Title

Early life stress and HPA axis function independently predict adult depressive symptoms in metropolitan Cebu, Philippines

Journal

American Journal of Biological Anthropology, 173(3)

ISSN

0002-9483

Authors

Kim, Andrew Wooyoung
Adam, Emma K
Bechayda, Sonny A
et al.

Publication Date

2020-11-01

DOI

10.1002/ajpa.24105

Peer reviewed

HHS Public Access

Author manuscript

Am J Phys Anthropol. Author manuscript; available in PMC 2021 January 29.

Published in final edited form as:

Am J Phys Anthropol. 2020 November ; 173(3): 448–462. doi:10.1002/ajpa.24105.

Early life stress and HPA axis function independently predict adult depressive symptoms in metropolitan Cebu, Philippines

Andrew Wooyoung Kim[1], **Emma K. Adam**[2,4], **Sonny A. Bechayda**[3], **Christopher W. Kuzawa**[1,4]

[1]Department of Anthropology, Northwestern University, Evanston, Illinois

[2]School of Education and Social Policy, Northwestern University, Evanston, Illinois

[3]Office of Population Studies, University of San Carlos, Cebu City, Philippines

[4]Institute for Policy Research, Northwestern University, Evanston, Illinois

Abstract

Objectives: Alterations in adult hypothalamic–pituitary–adrenal (HPA) axis activity have increasingly been linked with early life stress and adult depression, but a limited number of studies have used longitudinal data to explore HPA axis dysregulation as an underlying mechanism driving the long-term depressive impacts of early stressors. Here we address potential long-term impacts of early life, family-based stress on depressive symptoms among young adults in a longitudinal birth cohort study begun in 1983 in the Philippines.

Materials and methods: We relate a composite measure of family-based stressors experienced between birth and adolescence to circadian dynamics in adult salivary cortisol and depressive risk measured at 21–22 years of age. Multiple regression analyses were conducted to examine the relationship between early life stress levels and risk of adult depressive symptoms, as well as the role of adult diurnal cortisol activity in this relationship.

Results: Greater levels of early life familial stress predicted more severe depressive symptomatology at age 21–22 in a dose–response fashion ($p < .0001$) independent of adult diurnal cortisol patterns. Flatter diurnal cortisol slopes are directly associated with higher adult depressive symptoms, an effect mostly driven by evening cortisol levels ($p = .004$). When considering the cumulative effects of early life stress measures, however, exposure to more of these stressors during development is associated with even higher depressive symptoms.

Discussion: The long-term depressive effects of early life familial stress extend to this large sample of Cebuano young adults, and early life stress and HPA axis function may shape adult

Correspondence: Andrew Wooyoung Kim, 1810 Hinman Avenue, Evanston, IL 60208. andrewkim2022@u.northwestern.edu.

AUTHOR CONTRIBUTIONS

Andrew Kim: Conceptualization; data curation; formal analysis; investigation; methodology; writing-original draft. **Emma Adam:** Formal analysis; writing-review and editing. **Sonny Bechayda:** Project administration. **Christopher Kuzawa:** Conceptualization; formal analysis; writing-review and editing.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in UNC Dataverse at https://dataverse.unc.edu/.

depressive symptoms through independent pathways in this sample. Our findings provide further evidence that HPA axis activity is shaped by early life conditions and is associated with depressive symptoms.

Keywords

depression; developmental origins of health and disease; early life stress; family stress; global mental health; HPA axis; low- and middle-income countries; Philippines

1 | INTRODUCTION

Depression accounts for a large and growing burden of disease world-wide and disproportionately impacts individuals living in low- and middle-income countries (Patel 2007; Vigo et al. 2016). Increasing evidence suggests that physical, nutritional, and psychosocial insults increase the risk of adult depression and other forms of mental and physical illnesses, particularly when individuals endure these impacts during early development (Barker et al. 1999; Chapman et al., 2004). For example, numerous studies have consistently reported that histories of childhood stress and trauma elevate individual risk of developing depression during adulthood (Carr, Martins, Stingel, Lemgruber, & Juruena, 2013; Heim & Binder, 2012; Hovens et al., 2010; Kim, Nyengerai, & Mendenhall, 2020; Mandelli, Petrelli, & Serretti, 2015; Wiersma et al., 2009). The durable effects of early life psychosocial stress exposure are also known to predict adult depression beyond the influence of genetic predispositions, as these patterns have been reported in twin studies (Kendler et al., 2000; Nelson et al., 2002). Elucidating the possible underlying biological correlates, in diverse cultural contexts, can allow for the identification of universal biocultural pathways that contribute to the lasting impacts of early life experiences on adult depression and can illuminate potential opportunities to ameliorate the long-term poor health outcomes shaped by these adverse experiences and conditions.

The hypothalamic–pituitary–adrenal (HPA) axis, a primary physiological system involved in the mammalian stress response, has been implicated as an important biological system that sustains the impacts of early life psychosocial and environmental exposures and shapes later life mental health status (Heim & Binder, 2012; Miller, Chen, & Parker, 2011; Taylor, Way, & Seeman, 2011). Normal HPA axis activity follows a diurnal rhythm where circulating cortisol concentrations are elevated upon waking, surge post-waking to reach peak levels ~30 min after waking (a phenomenon known as the cortisol awakening response), and decrease across the day until reaching the body's lowest levels before slumber (Kirschbaum & Hellhammer, 1989; Pruessner et al., 1997; Weitzman et al., 1971). Early life stress exposure and adverse social, emotional, and physical conditions have consistently been reported as strong predictors of HPA axis dysregulation as indexed by abnormal diurnal cortisol rhythms and reactions to stressful events (Gustafsson, Janlert, Theorell, & Hammarström, 2010; Heim & Binder, 2012; Taylor et al., 2011; Thayer, Wilson, Kim, & Jaeggi, 2018), though the direction of these relationships has varied across the literature. For example, individuals who experienced early life stress have exhibited both higher (Luecken & Appelhans, 2006; Schalinski, Elbert, Steudte-Schmiedgen, & Kirschbaum, 2015; van der Vegt, Van Der Ende, Kirschbaum, Verhulst, & Tiemeier, 2009) and lower levels of basal

cortisol (DeSantis, Kuzawa, & Adam, 2015; Trickett, Noll, Susman, Shenk, & Putnam, 2010; van der Vegt et al., 2009) during adulthood. Early life stress is also related to an altered cortisol awakening response (Butler, Klaus, Edwards, & Pennington, 2017; Engert, Efanov, Dedovic, Dagher, & Pruessner, 2011; Fogelman & Canli, 2018; Gonzalez, Jenkins, Steiner, & Fleming, 2009) and evening cortisol levels (Engert et al., 2011; Gustafsson et al., 2010) in adulthood in both positive and negative directions. Additionally, adults with a history of child abuse and neglect have been reported to exhibit signs of HPA axis dysregulation as evidenced by greater (Heim et al., 2000; Luecken & Appelhans, 2006; Pesonen et al., 2010; Vaccarino, Levitan, & Ravindran, 2015) and blunted levels (Cărnuţ{t \hskip-0.7ex\char “B8}ă, Crişan, Vulturar, Opre, & Miu, 2015; Carpenter et al., 2007; Carpenter, Shattuck, Tyrka, Geracioti, & Price, 2011; Elzinga et al., 2008; Janusek, Tell, Gaylord-Harden, & Mathews, 2017; Lovallo, Farag, Sorocco, Cohoon, & Vincent, 2012) of cortisol reactivity in response to acute psychosocial stressors. Early life stress-induced HPA-axis dysregulation has also been seen in non-human primates. Unpredictable separations from the mother, unpredictable maternal feedings, or spontaneous maternal abusive behavior among captive rhesus macaque infants were found to predict altered diurnal cortisol rhythms characterized by lower morning levels, higher daytime levels, and flatter cortisol slopes across the day (Coplan et al., 1996; Sánchez et al., 2005). This pattern of diurnal rhythm disruption persisted for months to even years after the initial period of adversity.

Dysregulation of circadian HPA axis rhythms has consistently been characterized as a neuroendocrinological phenotype of depression in animal and human studies (Adam et al., 2010; Arborelius et al. 1999; Doane et al., 2013; Heim & Binder, 2012; Jarcho, Slavich, Tylova-Stein, Wolkowitz, & Burke, 2013; Mangold, Marino, & Javors, 2011; Plotsky, Owens, & Nemeroff, 1998; Vrshek-Schallhorn et al., 2013). Prior research has reported that depressed patients and individuals at high risk of depression tend to exhibit altered evening cortisol concentrations and cortisol awakening responses (CAR) (Adam et al., 2017; Engert et al., 2011; Pruessner, Hellhammer, Pruessner, & Lupien, 2003). For instance, elevated levels of evening cortisol have been reported to be characteristic of major depressive disorder (MDD) in both adolescents (Angold & Worthman, 1993; Dahl et al., 1991; Goodyer et al., 1996) and adults (Gold, Goodwin, & Chrousos, 1988; Plotsky et al., 1998; Young et al., 1994). Similarly, higher CAR levels have been associated longitudinally with a heightened risk of developing MDD (Adam et al., 2010). Cross-sectional studies have previously reported positive associations between CAR levels and depressive symptoms (Dahl et al., 1991; Pruessner et al., 2003). Although not all depressed patients display HPA axis dysregulation (Heim, Newport, Mletzko, Miller, & Nemeroff, 2008), these alterations in diurnal cortisol rhythms are thought to influence depression, possibly as a result of inflammation caused by glucocorticoid receptor insensitivity (Miller, Maletic, & Raison, 2009) and impairment of glucocorticoid-mediated negative feedback processes of the HPA axis (Pariante & Lightman, 2008). Thus, prior research has emphasized that alterations in HPA axis function are not only affected by the embodiment of early life and recent social experiences but may also predict individual risk for depression later in life.

The role of the HPA axis in shaping the depressive effects of early life stress, however, remains unclear as results from past studies have reported mixed findings (Engert et al., 2011; Gerritsen et al., 2010; Gonzalez et al., 2009; Mangold et al., 2011; Zilioli et al., 2016).

Although growing evidence has implicated early life stress-induced alterations in HPA axis function as a possible mechanism for adult depression, the potential psychobiological mechanisms that underlie the long-term depressive effects of early life stress are not well-known. Additionally, these studies have mostly been conducted among Western and industrialized populations, where cultural, economic, and psychosocial environments vary in comparison to low- and middle-income contexts, where the burden of mental illness is the greatest (Patel 2007; Vigo et al. 2016). Testing this pathway in diverse contexts and populations is necessary to assess the generalizability of the effects of early life social experience on downstream health outcomes and to identify the factors that may increase psychopathological risk. Additionally, few studies explore the durability of the effects of early life conditions on HPA axis function, as a majority of studies tend to examine early life stress retrospectively, rather than prospectively. Numerous scholars have made the call for further longitudinal studies on HPA axis function for these reasons (Heim et al., 2008; Koss & Gunnar, 2018; Tarullo & Gunnar, 2006).

Our aim in the current study is to explore whether the role of early life stress as a predictor of adult depression is accounted for by alterations in adult HPA axis function in a non-clinical, naturalistic setting. Data come from the Cebu Longitudinal Health and Nutrition Survey (CLHNS), a longitudinal population-based birth cohort study located in metropolitan Cebu, Philippines (Adair et al. 2011). Recent prevalence estimates of depression in the Philippines calculate that ~3.3 million adults, or ~3–4% of the total population, are affected by depression (WHO, 2017), and some cross-sectional studies report higher rates in higher risk groups such as those living in low income communities (22.5%) (Flores, Tuazon, Hernandez, & Evangelista, 2017). Between 2007 and 2017, depressive disorders accounted for the eighth-leading cause of disability in the Philippines (IHME, 2017). Previous research studies from the CLHNS sample have reported dramatically higher rates of depression among individuals who witnessed domestic violence growing up (Hindin & Gultiano, 2006) and that lifecourse socioeconomic status predicts altered adult diurnal cortisol rhythms (DeSantis et al., 2015). We build on this work to test the hypothesis that a composite measure of early life stressors will predict depressive symptoms during early adulthood. Additionally, we further hypothesize that altered HPA axis function, as reflected by elevated salivary bedtime cortisol and cortisol awakening response levels, will account for the depressive effects of early life stress.

2 | METHODS

2.1 | Study population and data collection

Data come from the Cebu Longitudinal Health and Nutrition Survey (CLHNS), an ongoing, population-based birth cohort study of mothers and their infants born in 1983–1984 in Cebu, Philippines (Adair et al., 2010). A single stage, random clustering sampling procedure selected 17 urban and 16 rural communities (*barangays*) among the 243 barangays in the metropolitan Cebu area, resulting in the recruitment of 3,327 pregnant women. Initial and follow-up surveys were conducted through question-based, in-home interviews. Data for this analysis come from survey rounds conducted in 1991–1992, 1994–1995, 1998, 2002, and 2005 (Adair et al., 2010). All interviews were completed in Cebuano. Complete socio-

demographic, psychosocial, mental health, and cortisol data were available for 1,244 participants. Participants with highly atypical sleep patterns were excluded from the sample as individuals with abnormal sleep behaviors, such as those of shift workers, are known to exhibit altered diurnal cortisol rhythms (Kudielka, Buchtal, Uhde, & Wust, 2007; Niu et al., 2011). Comparisons of our analytic sample with the larger cohort sample from the 2005 collection not included in this analysis show nonsignificant differences in household income at birth and 2005, the frequency of sibling death, feeling distant from one's father, and depressive symptom severity (all $p > .3$). Household income at birth and 2005 and depressive symptoms were lower in the analytical sample relative to the excluded sample, while the frequencies of sibling death and feeling distant from one's father were greater in the analytical sample. Conversely, education levels at 2005 ($p = .0067$) and assets at 2005 ($p = .0398$) were higher in the analytical sample, while maternal absence ($p = .00001$), paternal absence ($p = .00001$), and feeling close to one's mother ($p = .0141$) occurred more frequently in the excluded sample. The analytical sample tended to witness parental violence at a greater proportion ($p = .075$). Thus, the analytic sample is slightly more advantaged than the larger CLHNS cohort. This research was conducted under conditions of written informed consent with human subjects clearance from the Institutional Review Boards of the University of North Carolina, Chapel Hill, and Northwestern University.

2.2 | Measures of early life stress and depressive symptoms

Six measures of early life family-related stress were operationalized as dichotomous categorical variables and summed to create a composite score. Early life stress variables included measures of maternal absence, paternal instability, sibling death, witnessing domestic violence during childhood (Gettler et al 2015; Hindin & Gultiano, 2006), and reverse scored measures of feeling close to one's mother during childhood, and closeness to one's father during childhood (Hindin, 2005). Participants were classified as having experienced maternal absence if they lived in a separate household than their mother at 8.5 years old in 1991 or 11.5 years old in 1994. Individuals who were classified as having experienced "paternal instability" were those whose father was deceased or absent, whose mother was unmarried during their first year of life or beyond, or whose mother remarried during their childhood-juvenile period from birth up to age 11.5 (±0.4) years, which was in 1994. Sibling death was assessed based upon maternal reports of her children's births and deaths from 1983 until 1994 when participants were 11.5 years old, also in 1994. Finally, participants during the 2002 data collection wave (17–19 years of age) were asked "Do you remember if either of your parents/caretakers ever hit, slapped, kicked, or used other means like pushing or shoving to try to hurt the other physically when you were growing up?" as a measure of witnessing domestic violence during childhood.

Additionally, we evaluated the impact of negative parental relationship as reflected in a measure of parental support. Prior research has reported poorer mental health outcomes during adulthood when children experienced adverse parental care-taking (Mickelson, Kessler, & Shaver, 1997; Nickerson, Bryant, Aderka, Hinton, & Hofmann, 2013). Negative parenting measures were similarly limited and consisted of two variables that measured parental support and were reverse scored, specifically questions that asked whether the participant felt close to one's mother and father during childhood during the 2002 data

collection when children were 17–19 years old (Hock et al., 2016). Domestic violence questions were administered in 2002 as well. Whether an individual witnessed domestic violence and felt close to one's parents were retrospective reports of the individual's experience growing up, while measures of maternal absence, paternal absence, and sibling death were assessed at the time of data collection. After the six categorical stress variables were summed, the composite variable was recoded to four groups: 0, 1, 2, and 3+ stressors. Each level of this variable was dummy coded in order to examine dose–response or threshold effects. These six variables were among the small handful of data points on early life stress that were collected during the study, which was initially designed to study the long-term health impacts of infant feeding.

Depressive symptoms were measured using an adapted version of the Center for Epidemiologic Studies Depression Scale (CES-D), which is a commonly utilized mental health battery used to screen for depression and assess depressive symptomatology (Radloff, 1977). The CES-D was administered during the 2005 data collection wave for the CLHNS when participants were 21–22 years old. This survey queries both negative (e.g., difficulty eating and sleeping, feeling lonely, suicidal thoughts, etc.) and positive experiences (e.g., feeling happy, hopeful about the future, enjoyed daily activities, etc.). Ratings on a three-point scale ranged from "none of the time" (0), "occasionally" (1), to "most or all of the time" (2). Scores were summed across all questions, following reverse scoring of positive items, to generate an index of depressive symptoms. Cronbach's α was .7338, suggesting an acceptable degree of scale reliability.

2.3 | Cortisol collection, preparation, and measurement

During the 2005 survey, each participant was provided with instructions and three polypropylene tubes for saliva collection. Three samples representing cortisol levels at key points in time in the diurnal cortisol cycle were collected. The first was collected at bedtime, the next immediately upon waking, and the final sample 30 min after waking. This protocol allowed us to capture both morning and evening cortisol levels in a limited timeframe; we believe any error (or additional state variation) introduced by sampling evening levels on 1 day and morning levels on the next day is compensated for by the large sample size (~1,250 participants) associated with this study (Adam & Kumari, 2009). Each tube was pre-labeled to avoid confusion and contamination, and participants were further instructed to keep the other two empty tubes in a Ziploc bag beside their bed to more easily facilitate the collection of the second saliva sample immediately upon waking. Participants were also given timers to set to 30 min, at which time they provided the third sample, and were instructed not to brush their teeth or smoke 30 min before providing any samples. Participants were also provided diaries in which they were instructed to record the date and exact time the samples were provided (Adam & Kumari, 2009).

The cortisol awakening response was estimated by subtracting the waking cortisol values from the levels 30 min later, although we recognize that this calculation of CAR no longer meets the guidelines for optimal measurement (Stalder et al., 2016). All cortisol values were natural log transformed to correct strong positive skews, and measures in this analysis were standardized such that effect sizes could be easily compared across different cortisol

measures. Diurnal slopes were calculated by subtracting waking cortisol levels from evening levels and dividing this value by the length of the waking day in hours using data from both days of saliva sampling (DeSantis et al., 2015). An hourly rate of cortisol decline from morning levels to evening levels was therefore calculated, with steeper slopes reflected by a larger, more negative rate of decline, and flatter slopes associated with a smaller negative decline or an increase in cortisol from morning to evening levels.

Saliva tubes were collected later the second day by an interviewer, who placed the tubes on ice packs in a cooler while in transit to freezer storage at −35°C. Samples were shipped on dry ice to Northwestern University, where they were stored at −80°C. They were later thawed, centrifuged, supernatant separated, and aliquoted into smaller tubes for analysis of individual analytes. Cortisol was assayed in duplicate by a laboratory in Trier, Germany, using a time-resolved immunoassay with fluorometric detection (DELFIA). The intra- and inter-assay coefficients of variation (CVs) were between 4.0 and 6.7%, and 7.1 to 9.0%, respectively. Samples with CVs over 12% were rerun. Our analyses examined cortisol in log-transformed microgram per deciliter (μg/dl) units.

2.4 | Covariates

Covariates included sex, smoking status, time of evening saliva collection (Kudielka & Kirschbaum, 2003), and two measures of socioeconomic status. Food consumption and exercise were also tested as covariates but were not included in the final models since they were not significantly related to early life stress, depressive symptoms, or individual cortisol indices. Socioeconomic status (SES) was assessed using a multidimensional summary measure, which was comprised of the following variables: household income (weekly income in pesos standardized to year), a household assets (sum of the following items: home ownership, electricity in the home, type of housing material, and ownership of items such as air conditioner, television, refrigerator, or car), and educational attainment at both years (years of formal schooling). Each variable was standardized (mean = 0, $SD = 1$), and values were averaged to create the summary SES measure (McDade et al., 2019). Separate variables were created for each year the survey was conducted in 1983, 1986, 1991, 1994, and 2005.

In order to capture the overall SES environment during the timespan in which the experiences of early life stress occurred, between infancy and middle childhood, an “early life SES” variable was constructed by summing SES scores from the 1983, 1986, 1991, and 1994 surveys. Pairwise correlations indicate a high level of agreement between SES in 1983, 1986, 1991, and 1994 as the correlation coefficient ranged between R = 0.81 and R = 0.89, further justifying the construction of a summary early SES variable. For the young adulthood SES variable, participants’ own education (years of formal schooling) was used in place of parental education. Cronbach’s α for each survey was as follows: .72 (1983), .74 (1986), .78 (1991), and .56 (2005).

To control for the effects of recent stress, self-reported psychosocial stress experienced within the last month was quantified using a modified version of the 10-item perceived stress-scale (PSS) (Cohen, Kamarck, & Mermelstein, 1994). To ensure cultural appropriateness, all stress related questions were pilot tested and refined in focus groups.

Participants were asked to rate on a five-point scale (0 = never, 4 = very often) how often they experienced a particular form of stress. The PSS was administered in Cebuano after being translated from English and back-translated to confirm accuracy. As a result of preliminary research with the PSS in Cebu, prior to implementation in the 2005 survey, two questions (item 9, “how often have you been angered”; item 10, “how often have you felt difficulties were piling up”) were replaced with two new questions: “In the last 4 weeks, how often have you dealt successfully with irritating life hassles?” and “In the last 4 weeks, how often have you felt that you were effectively coping with important changes that were occurring in your life?” Scores were summed across all 10 questions, following reverse scoring of six positively stated items.

2.5 | Data analyses

All analyses were conducted using version 13.1 of Stata (Stata Corporation, College Station, TX). Depressive symptom scores, PSS, waking cortisol, cortisol awakening response, bedtime cortisol, diurnal cortisol slope, household income, household assets, educational attainment, and time of evening saliva collection were all analyzed as continuous variables. The data analysis plan consisted of four stages. First, bivariate associations between early life stress, cortisol measures, depressive symptom scores, and covariates were calculated (Tables 2a and 2b). Second, we considered sex as well as past and recent household SES as predictors. Our final model examined whether or not associations between early life stress and depressive symptoms are dependent on our HPA axis measures by including measures of PM cortisol and the cortisol awakening response, then diurnal slope and the cortisol awakening response. Diurnal slope and bedtime cortisol were not included in the same model because both variables strongly covaried with one another (Table 2b). All cortisol models were adjusted for time of saliva collection and smoking. $\alpha < .05$ was used as the criterion for statistical significance.

3 | RESULTS

Nearly half of all participants reported witnessing domestic violence in their household while growing up (Table 1). Approximately 14% of participants did not feel close with their mother during adolescence while 26% of individuals did not feel close with their father during adolescence. A smaller proportion of respondents had a sibling die during childhood (15.7%), faced paternal instability (2.7%), or experienced maternal absence (1.2%). Eight-hundred and fifty-four individuals experienced at least one stressful event and 92 adults experienced three or more stressful events. The average adapted depressive symptom score in the analytic sample was 9.3/29. Bivariate associations between major study variables are presented in Table 2a. Table 2b shows zero-order correlations between disaggregated early life stress measures and cortisol indices.

Our first model (Model 1) assessed the relationship between our early life stress composite measure and adult depressive symptoms controlling for sex (Table 3a). Greater number of early life stressors significantly predicted a higher levels of depressive symptoms at age 21–22. Results from this partial regression model also show a dose–response relationship between the number of early life stressors and adult depressive symptoms. Additionally, we

find that males have lower levels of depressive symptoms compared to women, which is consistent with past literature (Maciejewski, Prigerson, & Mazure, 2001; Nolen-Hoeksema, 2001; Weissman et al., 1993).

We then controlled for possible effects attributed to socioeconomic status at both early life and 2005 (Model 2) by adding the multidimensional summary measure for both timepoints of SES. After controlling for both past and recent SES, the relationship between early life stress and depressive symptoms is slightly weakened but remains significant. Females had higher levels of depressive symptoms. Household SES at 2005 was negatively associated with depression risk scores ($\beta = -.69$, $p = .002$) while household SES during early child development did not significantly predict adult depression risk.

Our next models (Models 3 and 4) assessed whether alterations in HPA circadian dynamics might affect relationships between early experiences and adult depressive symptoms. We tested the relationship between adult depressive symptoms and diurnal cortisol slope (the rate of change in cortisol concentrations from morning to evening) and the cortisol awakening response while controlling for time of evening saliva collection, smoking status, as well as recent stress, which was assessed by an adapted version of the Perceived Stress Scale (Cohen et al., 1994). Flatter cortisol slopes, indicated by greater positive values, at age 21–22 predicted higher levels of depressive symptoms ($p = .003$) (Table 3a, Model 4). The effect of the cortisol awakening response did not reach significance. Including the cortisol variables modestly altered the relationship between early life stress and depressive symptoms as indicated by the change in the coefficient of the early life stress composite variable from Model 2 (0.4006) to Model 4 (.353), the fully adjusted model, and the dummy coded stress groups. Greater levels of perceived stress are significantly related to elevated depressive symptom scores ($p < 0.0001$).

Because the measure of diurnal cortisol slope is calculated by subtracting evening levels from morning levels divided by the duration in time (Adam & Kumari, 2009; DeSantis et al., 2015), we disaggregated the cortisol slope variable into separate morning and evening levels to examine which component of the diurnal cortisol rhythm impacted depression risk (Models 5 and 6). The new fully-adjusted regression model, which includes the morning and evening measures in place of the slope and CAR variables, shows that on average, evening cortisol levels significantly predict adult depressive symptoms ($p = .004$) (Figure 1). Greater evening cortisol concentrations correspond with higher depressive symptom scores (Table 3a). The effect of waking cortisol on adult depressive symptom is not significant. Early life stress continues to significantly predict adult depressive symptoms in a dose–response fashion. Similar to the effects of diurnal slope and CAR variables in Models 3 and 4, the inclusion of the bedtime and waking cortisol variables led to very modest changes in the coefficient of the early life stress composite variable from Model 2 (0.4006) to Model 6 (0.39), the complete model, and the dummy coded stress groups.

We then disaggregated the early life stress composite measure to examine the effects of each early life stress variable, all of which were coded as categorical variables, on young adult depressive symptoms (Table 3b). One categorical predictor variable was removed to serve as the reference group. Witnessing parental violence significantly predicted depressive

symptoms at age 21–22 and increased an individual's depressive symptom score by an average of 0.75 points in fully adjusted models ($p < .0001$) (Figure 2). No other early life stress measures significantly predicted depression risk. Being male and greater socioeconomic status at 2005, but not during early life, corresponded with decreased depressive symptom severity. Similar to the previous model, higher levels of evening cortisol significantly associated with higher depressive symptom scores ($p = .005$).

Finally, we conducted a separate analysis to examine whether early life stress affected young adult cortisol rhythms. Our results show no significant relationships between the early life stress composite measure and any of the diurnal cortisol measures (e.g., waking, cortisol awakening response, evening, diurnal slope). After disaggregating the early life stress composite measure, however, those who witnessed domestic violence during childhood exhibited significantly lower levels of bedtime cortisol ($p = .018$).

4 | DISCUSSION

Our findings suggest that early life stress, witnessing domestic violence during childhood, and alterations in adult HPA axis function predict the severity of depressive symptoms during adulthood in this sample of Cebuano young adults. However, contrary to previous findings in the literature, these relationships appeared to be independent of one another, as indicated by the modest changes in the relationship between early life stress and adult depression risk after controlling for HPA axis measures (Tables 3a and 3b). Thus, we report that diurnal cortisol activity does not affect adult depressive symptoms as a result of early life stress during child development. Our early life stress composite measure also did not predict diurnal cortisol patterns during young adulthood in this sample, but witnessing domestic violence during childhood predicted lower bedtime cortisol levels.

Our findings linking early life stress and diurnal cortisol rhythms with depression are in general agreement with past work investigating similar questions. We confirm the overall positive association previously reported between early life stress and adult depressive symptoms (Heim & Binder, 2012; Taylor et al., 2011) as seen by the direct relationship between our composite measure of early life stress and adult depressive symptoms (Figure 3) as well as the long-term adult depressive impacts of witnessing domestic violence during childhood. When examining the relationships between each individual, disaggregated stress measure and young adult depression risk, with exception to witnessing domestic violence, none of our additional measures of early life stress significantly predicted depressive symptomatology independently (Table 3b). When considering the cumulative effects of these measures, however, exposure to more of these stressors during development is associated with worse depressive outcomes in early adulthood. This result indicates that it may take an accumulation of several stressful experiences and conditions to produce a larger and detectable impact on adult mental health in our sample. While some individual risk factors were nonsignificant in our analyses, past research suggests that these family-based stressors pose threats to future mental health in other groups. The deleterious effects of parental and sibling absence on mental health have been widely documented in the literature. In past studies, individuals who experienced parental loss, defined as either a prolonged absence or death of a parental figure, during childhood were more likely to report future

onset of symptoms of adult psychopathologies including depression and generalized anxiety disorder (Kendler, Heath, & Eaves, 1992; Tyrka et al., 2008) and exhibit signs of HPA axis dysregulation (Breier, 1989; Luecken, 2000; Meinlschmidt & Heim 2005; Nicolson, 2004; Tyrka, Wier, Price, Ross, & Carpenter, 2008). Similarly, experiencing the loss of a sibling during adolescence was significantly associated with symptoms of anxiety and depression during mid-adulthood among individuals who lost a sibling to cystic fibrosis (Fanos & Nickerson, 1991), though the literature on the long-term impacts of sibling loss is sparse. Further research may uncover potential sources of buffering against the long-term mental health impacts of parental and sibling loss.

Our results also report that flatter adult diurnal cortisol slopes, but not concentrations of waking cortisol or the cortisol awakening response, are directly associated with adult depressive symptoms. This finding is consistent with an increasing body of literature that strongly suggests that flatter diurnal cortisol rhythms may be a distinct characteristic of certain forms of depression and other physical and mental diseases (Adam, 2012; Balardin, Vedana, Luz, & Bromberg, 2011; Bhattacharyya, Molloy, & Steptoe, 2008; Jarcho et al., 2013; Knight, Avery, Janssen, & Powell, 2010; Weinrib et al., 2010). Past studies have found that flatter diurnal cortisol rhythms occur due to either lower morning cortisol, higher evening cortisol, or both, all of which are indications of HPA axis dysregulation (DeSantis et al., 2015; Doane et al., 2013; Lopez-Duran et al. 2009; Weinrib et al., 2010), a strongly implicated mechanism of adult depression (Adam et al., 2010; Arborelius et al. 1999; Doane et al., 2013; Heim & Binder, 2012; Jarcho et al., 2013; Mangold et al., 2011; Plotsky et al., 1998; Vrshek-Schallhorn et al., 2013). Disaggregating the slope measure showed that higher evening cortisol levels predominantly accounted for the effects of cortisol diurnal rhythms on adult depression symptomatology (Figure 1). The positive association between evening cortisol concentrations and adult depressive symptoms is also consistent with previous studies (Gold et al., 1988; Plotsky et al., 1998; Young et al., 1994). While we did not find any significant links between the cortisol awakening response and depressive symptoms, prior research has reported altered cortisol awakening responses among depressed adults. These findings tend to report elevated cortisol awakening responses during depression (Bhagwagar, Hafizi, & Cowen, 2003; Pruessner et al., 2003), though negative associations have also been reported (Stetler & Miller 2005; Ellenbogen et al. 2006; van der Vegt et al., 2009). Variations in the neuroendocrine profiles of depressed patients across studies may relate to the severity of depression considered in each study, which ranges from heightened depressed mood within the normal range of symptomatology to major depressive disorder (Chida & Steptoe, 2009).

We also find that individuals who witnessed domestic violence during adolescence tended to have lower bedtime cortisol levels at age 21–22, while there were no differences in the cortisol awakening response. The association between witnessing domestic violence and lower bedtime cortisol levels was an unexpected finding as past studies have generally found that early life adversity corresponds with greater evening levels. For example, Engert et al. (2011) and Nicolson (2004) found that individuals who received low early life parental care and experienced a loss of a parent either by death or separation exhibited higher bedtime cortisol levels during adulthood. Additionally, in a meta-analysis of chronic stress and HPA axis, experiencing chronic stressors that posed physical threats, were traumatic in nature,

and uncontrollable were associated with elevated evening cortisol levels (Miller, Chen, & Zhou, 2007). Although several studies have reported null associations between early life stress and adult evening cortisol concentrations (Gerritsen et al., 2010; Gonzalez et al., 2009; Miller et al., 2009; van der Vegt et al., 2009), a smaller number of studies have reported similar links between greater early adversity and lower evening cortisol levels that we report. Gustafsson et al. (2010) found that decreased evening levels among women who lived in low socioeconomic status households as adolescents. In our study, the association between decreased evening cortisol levels during young adulthood and witnessing domestic violence during adolescence may be a function of the timing since the onset of stress. In the same meta-analysis, Miller et al. (2007) argue that the seemingly contradictory findings between hyper- and hypocortisolism among chronically-stressed adults “simply reflect different timepoints during the stress process” (35). Upon exposure to stress, the HPA axis may become activated, causing a rise in circulating cortisol levels. Overtime, the HPA axis may mount a counter-regulatory response whereby cortisol output rebounds below normal levels (Miller et al., 2007). The transition from hypercortisolism to hypocortisolism has also been interpreted as a result of the HPA axis losing its resilience overtime (McEwen, 1998). Several studies that examine neuroendocrine patterns associated with past stressors have documented decreases in HPA axis output (Carpenter et al., 2007; Rohleder, Joksimovic, Wolf, & Kirschbaum, 2004; Yehuda et al., 1995; Yehuda, Boisonuae, Lowy, & Giller, 1995; Yehuda, Resnick, Schmeidler, Yang, & Pitman, 1998; Yehuda, Teicher, Trestman, Levengood, & Siever, 1996). Additionally, studies on the early life impacts on the cortisol awakening response tend to report positive relationships. For example, individuals exposed to an array of stressful life experiences during child development such as parental loss and child maltreatment (Gonzalez et al., 2009) and neglect and abuse (van der Vegt et al., 2009), and adverse social conditions such as low socioeconomic status (Gustafsson et al., 2010) generally exhibited heightened cortisol awakening responses compared to their respective comparison groups. Nonetheless, several studies have reported opposing or nonsignificant findings (Miller et al., 2009). Similar to our prior consideration with depression, differences in the early life stress-HPA axis relationship seen across these studies may be explained by the particular qualities of early life stress in question, such as the frequency, severity, and social meaning of the psychosocial stressor or environmental condition (Fogelman & Canli, 2018; Lyons & Parker, 2007; Miller et al., 2007).

Previous findings from CLHNS reported the predictive effects of witnessing domestic violence during child development on adult depressive symptoms (Hindin & Gultiano, 2006). This study confirms the positive relationship between witnessing domestic violence and adult depressive symptoms and expands the scope of stressful experiences measured between birth and late adolescence to include five additional measures of psychosocial stress, which include the absence of one’s father, the absence of one’s mother, death of a sibling, and feeling distant from one’s mother and father. This study further emphasizes the role that early life experiences have on shaping the HPA axis in this sample. DeSantis et al. (2015) reported that chronically low socioeconomic status from infancy to early adulthood predicted diurnal HPA axis rhythms in adulthood. The direction of the relationships between both measures of early life adversity and depression, however, were opposing. Cumulative economic strain from prenatal development to early adulthood was associated with higher

bedtime cortisol levels, lower CARs, and other characteristics of HPA axis dysregulation (i.e., lower total cortisol output, flatter cortisol slopes) while our findings show that witnessing domestic violence predicted lower bedtime cortisol levels. As previously mentioned, the nature of the stressor in question may explain the varying relationships between early life stress and HPA axis function seen across studies, though the lack of specificity in our survey question on witnessing domestic violence preclude us from ascertaining the particular qualities of the stressor that may explain our discrepant finding.

Considering the inverse relationship between witnessing domestic violence and adult evening cortisol levels, the finding that bedtime cortisol levels do not influence the relationship between early life stress and depressive symptoms is expected statistically but conceptually perplexing. The strengthened relationship between early life stress and adult depressive symptoms after including the bedtime cortisol variable suggests that early life stress predicts depressive symptoms despite the fact that individuals in our sample tend to exhibit cortisol levels of non-depressed individuals. We intended on conducting a mediation analysis to evaluate the links between early life stress, cortisol levels, and depressive risk, but our results did not meet the criteria for mediation analysis as all three variables were not significantly correlated to one another. While cross-sectional measure of HPA axis function may not be related to the depressive effects of early life stress during young adulthood, HPA axis function at earlier stages of development may still influence one's risk of later life depression (Adam et al., 2010; Bockting et al., 2012; Goodyer, Bacon, Ban, Croudace, & Herbert, 2009; Vrshek-Schallhorn et al., 2013). These findings also suggest that additional biological mechanisms may facilitate the durable effects of early life experiences on later life health. Other biological pathways of HPA axis function that have previously been implicated in the early life stress-adult depression pathway include upstream mechanisms like epigenetic variation (e.g., DNA methylation, histone modification) (Heim & Binder, 2012; Khulan et al., 2014; Smith, Parets, & Kim, 2014) and downstream pathways such as inflammatory (immune activation, gut-brain axis) (Pace et al., 2006) and neurobiological mechanisms (e.g., neurotransmission, neuroanatomic changes) (Gatt et al., 2010; Grant, Cannistraci, Hollon, Gore, & Shelton, 2011). For example, early life stress has been hypothesized to influence differential methylation signatures among HPA axis-related genes, such as the glucocorticoid receptor gene, which in may alter the binding of cortisol and its subsequent impact on adult depression (Heim & Binder, 2012; Jawahar, Murgatroyd, Harrison, & Baune, 2015).

Future studies can further elucidate the role of HPA axis function in contributing to the long-term effects of early life stress on adult depressive symptomatology by waiting to evaluate adult depressive risk a few months or years after cortisol measurements are collected. This longitudinal design can help clarify whether the durability of altered adult cortisol activity due to early life stress is what influences later life depressive symptoms and eliminates the possibility of reverse causality between cross-sectional measures of depressive symptoms and cortisol levels, as seen in our study. Reliable and culturally validated measures of early life stress and depression will also strengthen the internal validity of future studies, and multiple days of cortisol collection with daily assessments of mood, behaviors, and experience will better characterize typical diurnal cortisol rhythms. Finally, additional stress-sensitive mechanism that are both upstream and downstream of HPA axis function can be

assessed to identify other biological pathways involved in the long-term depressive effects of early life stress.

4.1 | Limitations

The first limitation of this study is our crude measure of early life stress. Our variables were limited to family-level experiences and conditions that were reduced to only six dummy variables. There are likely a wide variety of stressors across multiple domains and levels of life that may have similar long-term effects on mental health and, in general, affect the body. Different dimensions of psychosocial stress, such as a more diverse set of experiences and conditions (various forms of social oppression, disease and illness experience, teratogens, etc.), chronicity, severity, and sociocultural meaning, could have distinct and varied sequelae on HPA axis function (e.g., diurnal cortisol rhythm, stress reactivity) and later life health.

The cultural relevance and psychometric validity of the depression screener used in this study (i.e., CES-D) may be another source of bias. While the Cronbach's alpha meets the threshold for scale validity, the comprehensibility and relevance of the sub-constructs included in the CES-D may be compromised because of their lack of cultural relevance and salience. The same concern applies to other survey tools used in this study, such as the Perceived Stress Scale.

Third, our process of sampling and measuring the cortisol awakening response did not meet expert guidelines as outlined Stalder et al. (2016). Only two post-awakening samples were obtained to assess the CAR (at waking and 30 min later), rather than the recommended minimum of three. In addition, cortisol data were collected across 2 days—the first at bedtime and the next two immediately upon waking and 30 min later. Because momentary- and day-level changes in emotions and social experiences shape cortisol levels (Adam, 2006), it is preferred to collect samples for diurnal cortisol across multiple days (Adam & Kumari, 2009). Additionally, in order to maximize sample efficiency in this large, longitudinal sample for which home-based sample refrigeration was not available, the diurnal rhythm was first assessed at bedtime and followed into the next day. Low compliance to saliva collection instructions at specific timepoints may also bias cortisol data. Further analyses show, however, that there were no significant or considerable differences between the time of collection between the wake +30 min sample and the wake sample among individuals with low and high levels of depressive symptoms, steeper and flatter slopes, and lower and higher CARs. Finally, we did not assess mood states, daytime experiences, and stress levels at the times of saliva sampling nor utilize electronically monitor compliance with sampling protocols (Stalder et al., 2016). As part of a large population-based study, however, errors in reliability due to this minimized protocol are likely to be reduced by the large sample size (Adam & Kumari, 2009). Because the ongoing study already included an extensive protocol and was conducted across a large metropolitan area and many surrounding rural communities, the research team felt that reduced reliability was a reasonable tradeoff for the large sample size that is a representative 1-year birth cohort for the country's second-largest city.

5 | CONCLUSION

In summary, early life family-related stressors predicted greater severity of depressive symptoms at early adulthood in a dose–response fashion and witnessing domestic violence during child development predicted lower levels of evening cortisol in this large, naturalistic, non-Western, and longitudinal sample of individuals in metropolitan Cebu, Philippines. When considering the cumulative effects of early life family-based adversity, greater exposure to these stressors during development predicted worse depressive outcomes in early adulthood. While both bedtime cortisol and diurnal cortisol slopes significantly predicted adult depressive symptoms cross-sectionally, adult cortisol levels did not explain the effect of early life stress on adult depressive symptoms. Furthermore, this analysis does not support the notion that the depressive impacts of early life stress are influenced by HPA axis function in this particular stage of young adulthood and this sample. Given our limited saliva collection protocols and that we measured cortisol at only one stage of adulthood, more robust measures of HPA axis function across multiple time points throughout development may uncover possible sensitive periods that may be involved in the psychobiological development of adult depression. Additionally, we also note that our early life stress composite variable is limited as it is not a validated measure of family-based stress in Cebu. Nonetheless, these findings suggest that the long-term depressive effects of certain forms of early life stress extend to this large sample in the Philippines, and that early life stress and HPA axis function at age 21–22 in this sample may shape adult depression through independent pathways in our sample. Our results provide further evidence that HPA axis activity is shaped by early life conditions and is associated with depressive symptoms, and that early life development is an important period research and intervention for improving global mental health.

ACKNOWLEDGMENTS

We thank the many scholars and researchers at the Office of Population Studies, University of San Carlos, Cebu, Philippines, for their role in study design and data collection, and the Filipino participants who generously provided their time for this study.

Funding information

National Institutes of Health R01-HD19983A, R01-HD18880, P01-HD28076, R01-HD23182, R01-TW05596, R01-HL085144, R01-DK078150, R01-HD054501, and R03TW008133; Nestle Coordinating Center for Nutrition Research, Wyeth International, The Ford Foundation, The US National Academy of Science, The World Health Organization, The US Agency for International Development (via grants from Wellstart Interna- tional, the International Center for Research on Women, Family Health International, MEASURE), The Asian Development Bank, The World Bank, The Thrasher Research Fund, The Mellon Foundation, Nestle Research Foundation, and The Carolina Population Center

REFERENCES

Adair LS, Popkin BM, Akin JS, Guilkey DK, Gultiano S, Borja J, … Hindin MJ (2010). Cohort profile: The Cebu longitudinal health and nutrition survey. International Journal of Epidemiology, 40(3), 619–625. [PubMed: 20507864]

Adair LS, Popkin BM, Akin JS, Guilkey DK, Gultiano S, Borja J, Perez L, Kuzawa CW, McDade T & Hindin MJ (2011). Cohort profile: the Cebu longitudinal health and nutrition survey. International journal of epidemiology, 40(3), 619–625. [PubMed: 20507864]

Adam EK (2006). Transactions among adolescent trait and state emotion and diurnal and momentary cortisol activity in naturalistic settings. Psychoneuroendocrinology, 31(5), 664–679. [PubMed: 16584847]

Adam EK (2012). Emotion—Cortisol transactions occur over multiple time scales in development: Implications for research on emotion and the development of emotional disorders. Monographs of the Society for Research in Child Development, 77(2), 17–27.

Adam EK, Doane LD, Zinbarg RE, Mineka S, Craske MG, & Griffith JW (2010). Prospective prediction of major depressive disorder from cortisol awakening responses in adolescence. Psychoneuroendocrinology, 35(6), 921–931. [PubMed: 20079576]

Adam EK, & Kumari M (2009). Assessing salivary cortisol in large-scale, epidemiological research. Psychoneuroendocrinology, 34, 1423–1436. [PubMed: 19647372]

Adam EK, Quinn ME, Tavernier R, McQuillan MT, Dahlke KA, & Gilbert KE (2017). Diurnal cortisol slopes and mental and physical health outcomes: A systematic review and meta-analysis. Psychoneuroendocrinology, 83, 25–41. [PubMed: 28578301]

Angold A, & Worthman CW (1993). Puberty onset of gender differences in rates of depression: A developmental, epidemiologic and neuroendocrine perspective. Journal of Affective Disorders, 29(2), 145–158. [PubMed: 8300975]

Arborelius L, Owens MJ, Plotsky PM, & Nemeroff C (1999). The role of corticotropin-eleasing factor in depression and anxiety disorders. Journal of endocrinology, 160(1), 1–12.

Balardin JB, Vedana G, Luz C, & Bromberg E (2011). Subjective mild depressive symptoms are associated with abnormal diurnal cycle of salivary cortisol in older adults. Journal of Geriatric Psychiatry and Neurology, 24(1), 19–22. [PubMed: 20558832]

Barker DJ (1999). Fetal origins of cardiovascular disease. Annals of medicine, 31(sup1), 3–6.

Bhagwagar Z, Hafizi S, & Cowen PJ (2003). Increase in concentration of waking salivary cortisol in recovered patients with depression. The American Journal of Psychiatry, 160, 1890–1891. [PubMed: 14514508]

Bhattacharyya MR, Molloy GJ, & Steptoe A (2008). Depression is associated with flatter cortisol rhythms in patients with coronary artery disease. Journal of Psychosomatic Research, 65(2), 107–113. [PubMed: 18655854]

Bockting CL, Lok A, Visser I, Assies J, Koeter MW, Schene AH, & DELTA Study Group. (2012). Lower cortisol levels predict recurrence in remitted patients with recurrent depression: A 5.5 year prospective study. Psychiatry Research, 200(2–3), 281–287. [PubMed: 22503382]

Breier A (1989). Experimental approaches to human stress research: Assessment of neurobiological mechanisms of stress in volunteers and psychiatric patients. Biological Psychiatry, 26, 438–462. [PubMed: 2551397]

Butler K, Klaus K, Edwards L, & Pennington K (2017). Elevated cortisol awakening response associated with early life stress and impaired executive function in healthy adult males. Hormones and Behavior, 95, 13–21. [PubMed: 28760691]

Cărnuţă M, Crişan LG, Vulturar R, Opre A, & Miu AC (2015). Emotional non-acceptance links early life stress and blunted cortisol reactivity to social threat. Psychoneuroendocrinology, 51, 176–187. [PubMed: 25462891]

Carpenter LL, Carvalho JP, Tyrka AR, Wier LM, Mello AF, Mello MF, … Price LH (2007). Decreased adrenocorticotropic hormone and cortisol responses to stress in healthy adults reporting significant childhood maltreatment. Biological Psychiatry, 62, 1080–1087. [PubMed: 17662255]

Carpenter LL, Shattuck TT, Tyrka AR, Geracioti TD, & Price LH (2011). Effect of childhood physical abuse on cortisol stress response. Psychopharmacology, 214(1), 367–375. [PubMed: 20838776]

Carr CP, Martins CMS, Stingel AM, Lemgruber VB, & Juruena MF (2013). The role of early life stress in adult psychiatric disorders: A systematic review according to childhood trauma subtypes. The Journal of Nervous and Mental Disease, 201(12), 1007–1020. [PubMed: 24284634]

Chapman DP, Whitfield CL, Felitti VJ, Dube SR, Edwards VJ, & Anda RF (2004). Adverse childhood experiences and the risk of depressive disorders in adulthood. Journal of Affective Disorders, 82(2), 217–225. [PubMed: 15488250]

Chida Y, & Steptoe A (2009). Cortisol awakening response and psychosocial factors: A systematic review and meta-analysis. Biological Psychology, 80(3), 265–278. [PubMed: 19022335]

Cohen S, Kamarck T, & Mermelstein R (1994). Perceived stress scale. Measuring stress: A guide for health and social scientists.

Coplan JD, Andrews MW, Rosenblum LA, Owens MJ, Friedman S, Gorman JM, & Nemeroff CB (1996). Persistent elevations of cerebrospinal fluid concentrations of corticotropin releasing factor in adult non human primates exposed to early-life stressors: Implications for the pathophysiology of mood and anxiety disorders. Proceedings of the National Academy of Sciences of the United States of America, 93, 1619–1623. [PubMed: 8643680]

Dahl RE, Ryan ND, Puig-Antich J, Nguyen NA, Al-Shabbout M, Meyer VA, & Perel J (1991). 24-hour cortisol measures in adolescents with major depression: A controlled study. Biological Psychiatry, 30(1), 25–36. [PubMed: 1892959]

DeSantis AS, Adam EK, Mendelsohn KA, & Doane LD (2010). Concordance between self-reported and objective wakeup times in ambulatory salivary cortisol research. International Journal of Behavioral Medicine, 17(1), 74–78. [PubMed: 19597997]

DeSantis AS, Kuzawa CW, & Adam EK (2015). Developmental origins of flatter cortisol rhythms: Socioeconomic status and adult cortisol activity. American Journal of Human Biology, 27(4), 458–467. [PubMed: 25753264]

Doane LD, Mineka S, Zinbarg RE, Craske M, Griffith JW, & Adam EK (2013). Are flatter diurnal cortisol rhythms associated with major depression and anxiety disorders in late adolescence? The role of life stress and daily negative emotion. Development and Psychopathology, 25(3), 629–642. [PubMed: 23880381]

Ellenbogen MA, Hodgins S, Walker CD, Couture S, & Adam S (2006). Daytime cortisol and stress reactivity in the offspring of parents with bipolar disorder. Psychoneuroendocrinology, 31(10), 1164–1180. [PubMed: 17055665]

Elzinga BM, Roelofs K, Tollenaar MS, Bakvis P, van Pelt J, & Spinhoven P (2008). Diminished cortisol responses to psychosocial stress associated with lifetime adverse events: A study among healthy young subjects. Psychoneuroendocrinology, 33(2), 227–237. [PubMed: 18096322]

Engert V, Efanov SI, Dedovic K, Dagher A, & Pruessner JC (2011). Increased cortisol awakening response and afternoon/evening cortisol output in healthy young adults with low early life parental care. Psychopharmacology, 214(1), 261–268. [PubMed: 20596856]

Fanos JH, & Nickerson BG (1991). Long-term effects of sibling death during adolescence. Journal of Adolescent Research, 6(1), 70–82.

Flores JL, Tuazon JA, Hernandez MA, & Evangelista LS (2017). Prevalence and correlates of depression, anxiety and stress among Filipinos in The Philippines. Circulation, 136(suppl_1), A17228.

Fogelman N, & Canli T (2018). Early life stress and cortisol: A meta-analysis. Hormones and Behavior, 98, 63–76. [PubMed: 29289660]

Gatt JM, Nemeroff CB, Schofield PR, Paul RH, Clark CR, Gordon E, & Williams LM (2010). Early life stress combined with serotonin 3A receptor and brain-derived neurotrophic factor valine 66 to methionine genotypes impacts emotional brain and arousal correlates of risk for depression. Biological Psychiatry, 68(9), 818–824. [PubMed: 20728877]

Gerritsen L, Geerlings MI, Beekman AT, Deeg DJ, Penninx BW, & Comijs HC (2010). Early and late life events and salivary cortisol in older persons. Psychological Medicine, 40(9), 1569–1578. [PubMed: 19939325]

Gold PW, Goodwin FK, & Chrousos GP (1988). Clinical and biochemical manifestations of depression. Relation to neurobiology of stress. New England Journal of Medicine, 319, 413–420.

Gonzalez A, Jenkins JM, Steiner M, & Fleming AS (2009). The relation between early life adversity, cortisol awakening response and diurnal salivary cortisol levels in postpartum women. Psychoneuroendocrinology, 34(1), 76–86. [PubMed: 18835661]

Goodyer IM, Bacon A, Ban M, Croudace T, & Herbert J (2009). Serotonin transporter genotype, morning cortisol and subsequent depression in adolescents. The British Journal of Psychiatry, 195(1), 39–45. [PubMed: 19567894]

Goodyer IM, Herbert J, Altham PME, Pearson J, Secher SM, & Shiers HM (1996). Adrenal secretion during major depression in 8-to 16-year-olds, I. altered diurnal rhythms in salivary cortisol and

dehydroepiandrosterone (DHEA) at presentation. Psychological Medicine, 26 (2), 245–256. [PubMed: 8685281]

Grant MM, Cannistraci C, Hollon SD, Gore J, & Shelton R (2011). Childhood trauma history differentiates amygdala response to sad faces within MDD. Journal of Psychiatric Research, 45(7), 886–895. [PubMed: 21276593]

Gustafsson PE, Janlert U, Theorell T, & Hammarström A (2010). Life-course socioeconomic trajectories and diurnal cortisol regulation in adulthood. Psychoneuroendocrinology, 35(4), 613–623. [PubMed: 19879057]

Heim C, & Binder EB (2012). Current research trends in early life stress and depression: Review of human studies on sensitive periods, gene–environment interactions, and epigenetics. Experimental Neurology, 233(1), 102–111. [PubMed: 22101006]

Heim C, Newport DJ, Heit S, Graham YP, Wilcox M, Bonsall R, … Nemeroff CB (2000). Pituitary – Adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. Journal of the American Medical Association, 284, 592–597. [PubMed: 10918705]

Heim C, Newport DJ, Mletzko T, Miller AH, & Nemeroff CB (2008). The link between childhood trauma and depression: Insights from HPA axis studies in humans. Psychoneuroendocrinology, 33(6), 693–710. [PubMed: 18602762]

Hindin MJ (2005). Family dynamics, gender differences and educational attainment in Filipino adolescents. Journal of Adolescence, 28(3), 299–316. [PubMed: 15925683]

Hindin MJ, & Gultiano S (2006). Associations between witnessing parental domestic violence and experiencing depressive symptoms in Filipino adolescents. American Journal of Public Health, 96(4), 660–663. [PubMed: 16507722]

Hock RS, Hindin MJ, Bass JK, Surkan PJ, Bradshaw CP, & Mendelson T (2016). Parenting styles and emerging adult drug use in Cebu, The Philippines. International Journal of Culture and Mental Health, 9(2), 108–119.4. [PubMed: 27330559]

Hovens JG, Wiersma JE, Giltay EJ, Van Oppen P, Spinhoven P, Penninx BW, & Zitman FG (2010). Childhood life events and childhood trauma in adult patients with depressive, anxiety and comorbid disorders vs. controls. Acta Psychiatrica Scandinavica, 122(1), 66–74. [PubMed: 19878136]

Institute for Health Metrics and Evaluation. (2017). Country Profiles: Philippines. Retrieved from http://www.healthdata.org/philippines.

Janusek LW, Tell D, Gaylord-Harden N, & Mathews HL (2017). Relationship of childhood adversity and neighborhood violence to a proinflammatory phenotype in emerging adult African American men: An epigenetic link. Brain, Behavior, and Immunity, 60, 126–135.

Jarcho MR, Slavich GM, Tylova-Stein H, Wolkowitz OM, & Burke HM (2013). Dysregulated diurnal cortisol pattern is associated with glucocorticoid resistance in women with major depressive disorder. Biological Psychology, 93(1), 150–158. [PubMed: 23410758]

Jawahar MC, Murgatroyd C, Harrison EL, & Baune BT (2015). Epigenetic alterations following early postnatal stress: A review on novel aetiological mechanisms of common psychiatric disorders. Clinical Epigenetics, 7(1), 122. [PubMed: 26583053]

Kendler KS, Bulik CM, Silberg J, Hettema JM, Myers J, & Prescott CA (2000). Childhood sexual abuse and adult psychiatric and substance use disorders in women: An epidemiological and cotwin control analysis. Archives of General Psychiatry, 57(10), 953–959. [PubMed: 11015813]

Kendler KS, Heath AC, & Eaves J (1992). Childhood parental loss and adult psychopathology in women. Psychopathology in Women. Arch Gen Psychiatry, 49, 109–116. [PubMed: 1550463]

Khulan B, Manning JR, Dunbar DR, Seckl JR, Raikkonen K, Eriksson JG, & Drake AJ (2014). Epigenomic profiling of men exposed to early-life stress reveals DNA methylation differences in association with current mental state. Translational Psychiatry, 4(9), e448–e448. [PubMed: 25247593]

Kim AW, Nyengerai T, Mendenhall E (2020). Evaluating the Mental Health Impacts of the COVID-19 Pandemic in Urban South Africa: Perceived Risk of COVID-19 Infection and Childhood Trauma Predict Adult Depressive Symptoms. Under Review.

Kirschbaum C, & Hellhammer DH (1989). Salivary cortisol in psychobiological research: An overview. Neuropsychobiology, 22, 150–169. [PubMed: 2485862]

Knight JM, Avery EF, Janssen I, & Powell LH (2010). Cortisol and depressive symptoms in a population-based cohort of midlife women. Psychosomatic Medicine, 72(9), 855–861. [PubMed: 20841562]

Koss KJ, & Gunnar MR (2018). Annual Research Review: Early adversity, the hypothalamic–pituitary–adrenocortical axis, and child psychopathology. Journal of Child Psychology and Psychiatry, 59(4), 327–346. [PubMed: 28714126]

Kudielka BM, Buchtal J, Uhde A, & Wust S (2007). Circadian cortisol profiles and psychological self-reports in shift workers with and without recent change in the shift rotation system. Biological Psychology, 74(1), 92–103. [PubMed: 17101207]

Kudielka BM, & Kirschbaum C (2003). Awakening cortisol responses are influenced by health status and awakening time but not by menstrual cycle phase. Psychoneuroendocrinology, 28, 35–47. [PubMed: 12445835]

Lovallo WR, Farag NH, Sorocco KH, Cohoon AJ, & Vincent AS (2012). Lifetime adversity leads to blunted stress axis reactivity: Studies from the Oklahoma family health patterns project. Biological Psychiatry, 71(4), 344–349. [PubMed: 22112928]

Luecken LJ (2000). Parental caring and loss during childhood and adult cortisol responses to stress. Psychology and Health, 15, 841–851.

Luecken LJ, & Appelhans BM (2006). Early parental loss and salivary cortisol in young adulthood: The moderating role of family environment. Development and Psychopathology, 18, 295–308. [PubMed: 16478564]

Lopez-Duran NL, Kovacs M, & George CJ (2009). Hypothalamic–pituitary–adrenal axis dysregulation in depressed children and adolescents: A meta-analysis. Psychoneuroendocrinology, 34(9), 1272–1283. [PubMed: 19406581]

Lyons DM, & Parker KJ (2007). Stress inoculation-induced indications of resilience in monkeys. Journal of Traumatic Stress, 20(4), 423–433. [PubMed: 17721972]

Maciejewski PK, Prigerson HG, & Mazure CM (2001). Sex differences in event-related risk for major depression. Psychological Medicine, 31(4), 593–604. [PubMed: 11352362]

Mandelli L, Petrelli C, & Serretti A (2015). The role of specific early trauma in adult depression: A meta-analysis of published literature. Childhood trauma and adult depression. European Psychiatry, 30(6), 665–680. [PubMed: 26078093]

Mangold D, Marino E, & Javors M (2011). The cortisol awakening response predicts subclinical depressive symptomatology in Mexican American adults. Journal of Psychiatric Research, 45(7), 902–909. [PubMed: 21300376]

McDade TW, Ryan CP, Jones MJ, Hoke MK, Borja J, Miller GE, … Kobor MS (2019). Genome-wide analysis of DNA methylation in relation to socioeconomic status during development and early adulthood. American Journal of Physical Anthropology, 169(1), 3–11. [PubMed: 30771258]

McEwen BS (1998). Stress, adaptation, and disease: Allostasis and allostatic load. Annals of the New York Academy of Sciences, 840(1), 33–44. [PubMed: 9629234]

Meinlschmidt G, & Heim C (2005). Decreased cortisol awakening response after early loss experience. Psychoneuroendocrinology, 30(6), 568–576. [PubMed: 15808926]

Mickelson KD, Kessler RC, & Shaver PR (1997). Adult attachment in a nationally representative sample. Journal of Personality and Social Psychology, 73(5), 1092–1106. [PubMed: 9364763]

Miller AH, Maletic V, & Raison CL (2009). Inflammation and its discontents: The role of cytokines in the pathophysiology of major depression. Biological Psychiatry, 65(9), 732–741. [PubMed: 19150053]

Miller GE, Chen E, & Parker KJ (2011). Psychological stress in childhood and susceptibility to the chronic diseases of aging: Moving toward a model of behavioral and biological mechanisms. Psychological Bulletin, 137(6), 959–997. [PubMed: 21787044]

Miller GE, Chen E, & Zhou ES (2007). If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. Psychological Bulletin, 133(1), 25–45. [PubMed: 17201569]

Nelson EC, Heath AC, Madden PA, Cooper ML, Dinwiddie SH, Bucholz KK, … Martin NG (2002). Association between self-reported childhood sexual abuse and adverse psychosocial outcomes: Results from a twin study. Archives of General Psychiatry, 59(2), 139–145. [PubMed: 11825135]

Nickerson A, Bryant RA, Aderka IM, Hinton DE, & Hofmann SG (2013). The impacts of parental loss and adverse parenting on mental health: Findings from the National Comorbidity Survey-Replication. Psychological Trauma Theory Research Practice and Policy, 5(2), 119–127.

Nicolson NA (2004). Childhood parental loss and cortisol levels in adult men. Psychoneuroendocrinology, 29(8), 1012–1018. [PubMed: 15219652]

Niu SF, Chung MH, Chen CH, Hegney D, O'Brien A, & Chou KR (2011). The effect of shift rotation on employee cortisol profile, sleep quality, fatigue, and attention level: A systematic review. Journal of Nursing Research, 19(1), 68–81.

Nolen-Hoeksema S (2001). Gender differences in depression. Current Directions in Psychological Science, 10(5), 173–176.

Pace TW, Mletzko TC, Alagbe O, Musselman DL, Nemeroff CB, Miller AH, & Heim CM (2006). Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. American Journal of Psychiatry, 163(9), 1630–1633.

Pariante CM, & Lightman SL (2008). The HPA axis in major depression: Classical theories and new developments. Trends in Neurosciences, 31(9), 464–468. [PubMed: 18675469]

Pesonen AK, Raikkonen K, Feldt K, Heinonen K, Osmond C, Phillips DI, … Kajantie E (2010). Childhood separation experience predicts HPA axis hormonal responses in late adulthood: A natural experiment of world war II. Psychoneuroendocrinology, 35(5), 758–767. [PubMed: 19963324]

Patel V (2007). Mental health in low-and middle-income countries. British Medical Bulletin, 81(1), 81–96. [PubMed: 17470476]

Plotsky PM, Owens MJ, & Nemeroff CB (1998). Psychoneuroendocrinology of depression: Hypothalamic-pituitaryadrenal axis. Psychiatric Clinics of North America, 21(2), 293–307.

Pruessner JC, Wolf OT, Hellhammer DH, Buske-Kirschbaum A, von Auer K, Jobst S, … Kirschbaum C (1997). Free cortisol levels after awakening: A reliable biological marker for the assessment of adrenocortical activity. Life Sciences, 61(26), 2539–2549. [PubMed: 9416776]

Pruessner M, Hellhammer DH, Pruessner JC, & Lupien SJ (2003). Self-reported depressive symptoms and stress levels in healthy young men: Associations with the cortisol response to awakening. Psychosomatic Medicine, 65(1), 92–99. [PubMed: 12554820]

Radloff LS (1977). The CES-D scale: A self-report depression scale for research in the general population. Applied Psychological Measurement, 1(3), 385–401.

Rohleder N, Joksimovic L, Wolf JM, & Kirschbaum C (2004). Hypocortisolism and increased glucocorticoid sensitivity of proinflammatory cytokine production in Bosnian war refugees with post-traumatic stress disorder. Biological Psychiatry, 55(7), 745–751. [PubMed: 15039004]

Sánchez MM, Noble PM, Lyon CK, Plotsky PM, Davis M, Nemeroff CB, & Winslow JT (2005). Alterations in diurnal cortisol rhythm and acoustic startle response in nonhuman primates with adverse rearing. Biological Psychiatry, 57(4), 373–381. [PubMed: 15705353]

Schalinski I, Elbert T, Steudte-Schmiedgen S, & Kirschbaum C (2015). The cortisol paradox of trauma-related disorders: Lower phasic responses but higher tonic levels of cortisol are associated with sexual abuse in childhood. PLoS ONE, 10(8), e0136921. [PubMed: 26317554]

Smith AK, Parets SE, & Kim AW (2014). Epigenetics of psychopathology In Behavior genetics of psychopathology (pp. 283–309). New York, NY: Springer.

Stalder T, Kirschbaum C, Kudielka BM, Adam EK, Pruessner JC, Wüst S, … Miller R (2016). Assessment of the cortisol awakening response: Expert consensus guidelines. Psychoneuroendocrinology, 63, 414–432. [PubMed: 26563991]

Stetler C, & Miller GE (2005). Blunted cortisol response to awakening in mild to moderate depression: regulatory influences of sleep patterns and social contacts. Journal of abnormal psychology, 114(4), 697. [PubMed: 16351390]

Tarullo AR, & Gunnar MR (2006). Child maltreatment and the developing HPA axis. Hormones and Behavior, 50(4), 632–639. [PubMed: 16876168]

Taylor SE, Way BM, & Seeman TE (2011). Early adversity and adult health outcomes. Development and Psychopathology, 23(3), 939–954. [PubMed: 21756443]

Thayer ZM, Wilson MA, Kim AW, & Jaeggi AV (2018). Impact of prenatal stress on offspring glucocorticoid levels: A phylogenetic meta-analysis across 14 vertebrate species. Scientific Reports, 8 (1), 1–9. [PubMed: 29311619]

Trickett PK, Noll JG, Susman EJ, Shenk CE, & Putnam FW (2010). Attenuation of cortisol across development for victims of sexual abuse. Development and Psychopathology, 22, 165–175. [PubMed: 20102654]

Tyrka AR, Wier L, Price LH, Ross N, Anderson GM, Wilkinson CW, & Carpenter LL (2008). Childhood parental loss and adult hypothalamic-pituitary-adrenal function. Biological Psychiatry, 63(12), 1147–1154. [PubMed: 18339361]

Tyrka AR, Wier L, Price LH, Ross NS, & Carpenter LL (2008). Childhood parental loss and adult psychopathology: Effects of loss characteristics and contextual factors. The International Journal of Psychiatry in Medicine, 38(3), 329–344. [PubMed: 19069576]

Vaccarino O, Levitan R, & Ravindran A (2015). The cortisol response to social stress in social anxiety disorder. Asian Journal of Psychiatry, 14, 57–60. [PubMed: 25864645]

van der Vegt EJ, Van Der Ende J, Kirschbaum C, Verhulst FC, & Tiemeier H (2009). Early neglect and abuse predict diurnal cortisol patterns in adults: A study of international adoptees. Psychoneuroendocrinology, 34(5), 660–669. [PubMed: 19128884]

Vigo D, Thornicroft G, & Atun R (2016). Estimating the true global burden of mental illness. The Lancet Psychiatry, 3(2), 171–178. [PubMed: 26851330]

Vrshek-Schallhorn S, Doane LD, Mineka S, Zinbarg RE, Craske MG, & Adam EK (2013). The cortisol awakening response predicts major depression: Predictive stability over a 4-year follow-up and effect of depression history. Psychological Medicine, 43(3), 483–493. [PubMed: 22652338]

Weinrib AZ, Sephton SE, DeGeest K, Penedo F, Bender D, Zimmerman B, … Lutgendorf SK (2010). Diurnal cortisol dysregulation, functional disability, and depression in women with ovarian cancer. Cancer, 116(18), 4410–4419. [PubMed: 20564155]

Weissman MM, Bland R, Joyce PR, Newman S, Wells JE, & Wittchen HU (1993). Sex differences in rates of depression: Cross-national perspectives. Journal of Affective Disorders, 29(2–3), 77–84. [PubMed: 8300980]

Weitzman ED, Fukushima D, Nogeire C, Roffwarg H, Gallagher TF, & Hellman L (1971). Twenty-four hour pattern of the episodic secretion of cortisol in normal subjects. The Journal of Clinical Endocrinology & Metabolism, 33(1), 14–22. [PubMed: 4326799]

Wiersma JE, Hovens JG, van Oppen P, Giltay EJ, van Schaik DJ, Beekman AT, & Penninx BW (2009). The importance of childhood trauma and childhood life events for chronicity of depression in adults. Journal of Clinical Psychiatry, 70(7), 983–989.

World Health Organization. (2017). Depression and other common mental disorders: global health estimates (No. WHO/MSD/MER/2017.2) World Health Organization.

Yehuda R, Boisonuae D, Lowy MT, & Giller E (1995). Dose- response changes in plasma cortisol and lymphocyte glucocorticoid receptors following dexamethasone administration in combat veterans with and without post-traumatic stress disorder. Archives of General Psychiatry, 52, 583–593. [PubMed: 7598635]

Yehuda R, Kahana B, Binder-Brynes K, Southwick SM, Mason JW, & Giller EL (1995). Low urinary cortisol excretion in holocaust survivors with posttraumatic stress disorder. American Journal of PsyChiatry, 152, 982–986.

Yehuda R, Resnick HS, Schmeidler J, Yang RK, & Pitman RK (1998). Predictors of cortisol and 3-Methoxy-4-Hydroxy-phenylglycol responses in the acute aftermath of rape. Biological Psychiatry, 43, 855–859. [PubMed: 9611677]

Yehuda R, Teicher MH, Trestman RL, Levengood RA, & Siever LJ (1996). Cortisol regulation in posttraumatic stress disorder and major depression: A chronobiological analysis. Biological Psychiatry, 40(2), 79–88. [PubMed: 8793040]

Young EA, Haskett RF, Grunhaus L, Pande A, Weinberg VM, Watson SJ, & Akil H (1994). Increased evening activation of the hypothalamic-pituitary-adrenal axis in depressed patients. Archives of General Psychiatry, 51(9), 7.

Zilioli S, Slatcher RB, Chi P, Li X, Zhao J, & Zhao G (2016). Childhood adversity, self-esteem, and diurnal cortisol profiles across the life span. Psychological Science, 27(9), 1249–1265. [PubMed: 27481911]

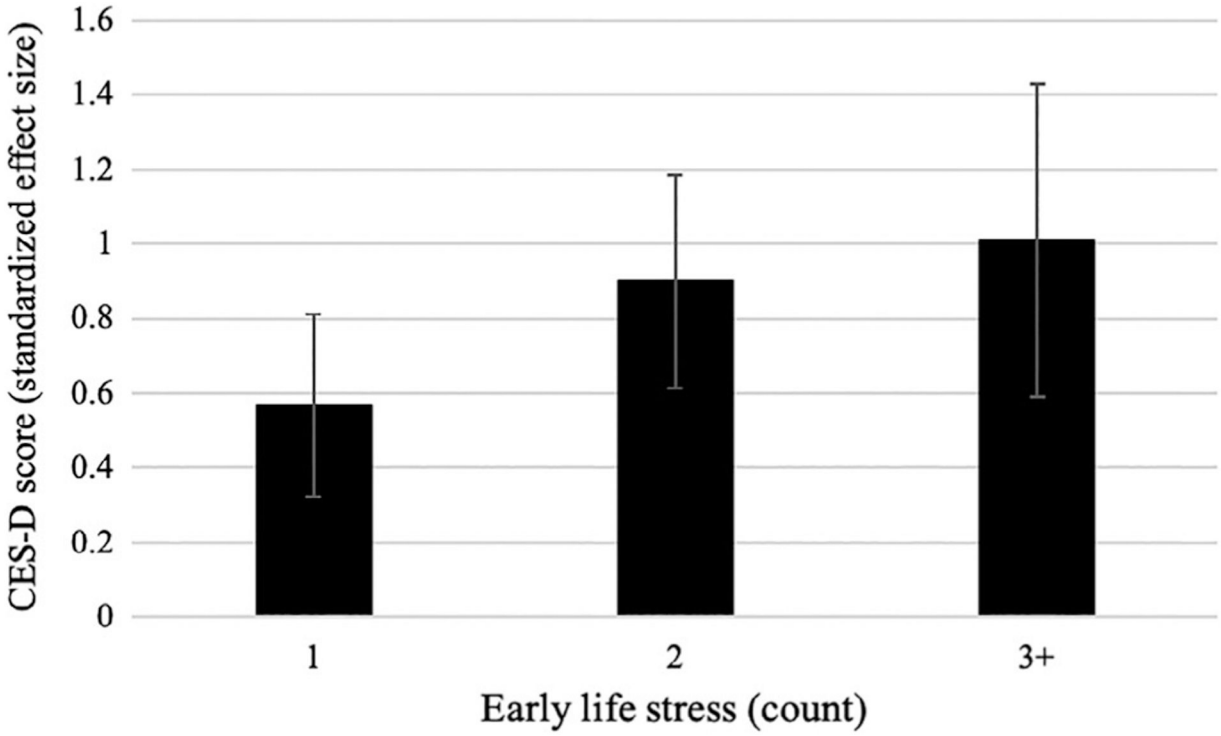

FIGURE 1.
Effect size of early life stress groups on depressive symptom scores ($p < .0001$)

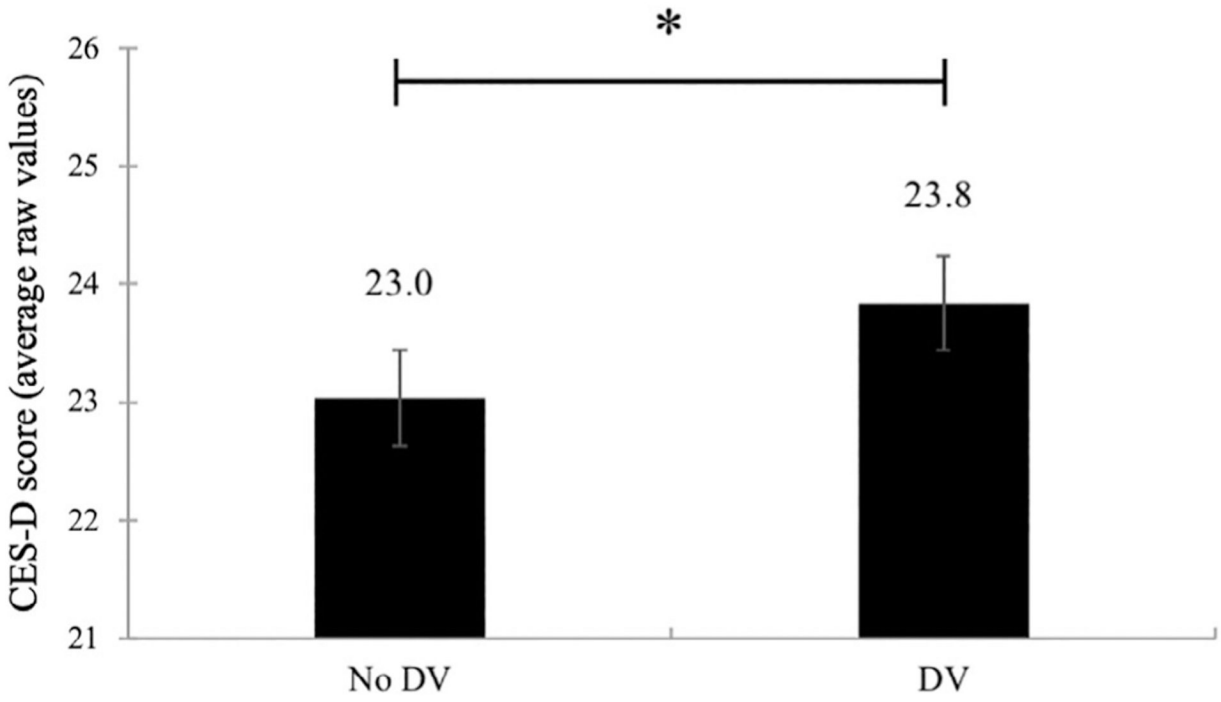

FIGURE 2.
Mean values of depressive symptom scores stratified by past history of witnessing domestic violence ($p < .0001$)

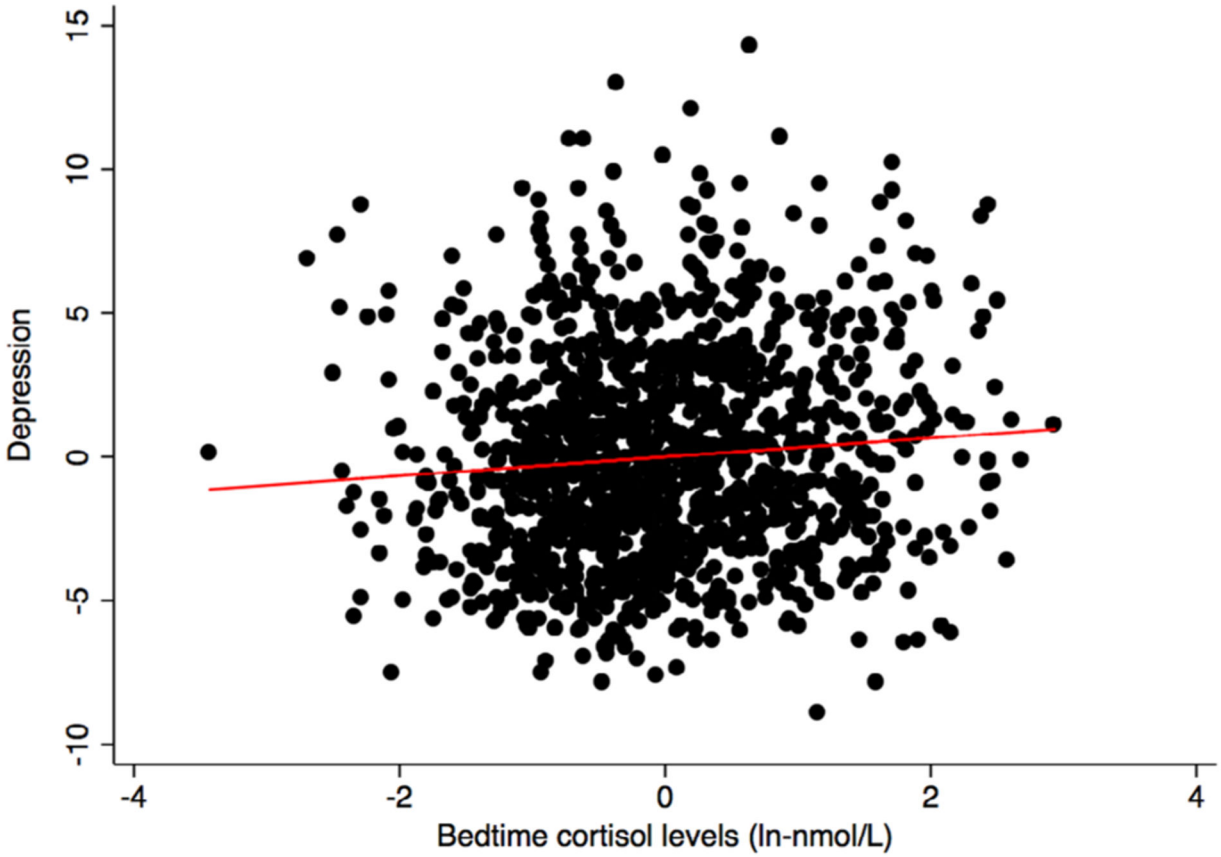

FIGURE 3.

Partial regression plot of CES-D residual values on natural logged and standardized residuals of bedtime cortisol (nmol/L). Residuals derived from separate regressions adjusting for times of saliva collections and smoking status ($p = .004$)

TABLE 1

Characteristics of participants, psychosocial environment, households

Variables	***n* = 1,244**	**Range**
Demographics		
Sex (% female)	47.9	
Age (years)	21.5 (0.3)	20.8 to 22.4
Early life SES	−0.01 (2.7)	−5.5 to 13.3
Household income 2005 (pesos)	599.8 (891.7)	−6.19 to 16,883.6
Household assets 2005 (count)	5.3 (2.0)	0 to 11
Educational attainment 2005 (year)	11.1	0 to 23
Adult SES 2005	0.02 (0.7)	−1.8 to 5.4
Early life stress		
Maternal absence (*n*, %)	15, 1.2	
Paternal absence (n, %)	33, 2.7	
Sibling death (*n*, %)	195, 15.7	
Witnessed domestic violence (*n*, %)	584, 47.0	
Not close with mother (*n*, %)	173, 13.9	
Not close with father (*n*, %)	326, 26.2	
Diurnal cortisol rhythm measurements		
Evening cortisol (nmol/L)	2.17 (2.48)	0.058 to 22.68
Waking cortisol (nmol/L)	7.50 (4.32)	0.21 to 61.01
Waking cortisol +30 min (nmol/L)	9.49 (5.08)	0.27 to 65.9
Cortisol awakening response (nmol/L)	1.95 (4.68)	−17.86 to 25.98
Depressive symptoms and PSS scores		
Depressive symptoms (CES-D)	9.34 (4.71)	0 to 29
Perceived stress scale (PSS)	19.71 (3.29)	11 to 34

TABLE 2a

Zero-order correlations across study variables

	1	2	3	4	5	6	7	8	9	10	11	12
1. Depressive symptoms	1											
2. ELS index	0.1338*	1										
3. Sex	−0.2322*	−0.0972*	1									
4. Early life SES	−0.1360*	−0.0718*	0.0193	1								
5. 2005 SES	−0.1428*	−0.0943*	−0.0782*	0.6277*	1							
6. Waking cortisol	0.003	−0.0247	−0.1245*	−0.0082	−0.0163	1						
7. CAR	0.0279	−0.0154	0.0045	0.0515	0.0619*	−0.3092*	1					
8. Bedtime cortisol	0.0788*	−0.0124	0.0325	−0.0967*	−0.1055*	0.17*	0.0158	1				
9. Slope	0.0627*	0.0004	0.0961*	−0.0565*	−0.051	−0.4452*	0.222*	0.7903*	1			
10. PM saliva collection time	−0.0747*	0.0544	0.0339	0.3248*	0.2971*	−0.0836*	0.0733*	0.0453	0.1765*	1		
11. AM saliva collection time	−0.0274	0.069*	0.0876*	0.2308*	0.119*	−0.1457*	−0.0331	0.0167	0.0487	0.3958*	1	
12. Smoking	0.0198	0.0084	0.1375*	−0.0145	−0.0898*	−0.0722*	0.0103	0.0348	0.0573*	−0.013	0.1166*	1
13. PSS	0.1336*	0.066*	−0.1297*	0.0210	0.0476	0.0613*	−0.0439	0.0161	−0.0158	0.0667*	0.0223	−0.001

*$p < .05$.

TABLE 2b

Zero-order correlations across early life stress and cortisol measures

	1	2	3	4	5	6	7	8	9	10
1. Parental instability	1									
2. Maternal absence	0.2568*	1								
3. Sibling died	−0.0574*	−0.0274	1							
4. Witnessing domestic violence	0.0251	0.0584*	0.0065	1						
5. Not close with mother	0.0493	0.0195	−0.0391	0.0502	1					
6. Not close with father	0.1291*	0.0347	−0.091*	0.0914*	0.30998	1				
7. Depressive symptoms	0.0018	−0.0199	0.0565	0.1122*	0.0293	0.0946*	1			
8. Waking cortisol	−0.0832*	−0.0013	0.0111	−0.0231	0.0225	−0.0262	0.003	1		
9. CAR	−0.0253	0.012	−0.0309	−0.0297	−0.0036	0.0345	0.0279	−0.30928	1	
10. Evening cortisol	0.0047	0.0334	0.0534	−0.0481	0.0356	−0.0438	0.0788	0.17*	0.0158*	1
11. Diurnal slope	0.0431	0.0326	0.0341	−0.0356	0.0185	−0.0151	0.0627	−0.44528	0.222*	0.7903*

* $p < .05$.

Am J Phys Anthropol. Author manuscript; available in PMC 2021 January 29.

TABLE 3a

Multiple regression models of cumulative risk composite variable predicting depressive symptoms

	Model 1	Model 2	Model 3[a]	Model 4[a]	Model 5	Model 6
Early life stress	0.47 ± 0.11***	0.4006 ± 0.11***	0.365 ± 0.12**	0.353 ± 0.12**	0.4007 ± 0.11***	0.39 ± 0.11**
1	0.69 ± 0.25**	0.61 ± 0.25*	0.68 ± 0.29**	0.63 ± 0.25*	0.61 ± 0.25*	0.57 ± 0.24*
2	1.06 ± 0.29***	0.93 ± 0.29**	0.86 ± 0.29**	0.82 ± 0.29**	0.93 ± 0.29**	0.90 ± 0.29**
3+	1.26 ± 0.42**	1.0 ± 0.42*	0.95 ± 0.43*	0.93 ± 0.43*	1.04 ± 0.42*	1.01 ± 0.42*
Sex (male)	−1.77 ± 0.21***	−1.75 ± 0.21***	−1.76 ± 0.21***	−1.67 ± 0.21***	−1.81 ± 0.21***	−1.73 ± 0.21***
Early life SES		−0.066 ± 0.049	−0.061 ± 0.05	−0.045 ± 0.50	−0.060 ± 0.21	−0.049 ± 0.49
2005 SES		−0.69 ± 0.20**	−0.74 ± 0.20***	−0.71 ± 0.21**	−0.67 ± 0.20**	−0.64 ± 0.20**
Diurnal slope[b]			0.31 ± 0.11**	0.34 ± 0.12**		
CAR[c]			0.008 ± 0.023	0.013 ± 0.11		
Evening cortisol					0.30 ± 0.11**	0.31 ± 0.11**
Waking cortisol					−0.24 ± 0.16	−0.28 ± 0.16
Time of bedtime saliva collection				−0.13 ± 0.073		−0.099 ± 0.70
Smoking				0.81 ± 0.72		0.81 ± 0.68
PSS				0.13 ± 0.032***		0.12 ± 0.031***
Intercept	23.8 ± 0.20***	23.8 ± 0.22***	23.8 ± 0.23***	24.0 ± 1.7***	24.3 ± 0.39***	25.1 ± 1.7***
Model adjusted R^2	0.0649	0.0870	0.0911	0.105	0.0921	0.104

[a]To account for saliva samples that were collected within the recommended window of time for the cortisol awakening response (t = 25–35 min after waking) (DeSantis, Adam, Mendelsohn, & Doane, 2010), the sample size for this model is $n = 1{,}194$.

[b]Values standardized and converted to z-score.

[c]Values converted to z-score.

*$p < .05$;

**$p < .01$;

***$p < .001$.

TABLE 3b

Multiple regression models predicting effects of early life stress measures and diurnal cortisol on depressive symptoms

	Model 1	Model 2	Model 3	Model 4[a]	Model 5
Maternal absence	−1.09 ±0.98	−1.31 ± 0.97	−1.30 ± 0.97	−1.58 ± 1.03	−1.36 ± 0.97
Paternal instability	0.34 ± 0.67	0.39 ± 0.66	0.37 ± 0.66	0.29 ± 0.69	0.28 ± 0.66
Sibling death	0.63 ± 0.29*	0.29 ± 0.29	0.22 ± 0.29	0.18 ± 0.30	0.19 ± 0.29
Witnessing domestic violence	0.86 ± 0.21**	0.78 ± 0.21***	0.72 ± 0.21**	0.75 ± 0.21***	0.75 ± 0.21***
Not close to mother	0.079 ± 0.30	0.083 ± 0.30	0.13 ± 0.30	0.028 ± 0.30	0.10 ± 0.30
Sex (male)	−1.77 ± 0.21***	−1.83 ± 0.21***	−1.75 ± 0.21***	−1.75 ± 0.21***	−1.81 ± 0.21***
Early life SES		−0.056 ± 0.049	−0.052 ± 0.049	−0.037 ± 0.051	−0.040 ± 0.049
2005 SES		−0.72 ± 0.20***	−0.70 ± 0.20**	−0.74 ± 0.21***	−0.67 ± 0.20**
Diurnal slope[b]				0.36 ± 0.12**	
CAR[c]				0.014 ± 0.23	
Evening cortisol					0.32 ± 0.11**
Waking cortisol					−0.28 ± 0.17
Time of bedtime saliva collection			−0.061 ± 0.70	−0.12 ± 0.73	−0.089 ± 0.07
Smoking			−.87 ± 0.68	0.73 ± 0.72	0.75 ± 0.68
PSS			0.12 ± 0.31***	0.13 ± 0.032***	0.12 ± 0.031***
Intercept	23.8 ± 0.19***	24.0 ± 0.19***	22.9 ± 1.63***	24.0 ± 1.7***	24.0 ± 1.7***
Model adjusted R^2	0.0668	0.088	0.0981	0.106	0.104

[a] To account for saliva samples that were collected within the recommended window of time for the cortisol awakening response (t = 25–35 min after waking) (DeSantis et al., 2010), the sample size for this model is n = 1,194.

[b] Values standardized and converted to z-score.

[c] Values converted to z-score.

* $p < .05$;

** $p < .01$;

*** $p < .001$.