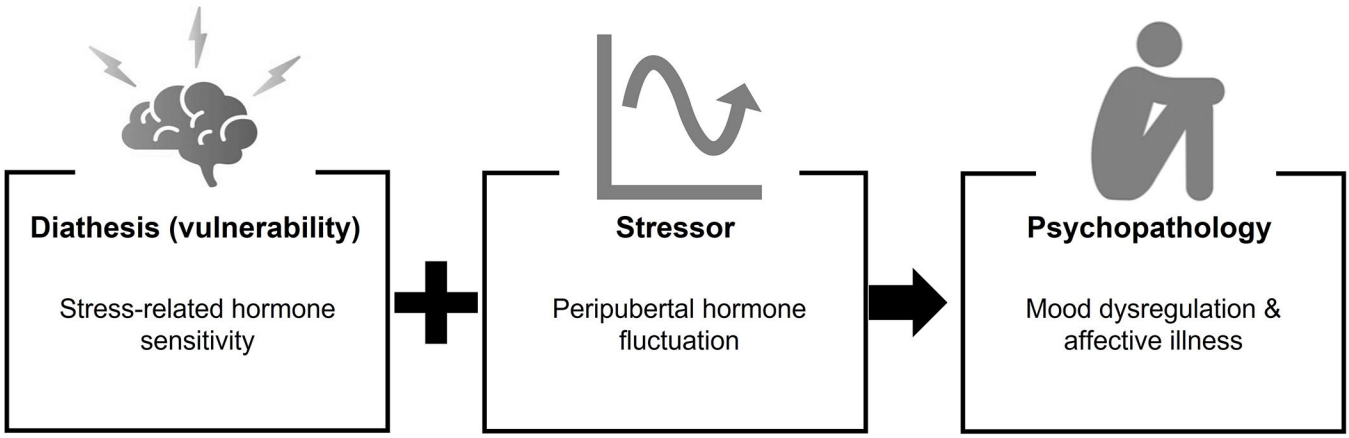


**Figure 1. Diathesis-Stress Model of Hormone-Related Mood Dysregulation and Affective Illness.**
Illustration of the proposed model in which life stress modifies the brain's sensitivity to hormone fluctuation and precipitates vulnerability (i.e., a diathesis) to depressive symptoms in the presence of normal peripubertal hormone flux (i.e., an acute hormonal stressor).

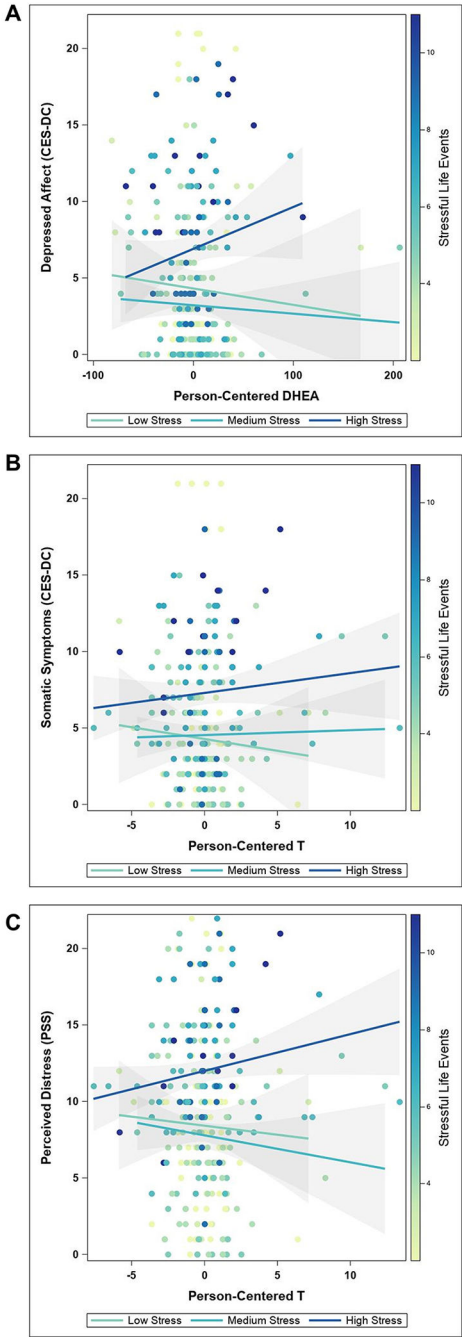


**Figure 2. Stress unmasks differential effects of within-person hormone deviations on affective symptoms.**

The stress context created a divergence in DHEA-related depressed affect (a) and testosterone-related somatic symptoms (b) and perceived distress (c). Stressful life events are presented as a gradient (with a low number of events indicated by yellow and a high number of events represented by dark blue colors). The regression lines represent tertile groups with 90% confidence intervals. DHEA: dehydroepiandrosterone, CES-DC: Center for Epidemiological Studies Depression Scale for Children, PSS: perceived stress scale.

**Table 1.**

Demographic and Sample Characteristics

| | N | Range (min - max) | Mean ± SD |
|---|---|---|---|
| Age (months) | | 132 – 176 | 149.77 ± 12.11 |
| Race | | | |
| *White* | 26 (74.3%) | | |
| *Black or African American* | 1 (2.9 %) | | |
| *Multiracial* | 4 (11.4%) | | |
| *Hispanic/Latino/Spanish* | 4 (11.4%) | | |
| BMI (z-score) | | −1.73 – 3.31 | −0.021 ± 1.09 |
| Female Gender Identity | 34 (97.1%) | | |
| Identify as LGBTQIA+ | | | |
| *No* | 29 (82.8%) | | |
| *Yes* | 3 (8.6%) | | |
| *No response* | 3 (8.6%) | | |
| Pubertal Development Score | | 1.8 – 3.8 | 2.66 ± 0.63 |
| PDS (avg) category score | | 5 – 12.5 | 8.33 ± 2.30 |
| Menarche status | 17 (48.6%) | | |
| Breast (pictorial score) | | 2 – 5 | 3.23 ± 0.69 |
| Pubic hair (pictorial score) | | 1 – 5 | 2.94 ± 0.87 |
| Stressful Life Events | | 2 – 11 | 5.03 ± 2.55 |
| Mood & Feelings | | 0 – 53 | 14.43 ± 13.32 |
| Parental Education (%) | | 4.5 – 7 | 6.26 ± 0.68 |
| High School Diploma | 0 | | |
| >4 Years of College | 5 (14.28%) | | |
| 4-Year College Degree | 15 (42.86%) | | |
| Professional Degree | 15 (42.86%) | | |
| Household Income | | | |
| <$30,000 | 1 (2.86%) | | |
| $30,000 – $70,000 | 1 (2.86%) | | |
| $70,000 – $100,000 | 6 (17.14%) | | |

| | N | Range (min - max) | Mean ± SD |
|---|---|---|---|
| $101,000 – $150,000 | 12 (34.29%) | | |
| $150,000+ | 15 (42.86%) | | |
| | **ICC** | **Range (min-max)** | **Mean ± SD** |
| **Weekly Self Report** | | | |
| CES-DC-interpersonal | 0.704 | 0 – 6 | 1.28 ± 1.73 |
| CES-DC-depressed | 0.760 | 0 – 18 | 4.14 ± 4.68 |
| CES-DC-somatic | 0.774 | 0 – 24 | 6.00 ± 5.62 |
| CES-DC-low positive affect | 0.770 | 0 – 12 | 3.81 ± 3.06 |
| PSS-coping | 0.581 | 0 – 14 | 6.02 ± 2.86 |
| PSS-distress | 0.652 | 0 – 22 | 9.38 ± 5.34 |
| **Hormones** | | | |
| Estrone | 0.364 | 0.20 ± 4.20 | 1.10 ± 0.68 |
| Testosterone | 0.638 | 1.50 ± 30.00 | 6.89 ± 4.28 |
| DHEA | 0.537 | 8.50 ± 319.00 | 77.68 ± 47.12 |

*Note. Means are presented ± standard deviation.* BMI: body mass index, LGBTQIA+: lesbian, gay, bisexual, transgender, queer, intersex, asexual and more, PDS: Pubertal Development Scale average category score (averaged PDS and tanner line staging score for breast development and pubic hair growth), Primary parent completed education level, CES-DC: Center for Epidemiological Studies Depression Scale for Children, PSS: Perceived Stress Scale, DHEA: dehydroepiandrosterone.

**Table 2.**

Fixed effects of stressful life events, within-person hormone deviations, and their interactions on symptoms.

| Parameter | Weekly CES-DC score: Somatic | | | | Low positive affect | | | | Depressed affect | | | | Interpersonal | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Model: E1 × SLE** | Est. | (SE) | *p* | $f^2$ | Est. | (SE) | *p* | $f^2$ | Est. | (SE) | *p* | $f^2$ | Est. | (SE) | *p* | $f^2$ |
| Intercept | 5.454 | 0.686 | <.0001 | | 3.838 | 0.445 | <.0001 | | 4.783 | 0.777 | <.0001 | | 1.277 | 0.246 | <.0001 | |
| zSLE | 1.725 | 0.701 | 0.019 | | 1.033 | 0.454 | 0.030 | | 1.816 | 0.794 | 0.029 | | 0.498 | 0.251 | 0.055 | |
| $E1_{CWP}$ | 0.396 | 0.290 | 0.172 | | 0.190 | 0.179 | 0.289 | | −0.115 | 0.304 | 0.706 | | 0.076 | 0.113 | 0.499 | |
| $zSLE*E1_{CWP}$ | 0.848 | 0.337 | 0.028 * | 0.119 | 0.155 | 0.208 | 0.482 * | 0.091 | 0.838 | 0.354 | 0.036 * | 0.103 | 0.342 | 0.132 | 0.026 * | 0.069 |
| **Model: T × SLE** | | | | | | | | | | | | | | | | |
| Intercept | 5.456 | 0.686 | <.0001 | | 3.839 | 0.445 | <.0001 | | 4.786 | 0.777 | <.0001 | | 1.277 | 0.246 | <.0001 | |
| zSLE | 1.721 | 0.701 | 0.019 | | 1.031 | 0.454 | 0.030 | | 1.812 | 0.793 | 0.029 | | 0.498 | 0.251 | 0.055 | |
| $T_{CWP}$ | 0.005 | 0.060 | 0.932 | | 0.005 | 0.037 | 0.888 | | −0.171 | 0.062 | 0.007 | | 0.022 | 0.024 | 0.360 | |
| $zSLE*T_{CWP}$ | 0.226 | 0.075 | 0.014 * | 0.122 | 0.086 | 0.046 | 0.091 * | 0.094 | 0.264 | 0.077 | 0.006 * | 0.111 | 0.054 | 0.029 | 0.091 * | 0.065 |
| **Model: DHEA × SLE** | | | | | | | | | | | | | | | | |
| Intercept | 5.446 | 0.686 | <.0001 | | 3.835 | 0.445 | <.0001 | | 4.774 | 0.777 | <.0001 | | 1.274 | 0.245 | <.0001 | |
| zSLE | 1.701 | 0.700 | 0.021 | | 1.023 | 0.454 | 0.031 | | 1.801 | 0.794 | 0.030 | | 0.492 | 0.250 | 0.058 | |
| $DHEA_{CWP}$ | 0.014 | 0.005 | 0.005 | | 0.002 | 0.003 | 0.449 | | −0.001 | 0.005 | 0.864 | | 0.003 | 0.002 | 0.193 | |
| $zSLE* DHEA_{CWP}$ | 0.015 | 0.005 | 0.014 * | 0.121 | 0.007 | 0.003 | 0.042 * | 0.095 | 0.015 | 0.005 | 0.019 * | 0.106 | 0.005 | 0.002 | 0.026 * | 0.072 |

| Parameter | Weekly PSS Score: Coping | | | | Distress | | | |
|---|---|---|---|---|---|---|---|---|
| **Model: E1 × SLE** | Est. | (SE) | *p* | $f^2$ | Est. | (SE) | *p* | $f^2$ |
| Intercept | 6.024 | 0.386 | <.0001 | | 9.453 | 0.707 | <.0001 | |
| zSLE | 0.449 | 0.395 | 0.263 | | 1.777 | 0.722 | 0.019 | |
| $E1_{CWP}$ | −0.010 | 0.223 | 0.966 | | 0.690 | 0.375 | 0.067 | |
| $zSLE*E1_{CWP}$ | −0.253 | 0.259 | 0.395 * | 0.013 | 0.775 | 0.437 | 0.099 * | 0.110 |
| **Model: T × SLE** | | | | | | | | |
| Intercept | 6.026 | 0.386 | <.0001 | | 9.458 | 0.707 | <.0001 | |
| zSLE | 0.450 | 0.395 | 0.262 | | 1.767 | 0.722 | 0.002 | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| $T_{CWP}$ | −0.081 | 0.046 | 0.083 | | −0.040 | 0.077 | 0.609 | |
| zSLE*$T_{CWP}$ | −0.030 | 0.057 | 0.595* | 0.013 | 0.377 | 0.095 | .0002* | 0.130 |
| **Model: DHEA × SLE** | | | | | | | | |
| Intercept | 6.023 | 0.386 | <.0001 | | 9.448 | 0.708 | <.0001 | |
| zSLE | 0.448 | 0.394 | 0.264 | | 1.756 | 0.724 | 0.021 | |
| $DHEA_{CWP}$ | −0.006 | 0.004 | 0.109 | | 0.008 | 0.006 | 0.215 | |
| zSLE* $DHEA_{CWP}$ | 0.003 | 0.004 | 0.482* | 0.014 | 0.016 | 0.007 | 0.030* | 0.112 |

*Note: Estimates are presented with standard error (SE) and p value.* SLE: stressful life events, zSLE: standardized stressful life events score, CWP: Centered Within Person, E1: estrone, T: testosterone, DHEA: dehydroepiandrosterone, CES-DC: Center for Epidemiological Studies Depression Scale for Children, PSS: perceived stress scale.

*FDR adjusted p-values