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Psychological resilience and diurnal salivary cortisol in young adulthood

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Abstract

Background: Adversity exposure and the negative psychological responses that often result have been linked with poor physical health outcomes and deteriorative physiological processes, like dysregulated circulating cortisol. Individuals exposed to early adversity who also demonstrate positive psychological functioning may be characterized as psychologically resilient, but few studies have evaluated whether psychological resilience may disrupt the health-damaging effects of adversity. We tested the hypothesis that among young adults exposed to early adversity, those who are psychologically resilient may manifest more normative diurnal cortisol patterns relative to those who experience more psychological distress. Methods: Data are from Growing Up Today Study I participants who provided information on psychological resilience and diurnal salivary cortisol (n=916). Psychological resilience was derived from self-report questionnaires administered between 2007–2010, and salivary cortisol was obtained from saliva samples collected between 2011–2014. The predictor of interest, psychological resilience, was defined using two domains: 1) adversity exposure measured via a count of 7 potential psychosocial

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adversities experienced before age 18, and 2) psychological health in young adulthood measured via a composite score reflecting low psychological distress and high positive affect. The outcome was mean log-transformed diurnal salivary cortisol across 4 samples from one day. Linear regressions evaluated associations of adversity, psychological health, and their potential multiplicative interaction with mean diurnal log-transformed cortisol, adjusting for baseline socio-demographic variables and biological and behavioral factors from the day of saliva sampling.

Results: Relatively few individuals with high adversity demonstrated positive psychological health. Both adversity exposure and psychological health were independently associated with mean log cortisol levels. Models stratified by lower versus higher adversity suggested complex relationships with cortisol, however the interaction between adversity and psychological health was not statistically significant. High adversity was associated with blunted cortisol levels, regardless of psychological health. Conversely, among those with lower adversity, overall levels of cortisol were higher and psychological health associated with more normative, lower cortisol levels.

Conclusions: Psychological resilience domains were independently associated with diurnal salivary cortisol in young adulthood. High burden of early adversity may disrupt the physiological stress system, while psychological health may be associated with more normative cortisol levels when adversity is low.

Keywords

psychological resilience; diurnal cortisol; early adversity; psychological health

1. Introduction

Exposure to early adversity is common. For example, estimates suggest that between 5% and 42% of adults in the United States retrospectively report experiences of child maltreatment, including physical, sexual, and emotional abuse (Hussey et al., 2006). Exposure to other psychosocial adversities, including maternal depression and parental separation, is also prevalent across geographic and sociodemographic strata (Sacks et al., 2014). These adversities may represent assaults on the developmental process, impacting psychological, behavioral, and physical health during youth and into adulthood (Copeland et al., 2018).

Although early adversity increases risk for negative psychological sequelae, there is wide variability in individual response and a large proportion of individuals recover and maintain psychological health (Rutter, 2007). We define psychological resilience as positive psychological functioning among individuals exposed to early life adversity expected to bring about negative psychological sequelae (Bonanno and Diminich, 2013; Luthar et al., 2000). This definition incorporates two relevant domains: 1) exposure to significant adversity, and 2) manifestations of positive psychological health. Adaptation therefore reflects positive psychological health, rather than simply absence of impaired functioning, and considers multiple possible manifestations of psychological distress (e.g., depression, anxiety). Indeed, researchers argue that in the context of adversity, experiencing low psychological distress and having the capacity for positive psychological states are separate but necessary aspects of resilience (Bonanno and Diminich, 2013; Luthar et al., 2000). It

remains unclear whether psychological health following adversity confers protection to other domains, including physiological functioning and physical health.

Early adversity may increase risk for subsequent physical health outcomes by impacting multiple neurobiological processes involving stress physiology, inflammation, epigenetic modifications, and allostatic load (Ehrlich et al., 2016). One key physiological mechanism is hypothalamic-pituitary-adrenal (HPA) axis dysregulation, which has been implicated in multiple disease processes through immune system suppression or alteration of cortisol receptors and metabolism (Miller et al., 2007). While a biological response resulting in increased circulating cortisol is adaptive for acute stress, chronic activation of stress response systems can lead to dysregulation of effective biological feedback loops. In fact, prior research suggests early life adversity leads to HPA axis hyper-reactivity, via frequent and pronounced HPA axis activity damaging hippocampal glucocorticoid receptors (GR) via methylation changes in GR genes and inhibiting negative feedback loops (Holochwost et al., 2021). Such dysregulation typically results in abnormally higher cortisol and hypercortisolism. However, hyporeactivity may also occur, whereby repeated activation can result in HPA habituation, negative feedback hypersensitivity of up-regulated GR receptors, and blunted responses to threat, ultimately resulting in lower cortisol and hypocorticolism (Holochwost et al., 2021; Ehlert, 2013). Dysregulation may also manifest as disruptions in the diurnal rhythm of cortisol, including flattened diurnal slope across the day, or greater variability in mean cortisol levels over time (Adam et al., 2017; Doom et al., 2014). Given this complex relationship between chronic stress and cortisol levels, most researchers have compared diurnal cortisol levels of individuals with versus without stress exposure rather than to pre-specified “unhealthy” levels. Consequently, evidence has demonstrated that chronic stress is associated with dysregulated cortisol levels, visible as either increases or decreases in cortisol output (Ehlert, 2013; Miller et al., 2007). Therefore, compared with healthy controls, either higher or lower average diurnal cortisol may indicate dysregulation and moderate levels may constitute better regulated diurnal levels.

Multiple studies have examined associations between both early adversity and psychological health with salivary cortisol. Somewhat surprisingly, a recent meta-analysis of 54 studies found early life stress was unassociated with multiple cortisol parameters, including mean levels, cortisol awakening response (CAR), and cortisol reactivity (Fogelman & Canli 2018). Estimates were largely unchanged when considering psychiatric symptoms as a covariate. However, some studies suggested that early life stress in conjunction with comorbid depression was associated with higher CAR or heightened cortisol reactivity (Fogelman & Canli 2018) or found early adversity was associated with lower morning cortisol levels, independent of psychological distress (Power et al., 2012, van der Vegt et al., 2009). Failure to find overall associations between adversity with cortisol and mixed findings in studies considering both early adversity and psychological symptoms reflects the complex relationship between stress and HPA axis functioning, which may be altered by time since adversity onset, adversity characteristics, emotions elicited by adversity, and psychological functioning prior to and after adversity (Miller et al., 2007). Moreover, smaller sample sizes and fewer sampling days or observations in this area of study can result in misestimations and misleading results (Segerstrom and Boggero, 2020).

Several studies have hypothesized that resilient individuals would demonstrate better regulated cortisol levels relative to non-resilient individuals. Most research has used self-reported resilience scales that determine individuals' perceived capacity to manage adversity, rather than directly measuring manifested resilience. Studies generally reported mixed findings with higher resilience associated with higher diurnal cortisol assessed with growth curve models (Chi et al., 2015), lower CAR over the first hour of the day (Ruiz-Robledillo et al., 2014), or unassociated with cortisol at 30–45 minutes post waking (Sharpley et al., 2018), with resilience measured using the Connor-Davidson Resilience Scale or the Brief Resilient Coping Scale. These studies are limited by small samples, populations exposed to specific adversities (e.g., caregivers of people with autism spectrum disorder), and self-reported scales that may not capture resilience as the product of life experience – a capacity manifested by positive psychological health among individuals who experienced early adversity. Moreover, differing resilience scales and examination of varied components of diurnal cortisol also limits comparability across studies.

Diurnal cortisol output may represent an important marker of downstream biological dysregulation in less versus more resilient individuals. In the current study, we examined the association of psychological resilience to early adversity with diurnal salivary cortisol in a large community sample of young adults. We characterized psychological resilience according to adversity exposure and subsequent psychological functioning. Prior work has considered extreme adversity (e.g., severe maltreatment among adoptees (van der Vegt et al., 2009)); here, we considered a broader range of adversities indicative of aversive developmental environments, including maltreatment, maternal psychopathology, and parental separation (Dube et al., 2003). Further, we characterized psychological health by lower distress *and* higher positive functioning. We selected covariates that may represent potential confounders (e.g., sex, race/ethnicity) or directly impact salivary cortisol (e.g., body mass index [BMI], smoking). Based on prior work, we also examined effect modification by sex (Bonanno and Diminich, 2013; Kirschbaum et al., 1992).

Although meta-analyses indicate no relationship between early adversity and mean cortisol levels, additional studies that examine early adversity and psychological symptoms concurrently and those assessing resilience scales indicate potential associations between resilience and diurnal cortisol output. Therefore, we hypothesized psychological resilience, indicated by higher adversity exposure and higher psychological health, would be associated with less dysregulated cortisol (i.e., more similar to unexposed individuals with high psychological health) compared to individuals who were less psychologically resilient. Specifically, we hypothesized an interaction effect between the two psychological resilience domains such that those with higher early adversity *and* higher psychological health, compared to lower psychological health, would have less dysregulated cortisol levels (See Supplemental Figure A1).

2. Methods

2.1 Study Design and Sample

Data are from the Growing Up Today Study I (GUTS1), an ongoing longitudinal cohort of 16,882 youth across the United States (Field et al., 1999). Participants are children

of women in the Nurses' Health Study II (NHS2), a separate prospective cohort of over 116,000 female professional nurses enrolled in 1989 (Solomon et al., 1997). In 1996, NHS2 participants with at least one child between 9–14 years of age were contacted to recruit their children into GUTS1. Mothers provided children's names, and invitation letters and baseline questionnaires were sent to all children. Thereafter, GUTS1 participants completed self-report questionnaires that assessed mental, physical, and behavioral factors approximately every 1 to 2 years.

In 2011, a subset of the GUTS1 cohort (aged 24–29 in 2011) who had completed the 2010 biennial questionnaire were invited to participate in a Saliva Substudy (Austin et al., 2016) to assess the stress-related biology of sexual minorities; thus, individuals who self-identified as sexual minorities (e.g., lesbian, gay, bisexual) were oversampled (31.4% of the analytic sample were sexual minorities). Of those invited (n=5,807), 1,602 (27.6%) were considered ineligible due to current pregnancy or pregnancy in the previous six months, past month use of oral or inhaled steroids, or history of cancer treatment or endocrine disorder diagnosis. Among the eligible invited individuals (n=4,205), 1,194 (28.4%) participated by providing salivary samples and completing an additional questionnaire specific to saliva collection between August 2011 and February 2014.

Among the 1,194 participants, 1,019 (85.3%) had complete data on all cortisol assessments. 951 (79.6%) also provided information for psychological resilience on 2007 and 2010 biennial questionnaires; therefore, 2010 was considered baseline for the current analyses. Due to the nature of recruitment, siblings were enrolled in GUTS1; a total of 35 sibling pairs were identified in this subsample, and one of each sibling pair was randomly dropped to eliminate issues of familial clustering. The resulting analytic sample was 916. Compared to the analytic sample, those who completed the 2010 biennial questionnaire but were not in the analytic sample (n=7,772) were more likely to be male, identify as a heterosexual, and be overweight at baseline (all p's<0.05), but did not differ by age, race/ethnicity, or father's educational attainment (all p's>0.05). The study protocol was approved by the Institutional Review Boards of the Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health.

2.2 Measures

2.2.1 Exposure: psychological resilience—Psychological resilience was defined by assessments in two domains: 1) exposure to adversity during childhood and/or adolescence (i.e., maltreatment and psychosocial adversities before age 18) and 2) young adult psychological health (i.e., a composite score reflecting low psychological distress and high positive affect). Prior studies have defined resilience using combinations of adversity and psychological health or other functioning indicators categorically (e.g., high versus low adversity by high versus low functioning, Masten et al., 1999), though we included these domains as continuous variables because dichotomizing can reduce power and limit measurement reliability (Segerstrom 2019).

A measure of early adversity exposure drew on assessments of maltreatment and other psychosocial adversities occurring prior to age 18. Maltreatment exposure before age 18 was retrospectively reported in the 2007 GUTS1 biennial questionnaire with validated

self-report measures assessing frequency of maltreatment experiences: physical abuse (three items adapted from the Physical and Emotional Abuse Subscale of the Childhood Trauma Questionnaire (Bernstein et al., 1994) and the Physical Assault Scale of the Conflict Tactics Scales (Straus et al., 1998)), emotional abuse (four items adapted from the Physical and Emotional Abuse Subscale of the Childhood Trauma Questionnaire (Bernstein et al., 1994)), sexual abuse (two items from the Sexual Maltreatment Scale of the Parent-Child Conflict Tactics Scales (Straus et al., 1998)), and two items assessing frequency of witnessing physical or verbal abuse in the household. We derived cut points to indicate exposure (yes/no) for each type of maltreatment based on prior work in this sample (Katz-Wise et al., 2014). Experiences of physical or emotional abuse items included response options “never”, “rarely”, “sometimes”, “often”, and “very often”. For each type of abuse, participants reporting “sometimes” or more frequently on any item were categorized as exposed. Experiences of sexual abuse items included response options “never”, “once”, and “more than once”, and participants were categorized as exposed if they responded “once” or “more than once” on either item. Items assessing witnessing household abuse included response options “never”, “once”, “a few times”, “more than a few times” and “all the time”, and participants were categorized as exposed to witnessing household abuse if they reported frequency of occurrence “once” or more often.

Other maternal-reported early life adversities included maternal depression and maternal divorce or being widowed occurring between enrollment in NHS2 (1989) to the time when the GUTS1 participant turned 18; these were assessed on NHS2 questionnaires (completed by GUTS1 participants’ mothers). Maternal depression was measured using multiple indicators repeatedly assessed on NHS2 questionnaires, including self-reported physician diagnosed depression, regular use of antidepressants, and elevated distress symptoms on the Mental Health Index (MHI-5; total scores ≤60 indicate elevated symptoms) (McHorney et al., 1993). Participants were characterized as exposed to maternal depression if mothers endorsed any of the depression indicators across any NHS2 questionnaires between enrollment in NHS2 to the time the GUTS1 participant turned 18. Similarly, participants were characterized as exposed to maternal divorce or widowed if either of these statuses were reported on any NHS2 questionnaire between enrollment in NHS2 until the GUTS1 participant turned 18.

After characterizing exposure on each of the 7 adversities queried (physical abuse, emotional abuse, sexual abuse, witnessing household abuse, maternal depression, maternal divorce, mother widowed), we created a count of the number of adversities to which participants were exposed (possible range 0–7). To categorize individuals into those with higher exposure versus moderate or lower adversity exposure and examine potential threshold effects of adversity exposure, we also dichotomized the adversity count score, with the top tercile (3 or more adversities) indicating higher adversity exposure and the bottom two terciles (0 to 2 adversities) indicating lower adversity exposure. This cutoff is consistent with other work stratifying samples by tercile of adversity exposure (Miller-Lewis et al., 2013).

Psychological health was assessed via self-report measures of two forms of psychological distress (depressive symptoms, anxiety symptoms) and one measure of positive functioning, all assessed on the 2010 GUTS1 biennial questionnaire. Past week depressive symptoms

were assessed using sum scores from the 10-item Center for Epidemiologic Studies Depression (CES-D) Scale (Radloff, 1991) and past week anxiety symptoms were assessed using sum scores from the 9-item Worry/Oversensitivity Subscale from the Revised Children's Manifest Anxiety Scale (RCMAS) (Reynolds and Richmond, 1979). Past month positive psychological functioning was assessed using sum scores of the 10-item positive affect subscale from the Mental Health Inventory (MHI) (Veit and Ware, 1983). There was minimal item-level missingness across psychological scales (n=12 to 18 were missing between 1–4 items across measures, most individuals were missing only one item). Therefore, following prior work (Shrive et al., 2006), individuals' mean score on completed items was used to impute the total score. We created a composite measure of psychological health by z-scoring each continuous psychological symptom score, taking the inverse of psychological distress z-scores, and summing these with the positive affect z-score. Higher scores indicate better or more positive psychological health.

2.2.2 Outcome: diurnal salivary cortisol—Saliva samples were collected between 2011 and 2014 via mailed sample collection tubes. Following a standard protocol, participants provided five passive-drool saliva samples over the course of a single day (upon awakening, 45 minutes, 4, and 10 hours after waking, and at bedtime). Samples were refrigerated until sampling was complete and then sent on ice via two-day delivery to the Channing Division of Network Medicine (CDNM). Samples were stored at the CDNM biorepository in a −20 degrees Centigrade freezer, and cortisol was assayed by the Rohleder Lab at Brandeis University using a competitive chemiluminescence immunoassay. Quality control (QC) samples and coefficients of variation (CVs) met the biorepository standard of <15%: overall CV 13.3% and within-batch CV 11.0%.

Due to significant skewness in raw mean cortisol level (skewness=4.79), log transformed values of cortisol were used for all analyses. Following prior work, diurnal mean log-transformed cortisol (in nmol/L) was derived across 4 of 5 samples: awakening, 4 and 10 hours after waking, and bedtime, excluding the 45 minutes post-waking sample, as it is affected by the CAR (Segerstrom et al., 2014). The mean log diurnal cortisol was relatively normally distributed in our sample (mean=1.80 (SD=0.4); skewness=0.76). Mean diurnal cortisol has higher measurement reliability relative to other diurnal summary measures, particularly when salivary samples are available from only a single day (Segerstrom et al., 2014) and may be a better index of overall HPA axis functioning relative to CAR, which assesses more acute impacts of stress (Kuhlman et al., 2019). We performed simulation analyses (c.f., Segerstrom and Boggero, 2020) given our current sample size and assuming a small effect size that estimated sign (i.e., estimated effect has the opposite sign from the true underlying effect) and magnitude (i.e., estimated effect is meaningfully larger or smaller than the true underlying effect, set to be $r = .10$ magnitude difference) errors at 5.4% and 10.3% for mean diurnal cortisol, respectively, suggesting that our findings were not substantially impacted by measurement error. CAR relative to increase (i.e., absolute increase in cortisol from waking to 45 minutes post-waking) was derived as a secondary cortisol measure.

2.2.3 Covariates—Covariates included variables assessed at baseline (i.e., age, sex, race/ethnicity, sexual orientation, father's educational attainment, BMI) and variables assessed on the day saliva samples were obtained (i.e., hormonal contraception use, past night sleep duration, waking time, cigarette smoking, and vigorous physical activity on the day of saliva collection). Age (continuous in years), sex (female/male), race/ethnicity (white/non-white), sexual orientation (heterosexual/not heterosexual), and self-reported height and weight were reported on the 2010 biennial GUTS1 questionnaire. BMI was derived from self-reported height and weight in continuous kg/m^2. As an indicator of childhood socioeconomic status, father's educational attainment (some high school or high school graduate, 2-year college, 4-year college or graduate school) was reported by mothers of GUTS1 participants on the 2001 NHS2 biennial questionnaire. Hormonal contraception use (women only; including any birth control pills, patch, ring, intrauterine devices, implants or injections; yes/no), past night sleep duration, waking time, cigarette smoking (yes/no), and vigorous physical activity (yes/no) were reported on the saliva collection questionnaire. As the time from exposure assessment (2010) to saliva sample ranged from 5 months to 3.75 years (mean time=25.2 months, SD=9.0), time in months from baseline to saliva assessment was also included as a covariate. All continuous covariates were grand mean centered to improve interpretation of effect estimates.

Post-traumatic stress disorder (PTSD) symptoms are often evaluated in relation to adversity, and absence of symptoms has sometimes been used to indicate resilience (Bonanno et al., 2006). As PTSD symptoms are, by definition, dependent on trauma exposure, we did not include PTSD symptoms in the primary definition of psychological health which represented psychological health regardless of adversity. However, as a sensitivity analysis, for individuals who had at least one childhood adversity exposure and reported PTSD symptoms in relation to that exposure, we incorporated PTSD symptoms into the composite psychological health variable. PTSD symptoms were assessed in relation to a childhood trauma or adversity as reported on the Short Screening Scale for DSM-IV PTSD on the 2007 GUTS1 biennial questionnaire (Breslau et al., 1999). The 7-item screening scale determined presence of posttraumatic stress symptoms, and sum scores were calculated to include in the composite psychological health measure.

2.3 Analytic Approach

We conducted univariate analyses to assess distributions of exposures (i.e., adversity count, psychological health), outcome (i.e., diurnal mean of log-transformed salivary cortisol), and covariates. We also conducted bivariate analyses for the distribution of covariates across both exposures and mean log cortisol.

The analytic sample had complete exposure and outcome data, however there was some missing covariate information: father's educational attainment (n=62), exercise (n=14), wake time (n=10), sexual orientation (n=8), BMI (n=7), sleep duration (n=5), race/ethnicity (n=3), smoking (n=1), and hormonal contraceptive use (n=1). To reduce bias, prior to analyses we imputed missing covariate data using the MI procedure in SAS, creating 25 imputed datasets (White et al., 2011). The reported regression results were obtained by pooling estimates from multiply imputed datasets with the MIANALYZE procedure.

We conducted a series of linear regression models considering adversity count and psychological health in relation to diurnal mean log cortisol. In all models, we examined whether the impact of adversity count on mean log cortisol depended on level of psychological health by including standardized adversity count and psychological health (both z-scored, mean=0, SD=1) and their interaction as predictors. A series of models increasingly adjusted for the following covariates: Model 1) age and sex, Model 2) model 1 plus other baseline sociodemographic variables (i.e., race/ethnicity, sexual orientation, father's educational attainment), Model 3) model 2 plus biological and behavioral factors from the day of saliva sampling (i.e., BMI, hormonal contraceptive use, sleep duration, wake time, smoking, physical activity, time from baseline). To examine a potential non-linear association between adversity count and cortisol, we estimated a quadratic adversity term (adversity count^2). Following examination of interaction terms, post-hoc adversity stratified models were performed with psychological health predicting mean log cortisol. To interpret effects, we estimated the effects of the log-transformed outcome as percentage change in the outcome per unit change in the predictor by applying the following transformation: $\beta_{\%change} = [\exp(\beta_{raw})] - 1$. As an additional post-hoc analysis to examine our a priori categorization of higher versus lower adversity exposure, we estimated associations between psychological health with mean log cortisol at each level of adversity exposure: 0, 1, 2, 3, 4, and 5 or 6 adversities (5 or 6 adversities were collapsed due to small cell size; no participant experienced all 7 adversities).

To determine if there were sex differences in the associations between psychological resilience and mean log cortisol, interaction terms for sex and the primary predictors were estimated. Given the overrepresentation of sexual minorities, we tested interaction terms for sexual orientation and the primary predictors. To estimate which, if any, of the individual forms of psychological distress or positive affect were driving associations of psychological health with mean log cortisol, the primary models were estimated with each individual psychological health variable separately (i.e., separate models for depressive symptoms, anxiety symptoms, and positive affect). We also ran the primary models with PTSD symptoms incorporated into the psychological health variable. Lastly, we conducted the primary models predicting mean level of cortisol at each time point: waking, 45-minutes, 4 hours, and 10 hours post waking, and bedtime, as well as with CAR as the outcome. All analyses were conducted using PROC GLM with SAS v9.4 (SAS Institute, Inc., Cary, North Carolina).

3. Results

3.1 Descriptive Results

The analytic sample was mostly female (69.9%) and white (92.3%), with a mean age of 25.3 at baseline (Table 1). Participants' fathers' educational attainment was relatively high (68.9% of fathers attended 4-year college or graduate school). A substantial minority (31.4%) of the sample identified as not completely heterosexual, a higher proportion than the general population due to specific oversampling of sexual minorities (Austin et al., 2016).

Average count of adversities among the sample was 1.67 (SD=1.3) and count of adversities was negatively correlated with psychological health (r=−0.21, p<.0001) (correlations between adversity and separate psychological health variables are presented in Table A.1). The distribution of adversity count and psychological health varied across sociodemographic factors (Table 1; correlations between adversity and psychological health with each covariate are presented in Table A.2). With respect to adversity count, non-white (vs. white) individuals, those with low (vs. higher) father's education, and those identifying as not heterosexual (vs. heterosexual) had significantly higher adversity exposure (all p<.05). Comparing levels of psychological health, males (vs. females) and those identifying as heterosexual (vs. not heterosexual) had significantly higher psychological health (both p<.05). Few covariates from the day of saliva sampling were associated with either adversity count or psychological health.

Based on dichotomized adversity count, those with lower adversity levels had higher psychological health (lower adversity n=678, psychological health mean=0.10; SD 1.0) compared to those with higher adversity levels (higher adversity n=238, psychological health mean=−0.27; SD 1.1; p<.0001).

Multiple variables from baseline and the day of saliva collection were significantly associated with mean log cortisol (Table 2). Being female (vs. male) and non-white (vs. white) were associated with higher cortisol levels (both p<.05). Use of any hormonal contraception, smoking, and vigorous physical activity were associated with higher cortisol levels (all p<.05); sleep duration and waking time were each negatively correlated with cortisol levels (p<.05; sleep duration and waking time were correlated at r=0.40).

3.2 Psychological resilience and mean cortisol

In adjusted models, higher levels of adversity were associated with 4% lower mean cortisol levels, accounting for psychological health and covariates (Model 3 $\beta_{\%change}$=−4.1%, 95%CI −6.4, −1.7, p=0.001). Psychological health was also significantly associated with 3% lower mean cortisol in adjusted models, accounting for adversity count (Model 3 $\beta_{\%change}$ =−2.7%, 95%CI −5.0, −0.4, p=0.024). The effect of psychological health seemed to be driven by the association between lower distress symptoms, particularly anxiety, with lower mean cortisol (standardized inversed depressive symptoms: Model 3 $\beta_{\%change}$=−2.3%, 95%CI −4.6, 0.1, p=0.06; standardized inversed anxiety symptoms: Model 3 $\beta_{\%change}$=−3.1%, 95%CI −5.3, −0.7, p=0.01; standardized positive affect: Model 3 $\beta_{\%change}$=−1.6%, 95%CI −3.9, 0.8, p=0.19; Table A.3 for mean log-transformed cortisol estimates). There was no evidence of a multiplicative interaction between adversity count and psychological health for mean cortisol (interaction term: Model 3 $\beta_{\%change}$=0.9%, 95%CI −1.3, 2.9, p=0.45). There was also no evidence of a quadratic effect of adversity (adversity count^2 term was not significant; data not shown). See Table 3 for results showing the effect of resilience predictors on estimates of mean log-transformed diurnal cortisol.

Additionally, effects of adversity count and psychological health on mean log cortisol did not appear to differ across sex or sexual orientation (no statistically significant interaction terms across all models, all p>.10; data not shown). Further, sensitivity analyses including PTSD symptoms in the composite psychological health variable were largely consistent with

primary models, suggesting posttraumatic stress symptoms function similarly to the other forms of distress captured in our primary psychological health definition (Table A.4).

Although the multiplicative interaction was not statistically significant, the magnitude of the interaction effect was suggestive of potentially differential effects. Moreover, differential effects of psychological health by adversity exposure were our primary hypothesis, therefore we conducted post-hoc analyses stratified by level of adversity to further examine associations. Of note, those with higher adversity exposure had significantly lower mean log cortisol levels than those with lower adversity (higher adversity: mean log cortisol=1.74, SD=0.4 versus lower adversity: mean log cortisol=1.82, SD=0.4; p=0.003). Stratified models suggested that among individuals with lower adversity exposure, a standard deviation increase in psychological health was associated with 3% lower mean cortisol (Model 3 $\beta_{\%change}$=−3.1%, 95%CI −5.9, −0.2, p=0.04; Figure 1). Conversely, among those with higher adversity exposure, psychological health was unassociated with mean cortisol levels in all models. Post-hoc analyses stratified by each level of adversity count largely suggest that our a priori cutoff of 3+ adversities reflects a relevant threshold. Psychological health was generally associated with lower cortisol among those with 0 to 2 adversities but was unassociated with cortisol among those with 3 or more adversities (Table A.5).

A sensitivity analysis assessed the effects of adversity count and psychological health and their interaction at each time point of saliva sampling (Table A.6). Patterns of association were largely similar across time points. Adversity count and psychological health were unassociated with CAR (Table A.7).

4. Discussion

The present study investigated potential biological correlates of psychological resilience from early adversity in a large community sample of young adults. We hypothesized that psychological resilience, early adversity and high psychological health, would be associated with less dysregulated cortisol compared to those with worse psychological health. Several interesting findings emerged in partial support of our hypothesis. Both higher early adversity exposure and psychological health were associated with lower levels of mean diurnal salivary cortisol, and associations between higher psychological health with lower cortisol was mainly present when adversity was low. Therefore, seemingly counterintuitively, those with greater exposure to adversity and also those with higher psychological health had lower cortisol levels on average. Although not directly testable in available data, it is possible to interpret the blunted or abnormally low cortisol among those with high adversity as dysregulated levels. Comparisons across studies are difficult given differing protocols for saliva collection and cortisol summary measure presentation. However, our sample appears to have relatively high average cortisol levels compared to norms; prior work has reported among 21- to 30-year-olds (e.g., norm mean log diurnal cortisol values 50th percentile=0.78, 95th percentile=2.04 versus our sample mean log diurnal cortisol values=1.80) (Miller et al., 2016). Differences between our sample and normative values may be due to differing sample demographics and composition, assays used, and sampling timing. Moreover, among those with high adversity, levels of cortisol were unassociated with psychological health. Conversely, in the context of low adversity, overall cortisol levels were higher than levels in

high adversity and better psychological health was associated with relatively lower cortisol, suggesting that positive psychological health may be associated with a more normative or healthy cortisol level within this group. Of note, our operationalization of psychological resilience resulted in few individuals with higher adversity exposure *and* high levels of psychological health. This may be due to stringent psychological health criteria, requiring both low distress across multiple domains and high positive affect. The low prevalence of individuals who met our criteria for being "psychologically resilient" potentially limited our ability to determine the nature of cortisol levels among individuals with this profile.

Our first key finding was that higher levels of adversity exposure were associated with lower levels of diurnal salivary cortisol, suggested a blunting of cortisol. More chronic, prolonged or frequent exposure to early adversity may disrupt HPA axis activity in a way that produces lower basal levels of circulating cortisol later in life (Koss and Gunnar, 2018). Early stress may result in physiological changes leading to chronic HPA axis activation, resulting in blunted HPA responses to later stressors as well as dysregulated functioning in general (Deighton et al., 2018; Koss and Gunnar, 2018). Because we modeled adversity exposure via a count of psychosocial experiences and a quadratic effect was not identified, our results suggest that additive increases in exposure to different types of adversities result in increasingly dysregulated cortisol levels (in this case, relatively lower levels).

Second, we found that better psychological health was also associated with lower levels of diurnal salivary cortisol. This is generally consistent with prior work (Knorr et al., 2010; Ryff et al., 2006) which has suggested such relationships are indicative of healthier or more normative HPA axis function. Most prior work measured a single facet of psychological functioning, whereas our definition of psychological health reflected a composite of multiple distress measures and a positive functioning measure. Previous evidence has largely considered psychological distress, measured by depression and anxiety, finding lower distress is associated with relatively lower basal cortisol levels (Knorr et al., 2010). Indeed, lower distress symptoms were associated with lower cortisol levels in our sample, potentially driving much of our identified association between better psychological health and lower cortisol. Although there are fewer studies of positive psychological health measures and basal cortisol, at least one suggested that greater well-being was associated with relatively lower cortisol levels (Ryff et al., 2006). Together with prior findings, our study suggests that better psychological health may be associated with more normative, less-dysregulated cortisol levels - indicated by relatively lower salivary cortisol levels in our study.

Third, although the multiplicative interaction was not significant, we found that higher psychological health was more strongly associated with lower cortisol levels when adversity exposure was low versus high. This is inconsistent with our initial hypothesis that higher psychological health would be associated with relatively lower cortisol levels in the context of high adversity, or that psychological health would buffer the impact of high adversity on cortisol levels. Our findings suggest there may be a threshold of adversity after which positive psychological health is not related to favorable physiological outcomes. It is possible that beyond a certain level, the negative impact of adversity may overwhelm the physiological stress system and result in dysregulation regardless of current psychological

resources. Average diurnal cortisol was significantly lower among those with higher relative to lower adversity exposure in our sample, suggesting that the overall distribution of cortisol levels differed by level of adversity. In contrast, those with high adversity display significantly lower cortisol levels in general, potentially indicating physiological dysregulation. These associations may be mediated by separate neurobiological mechanisms (e.g., adversity exposure could lead to up-regulated GR receptors and increased negative feedback hypersensitivity (Holochwost et al., 2021; Ehlert, 2013), positive psychological health could reduce likelihood of repeated HPA axis activation as seen in depression (Knorr et al., 2010) or increase inhibition of glucocorticoids via increased oxytocin (Polk et al., 2005)), both ultimately contributing to lower cortisol output. Future studies should examine processes linking both early adversity and later psychological health with HPA axis functioning, as the joint impact of these two resilience components is of interest. Overall, these stratified findings suggest it may be important to consider both adversity and psychological health when examining levels of diurnal cortisol in young adulthood.

Although our findings are largely consistent with previous work considering separate effects of early adversity and mental health on salivary cortisol, our finding that both adversity exposure and psychological health were associated with relatively lower cortisol is not fully consistent with prior literature. Some studies have found that early adversity is an independent predictor of diurnal cortisol while accounting for psychological functioning in young adulthood, however directions of association varied (Nicolson, 2004; Power et al., 2012; van der Vegt et al., 2009). Consistent with our findings, one study among 623 international adoptees in young adulthood found that severe maltreatment was associated with 0.63 nmol/L lower average square root-transformed diurnal cortisol compared to unexposed peers, adjusting for current psychiatric problems (van der Vegt et al., 2009). The independent association of psychiatric problems with cortisol was not reported. This study's adversity-cortisol association was large relative to our findings, potentially because we incorporated less severe forms of adversity and estimated the effect of continuous adversity count rather than exposure versus unexposed. Additionally, among men only, one prior study found that psychological distress was associated with cortisol levels when maltreatment exposure was high, but not low (Power et al., 2012); again, in contrast to our findings where psychological health was associated with cortisol when adversity was low, but not high. Conversely, other studies found that psychological status predicted differences in diurnal cortisol levels, while early adversity was unassociated (Lindley et al., 2004; Lopes et al., 2012). For example, in a small study of 34 adults, individuals with PTSD had elevated cortisol relative to healthy controls, regardless of childhood abuse history (Lindley et al., 2004). Still other studies that considered both adversity and psychological status found no differences in diurnal cortisol across adversity and psychological health constructs (Eckart et al., 2009; Muhtz et al., 2011). Of note, it is difficult to compare across the literature due to different measures of diurnal cortisol (e.g., diurnal slope, waking cortisol, CAR) and methods for modeling and reporting adversity and psychological health effects (e.g., psychological health as covariates, not primary predictors). Further, very few studies have considered the interaction of early adversity and psychological health on diurnal salivary cortisol.

Our results must be viewed in light of several study-specific methodological limitations. First, although the exposure assessment temporally preceded the one-time outcome assessment, analyses are effectively cross-sectional which limits our ability to draw causal conclusions. Second, some early adversities were retrospectively self-reported in young adulthood. However, retrospective reports of childhood adversity are typically underreported (Hardt and Rutter, 2004) and potentially biased estimates towards the null. Third, generalizations to more diverse populations are not possible. Nevertheless, assessing the associations within a relatively homogeneous sample provides evidence of these relationships even among higher socio-economic status, mostly white individuals. The overrepresentation of sexual minorities may have influenced associations as those identifying as a sexual minority had higher early adversity and lower psychological health in bivariate associations. However, prior work in this sample accounting for relevant covariates has found no substantial differences in diurnal cortisol between sexual minority groups (Austin et al., 2016), which is consistent with work in other samples (Juster et al., 2013; Williams 2017). Moreover, sexual orientation was unassociated with mean cortisol levels in our sample, and we adjusted for sexual orientation and found no evidence of effect modification, limiting the potential for our findings to be biased due to the overrepresentation of sexual minorities. Fourth, with any observational study, it is possible the estimates were impacted by unmeasured confounding.

The somewhat contradictory findings from our study highlight several important challenges with using salivary cortisol to assess potential effects of resilience on biological dysregulation. First, while we had adequate power to detect true differences in mean diurnal cortisol, measurement reliability of diurnal salivary cortisol from a single day of assessment is limited (Segerstrom et al., 2014). Future studies may benefit from obtaining repeated measures across multiple days (e.g., 5 consecutive days) as well as multiple occasions (e.g., sampling once a month for 3 months), which would result in more precise measurement (Segerstrom et al., 2014). Second, unlike other biological systems like blood pressure or cholesterol, there are no clear standards for quantifying abnormal or dysregulated cortisol. Therefore, results are relative, primarily interpretable within a given study sample making interpretation and comparison across studies difficult. As such, most studies compare cortisol levels in the group of interest (e.g., those resilient or psychologically distressed) with “healthy controls” or with another comparison group defined based on the research question under study. Relatedly, it is not clear what level of cortisol elevation, dampening, or variability is clinically meaningful. Although there are a few studies relating cortisol measures to clinical outcomes, including linkages between less diurnal cortisol decline with increased coronary calcification or mortality, these do not provide clear cutpoints for use across studies (Kumari et al., 2011; Matthews et al., 2006). These studies and additional work on health implications of cortisol dysregulation could extend the interpretability of our current findings and other similar studies of psychosocial determinants and diurnal cortisol. Finally, our findings may not provide a clear picture of relevant biological consequences of psychological resilience, because diurnal salivary cortisol is the product of a complex set of physiological processes, including feedback loops and dynamic diurnal rhythms. Resilience may be associated with other manifestations of cortisol dysregulation, such as flattened slope or variability across days, which we could not validly assess in the current

study. Sensitivity analyses indicated that resilience domains were unassociated with CAR in our sample, which notably has differing neurobiological processes compared to overall output as measured using the diurnal mean (Segerstrom et al., 2014). Future studies should consider other biological processes, such as measures of the epigenome or microbiome, that are increasingly available in population-based samples that may provide deeper insight into physiological implications of adversity and mental health.

4.1 Conclusions

This study suggests early adversity and psychological health are independently associated with altered levels of diurnal cortisol in young adulthood. Both the potentially damaging exposure of early adversity and the positive asset of psychological health were associated with relatively lower cortisol levels. These effects may be interpreted as a dysregulated, blunted cortisol level associated with high early adversity, with a potentially beneficial lower, more normative cortisol level associated with better psychological health. However, our findings point to a complex biological process that may be difficult to disentangle fully with our current measure of salivary cortisol. Further examination of early adversity and later psychological health with more dynamic or comprehensive measures of biological dysregulation is warranted. Nevertheless, this study adds to the literature in several important ways. We have operationalized psychological resilience to incorporate a range of early adversities and multiple forms of distress and positive psychological functioning. Our study benefits from a large, community-based sample of young adults, an important transition time for psychological, social, and physical health development and when long-term health trajectories are often laid down. Future research should assess prospective relationships between early adversity, psychological health, and HPA axis functioning or other biological indicators over time to determine causality more clearly and explore the relationship between the process of psychological resilience and other forms of biological dysregulation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Both early adversity and psychological health were associated with diurnal cortisol
- In high adversity, diurnal cortisol was blunted, regardless of psychological health
- In low adversity, better psychological health related to relatively lower cortisol

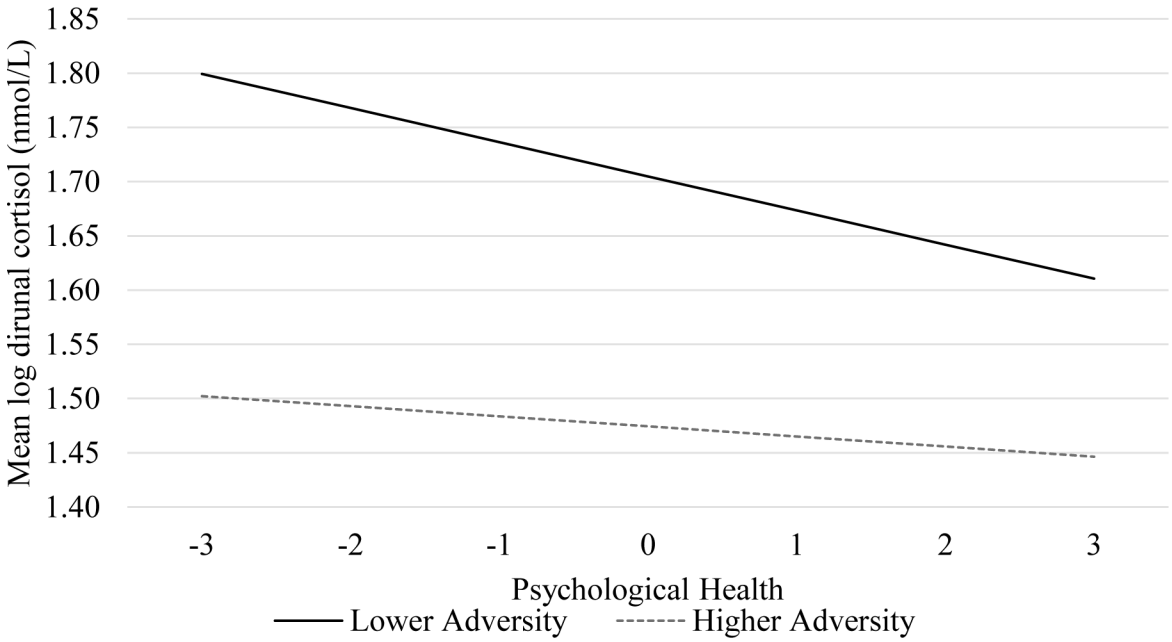

Figure 1.

Values of mean log diurnal cortisol predicted by psychological health, stratified by lower versus higher adversity exposure count

The figure plots predicted values from fully adjusted (Model 3) linear regression models with standardized psychological health predicting mean log diurnal cortisol, stratified by lower (0–2 adversities, n=678) and higher (3+ adversities, n=238) adversity level.

Table 1.

Distribution of baseline covariates in the total sample and by adversity count and psychological health in GUTS1 Saliva Substudy participants (n=916)

Covariates	*N (%)*	Adversity Count *Mean (SD) or Correlation*	Psychological Health *Mean (SD) or Correlation*
Baseline Variables			
Age (*Mean (SD)*)	25.33 (1.6)	0.01	0.03
Sex			
Female	640 (69.9)	1.70 (1.4)	**−0.05 (1.0)**
Male	276 (30.1)	1.61 (1.3)	**0.12 (0.9)**
Race			
White	843 (92.3)	**1.63 (1.3)**	0.01 (1.0)
Non-White	70 (7.7)	**2.20 (1.4)**	−0.10 (1.0)
Sexual Orientation			
Heterosexual	623 (68.6)	**1.58 (1.3)**	**0.13 (0.9)**
Not heterosexual	285 (31.4)	**1.90 (1.3)**	**−0.27 (1.1)**
Father's Education			
Some High School or HS Grad	118 (13.8)	**1.97 (1.5)**	−0.05 (1.1)
2-year College	148 (17.3)	**1.51 (1.2)**	−0.01 (1.0)
4-year College or Grad School	588 (68.9)	**1.57 (1.3)**	0.01 (1.0)
BMI (*Mean (SD)*)	24.68 (4.9)	0.06	**−0.07**
Day Saliva Samples are Obtained Hormonal Contraception			
Any hormonal contraception use	327 (35.7)	1.64 (1.3)	−0.02 (1.1)
No hormonal contraception use	588 (64.3)	1.69 (1.3)	0.01 (1.0)
Sleep Duration, hours (*Mean (SD)*)	7.50 (1.3)	−0.04	−0.02
Waking Time, hours past midnight (*Mean (SD)*)	7.57 (1.6)	0.04	**−0.10**
Smoking			
Any smoking	34 (3.7)	1.71 (1.4)	−0.24 (1.0)
No smoking	881 (96.3)	1.67 (1.3)	0.01 (1.0)
Vigorous Physical Activity			
Any physical activity	306 (33.9)	**1.53 (1.3)**	0.05 (1.0)
No physical activity	596 (66.1)	**1.73 (1.4)**	−0.03 (1.0)
Time to saliva sample, months (*Mean (SD)*)	25.23 (9.0)	**−0.25**	0.03

Adversity count is the count of 7 potential psychosocial adversities experienced before age 18; psychological health is the sum of z-scores of: depression and anxiety symptoms (both inversed) and positive affect; higher scores indicate better functioning.

Time to saliva sample is the time in months between baseline (in 2010) and cortisol assessment (between 2011 and 2014).

p<.05 are **bolded**; p-values refer to T-tests for binary categorical covariates, F-statistics for categorical covariates (>2 categories), and Pearson correlations for continuous covariates and mean adversity count and psychological health.

Table 2.

Distribution of mean log diurnal cortisol by baseline covariates (n=916)

Covariates	*N (%)*	Mean Log Diurnal Cortisol (nmol/L) *Mean (SD) or Correlation*
Baseline Variables		
Age (*Mean (SD)*)	25.33 (1.6)	0.00
Sex		
Female	640 (69.9)	**1.85 (0.4)**
Male	276 (30.1)	**1.69 (0.4)**
Race		
White	843 (92.3)	**1.79 (0.4)**
Non-White	70 (7.7)	**1.91 (0.5)**
Sexual Orientation		
Heterosexual	623 (68.6)	1.80 (0.3)
Not heterosexual	285 (31.4)	1.79 (0.4)
Father's Education		
Some High School or HS Grad	118 (13.8)	1.78 (0.4)
2-year College	148 (17.3)	1.82 (0.4)
4-year College or Grad School	588 (68.9)	1.81 (0.4)
BMI (*Mean (SD)*)	24.68 (4.9)	−0.05
Day Saliva Samples are Obtained		
Hormonal Contraception		
Any hormonal contraception use	327 (35.7)	**1.90 (0.3)**
No hormonal contraception use	588 (64.3)	**1.75 (0.4)**
Sleep Duration, hours (*Mean (SD)*)	7.50 (1.3)	**−0.08**
Waking Time, hours past midnight (*Mean (SD)*)	7.57 (1.6)	**−0.08**
Smoking		
Any smoking	34 (3.7)	**1.98 (0.5)**
No smoking	881 (96.3)	**1.79 (0.4)**
Vigorous Physical Activity		
Any physical activity	306 (33.9)	**1.86 (0.3)**
No physical activity	596 (66.1)	**1.77 (0.4)**
Time to saliva sample, months (*Mean (SD)*)	25.23 (9.0)	0.04

Time to saliva sample is the time in months between baseline (in 2010) and saliva assessment for cortisol (between 2011 and 2014).

N (%) are presented for categorical covariates, Mean (SD) are presented for continuous covariates. Mean (SD) of mean log-transformed diurnal cortisol is presented for each level of categorical covariates, correlations between cortisol and continuous covariates are presented.

p<.05 are **bolded**, p<.10 are *italicized*; p-values refer to T-tests for binary categorical covariates and mean log cortisol, F-statistics for categorical covariates (> 2 categories) and mean log cortisol, and Pearson correlations for continuous covariates and mean log cortisol.

Table 3.

Linear regression models for adversity exposure count and psychological health with mean log diurnal cortisol (nmol/L) (n=916)

Interaction Models						
	Model 1		**Model 2**		**Model 3**	
	β	*95%CI*	*β*	*95%CI*	*β*	*95%CI*
Intercept	**1.69**	**1.65, 1.73**	**1.65**	**1.56, 1.75**	**1.63**	**1.54, 1.73**
Adversity Count	**−0.04**	**−0.07, −0.02**	**−0.04**	**−0.07, −0.02**	**−0.04**	**−0.07, −0.02**
Psychological Health	*−0.02*	*−0.05, 0.001*	**−0.02**	**−0.05, −0.0004**	**−0.03**	**−0.05, −0.004**
Adversity Count X Psychological Health	0.01	−0.02, 0.03	0.004	−0.02, 0.03	0.01	−0.01, 0.03
Adversity Stratified Models						
	Model 1		**Model 2**		**Model 3**	
	β	*95%CI*	*β*	*95%CI*	*β*	*95%CI*
Lower Adversity (n=678)						
Intercept	**1.73**	**1.68, 1.78**	**1.72**	**1.60, 1.84**	**1.71**	**1.58, 1.83**
Psychological Health	*−0.03*	*−0.06, 0.001*	*−0.03*	*−0.06, 0.001*	**−0.03**	**−0.06, −0.002**
Higher Adversity (n=238)						
Intercept	**1.58**	**1.50, 1.67**	**1.53**	**1.38, 1.69**	**1.47**	**1.32, 1.63**
Psychological Health	−0.01	−0.05, 0.03	−0.01	−0.05, 0.04	−0.01	−0.05, 0.03

Outcome is mean logarithmic-transformed diurnal cortisol levels (nmol/L).

Adversity count and psychological health (sum of z-scores of: depression and anxiety symptoms (both inversed) and positive affect; higher scores indicate better functioning) are standardized. Lower adversity is 0–2 adversity types, higher adversity is 3+ adversity types.

Model 1: age (continuous, mean centered) and sex (reference=male).

Model 2: Model 1 and race (reference=white), sexual orientation (reference=heterosexual), and father's educational attainment (reference=4-year college or grad school).

Model 3: Model 2 and BMI (continuous, mean centered), time to cortisol assessment (continuous, mean centered), hormonal contraception use (reference=no use), sleep duration (continuous, mean centered) waking time (continuous, mean centered), smoking (reference=no smoking), and vigorous physical activity (reference=no physical activity).

Effects p<.05 are **bolded**. Effects p<.10 are *italicized*.