

The Dual Impact of Early and Concurrent Life Stress on Adults' Diurnal Cortisol Patterns: A Prospective Study

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Abstract

Major life stress often produces a flat diurnal cortisol slope, an indicator of potential long-term health problems. Exposure to stress early in childhood or the accumulation of stress across the life span may be responsible for this pattern. However, the relative impact of life stress at different life stages on diurnal cortisol is unknown. Using a longitudinal sample of adults followed from birth, we examined three models of the effect of stress exposure on diurnal cortisol: the cumulative model, the biological-embedding model, and the sensitization model. As its name implies, the cumulative model focuses on cumulative life stress. In contrast, the biological-embedding model implicates early childhood stress, and the sensitization model posits that current life stress interacts with early life stress to produce flat diurnal cortisol slopes. Our analyses are consistent with the sensitization model, as they indicate that the combination of high stress exposure early in life and high current stress predict flat diurnal cortisol slopes. These novel findings advance understanding of diurnal cortisol patterns and point to avenues for intervention.

Keywords

diurnal cortisol, life stress, cumulative stress, allostatic load, development

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Much research has documented that experiencing more stress during childhood is associated with poorer long-term health outcomes (Miller, Chen, & Parker, 2011). The hypothalamic-pituitary-adrenal (HPA) axis, in particular, is one of the key biological systems that is responsive to stressful life events and is responsible for mobilizing energetic resources to help people confront and cope with environmental challenges (McEwen, 1998, 2008). However, major life stress can lead to dysregulated circadian patterns of cortisol secretion, such as a flatter cortisol slope across the day (Adam et al., 2017; Heim, Ehlert, & Hellhammer, 2000; Miller, Chen, & Cole, 2009), which affects the functioning of various bodily systems (e.g., the nervous, immune, vascular, and metabolic systems) and makes people vulnerable to mental and physical health problems (Adam & Kumari, 2009; Adam et al., 2017; Kumari et al., 2009; Kumari, Shipley, Stafford, & Kivimaki, 2011).

Few (if any) prospective, longitudinal studies have examined whether the amount of stress experienced at particular periods of development (e.g., early childhood, adolescence) versus over the life span is systematically related to HPA-axis dysregulation in adults; virtually all existing research either has been cross-sectional or has relied on retrospective reports of prior stress exposure. Moreover, we do not know whether the impact of stress experienced at different time periods is additive or statistically interacts to predict HPA-axis dysregulation in adults (Ross, Murphy, Adam, Chen, & Miller, 2014; Smyth et al., 1997; Stone et al., 2001). Addressing these important gaps in our knowledge

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could bring greater theoretical clarity to stress research, a field where understanding how, when, and why stress contributes to HPA-axis dysregulation is a fundamental, unresolved question.

In most individuals, basal cortisol starts at a high level in the morning, reaching a peak 30 to 45 min after awakening, and then gradually declines throughout the day, with brief increases around the midday meal (Miller, Chen, & Zhou, 2007; Smyth et al., 1997; Stone et al., 2001). A flattening of this typical pattern is associated with impaired health (Adam et al., 2017; Kumari et al., 2009; Kumari et al., 2011). Two forms of flattened slopes have been found to be associated with chronic stress: In one pattern, the early-morning level is lower than typical and there is less decline over the day (Gunnar & Quevedo, 2007); in the other, the late-afternoon and evening level is elevated, which also results in less decline over the day (Miller et al., 2009; Miller et al., 2007). Deviations from the typical pattern—particularly, the flattened profile in which morning levels of cortisol decline at a slower rate across the day than expected (Adam et al., 2017)—are associated with poorer long-term physical health.

Individuals who report retrospectively that they had encountered highly stressful conditions during childhood, such as maltreatment or low socioeconomic status (SES), also tend to have flattened, dysregulated diurnal cortisol slopes across the day (Gunnar & Quevedo, 2007; Lupien, McEwen, Gunnar, & Heim, 2009; Miller et al., 2009; Miller et al., 2007). Retrospective reports of stressful experiences, however, can be problematic because memory is imperfect (Rubin, Rahhal, & Poon, 1998) and current psychological states (Reuben et al., 2016) or unmeasured variables may cause people to have distorted perceptions of their earlier experiences. Thus, using such reports can increase confounding and measurement error. In contrast, prospective measures, which better capture variance in life stress as it occurs (Farrell, Simpson, Carlson, Englund, & Sung, 2017), can provide more accurate insights into the impact of stressful experiences on HPA functioning at different life stages.

Three plausible models could explain how stress exposure affects diurnal HPA-axis functioning in adulthood. The cumulative model suggests that chronic activation of the HPA axis produces dysregulation of stress-mediating systems, such as the HPA axis, and eventual physical wear and tear on the body (Karatsoreos & McEwen, 2013; McEwen, 1998, 2008). Despite the adaptive short-term benefits of the HPA response (Karatsoreos & McEwen, 2013), continued activation of this stress system typically produces cell damage and long-term health problems. Although this model acknowledges the possible role of sensitive periods when stress might have a particularly strong impact on long-term health outcomes, it assumes that the total

amount of stress experienced across life is the key variable generating HPA-axis dysregulation.

The biological-embedding model, in contrast, claims that stress experienced during certain sensitive periods influences HPA-axis development in an enduring manner (Hertzman, 1999; Lupien et al., 2009; Miller et al., 2011; Power & Hertzman, 1997; Shonkoff, Boyce, & McEwen, 2009). The most important sensitive period is early childhood (i.e., the first few years of life), during which biological systems are developing and are most vulnerable to stress (Lupien et al., 2009). Accordingly, stress experienced during early childhood is believed to calibrate the HPA axis, and thus affect how it functions throughout life (Lupien et al., 2009). The early empirical support for this model came from animal research (Levine, 2005; Meaney, 2001), and current tests in humans are yielding increasing supportive evidence (Koss, Mliner, Donzella, & Gunnar, 2016; McLaughlin et al., 2015; Roisman et al., 2009).

The sensitization model also claims that stress in early life calibrates HPA functioning but extends the biological-embedding model by proposing that early life experiences shape how the HPA axis responds to stressful experiences later in life (Daskalakis, Bagot, Parker, Vinkers, & de Kloet, 2013). According to this view, HPA functioning depends on both early life stress and current stress levels, which means that early life stress should statistically interact with current stress to predict HPA functioning, including the flattened diurnal pattern.

All three models claim that higher stress should result in greater HPA dysregulation, indicating that interventions should be aimed at reducing or eliminating psychosocial stressors that negatively impact most people. In contrast to the cumulative model, however, the biological-embedding and sensitization models suggest that early intervention should be critical for ameliorating the negative effects of stress on HPA dysregulation. Additionally, unlike the biological-embedding model, the cumulative and sensitization models suggest that interventions that reduce the effect of chronic stress across the life span, such as teaching people more adaptive coping strategies, may also improve HPA regulation. The sensitization model, however, suggests that such interventions might be most effective for individuals who have experienced early life stress.

We tested these three models using 37 years of prospective, longitudinal data from a high-risk birth cohort participating in the Minnesota Longitudinal Study of Risk and Adaptation (MLSRA; Sroufe, Egeland, Carlson, & Collins, 2005). The MLSRA is well positioned to test these models because it provides 19 waves of objective life-stress data collected across the lives of its participants. When participants were 37 years old, diurnal cortisol was measured on 2 days following standard cortisol collection techniques.

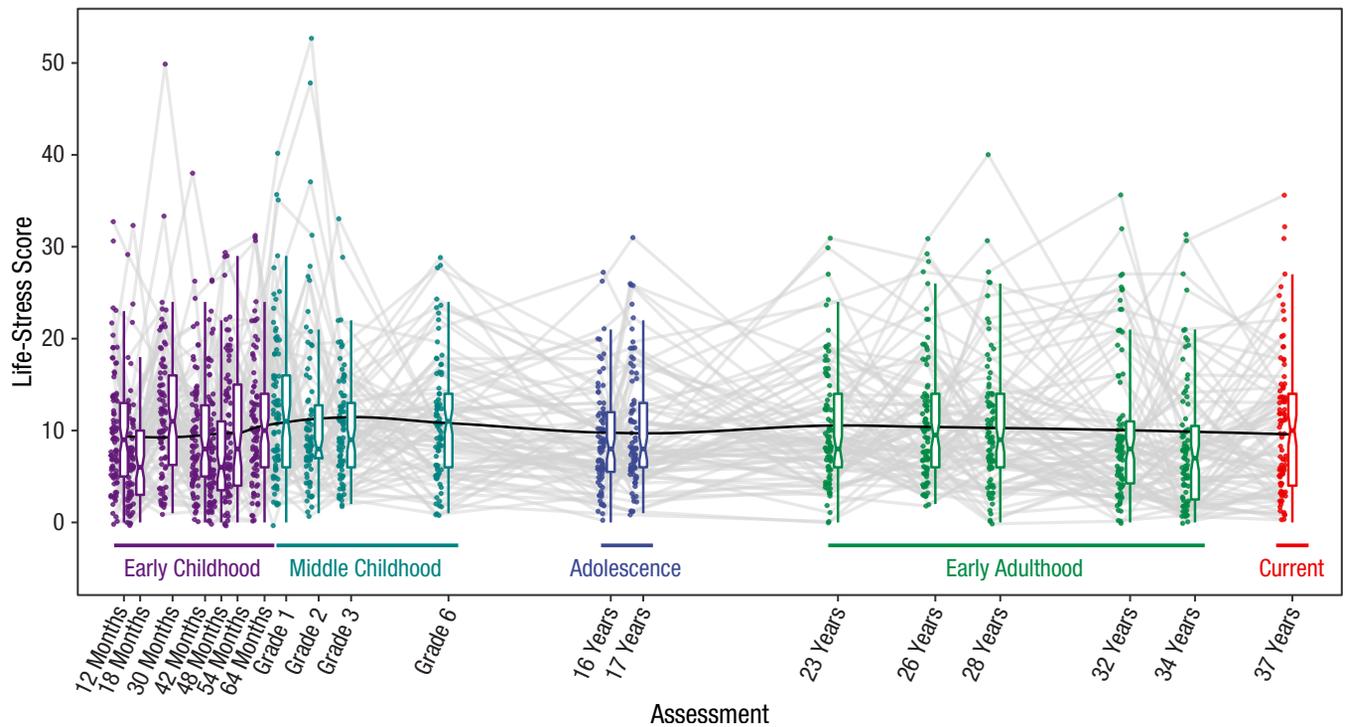


Fig. 1. Life-stress scores as a function of assessment. Box plots of life-stress scores are plotted alongside raw data for each life-stress assessment. Lower and upper hinges of each box plot represent the 25th and 75th percentiles, respectively. The whiskers represent values between each hinge and 1.5 times the interquartile range. Horizontal solid lines within each box plot represent median stress scores. Each gray line shows the trajectory of the scores of an individual participant. The black line represents a smoothed sample average of the trend across all assessments.

Method

Participants

In 1975 and 1976, 267 pregnant women were recruited for the MLSRA (mean age = 20.6 years, range = 12–34 years). At recruitment, all these women were living below the poverty line, receiving free health-care services, and expecting their first-born child. The children of these mothers are the target participants in the MLSRA. At the time of the participants' birth, 48% of their mothers were teenagers, 65% were single, and 42% had not completed high school. For the current analyses, we focused on all participants for whom we had complete data on salivary cortisol and early life stress and who were not pregnant at the age-37 data collection. Thus, the current analyses are based on 90 participants (51 females, 39 males) who met these criteria. This subset of participants did not differ from the original sample in gender, ethnicity, or SES.

Measures

Life stress. The mothers completed the Life Events Schedule (LES) interview when the target participants were 12, 18, 30, 42, 48, 54, and 64 months old; in Grades 1, 2, 3, and 6; and 16 and 17 years old. When the target participants were 23, 26, 28, 32, 34, and 37 years old, they

completed the LES themselves. The LES interview asked mothers, and later the targets, about life events that might have occurred and caused stress since the last interview (or within the past year). These included potentially stressful events associated with financial troubles (e.g., job changes, lack of money, debt), relationships (e.g. family members or partners drinking heavily, partners moving in or out, separations and breakups), and physical danger or mortality (e.g., death or illness of a family member, getting into physical fights). Responses were audio-taped and transcribed. Trained coders then rated each event for the level of disruption it caused, using a scale from 0 (*no disruption*) to 3 (*severe disruption*).

The sum of all coded responses was calculated as the measure of life stress at each assessment period. Current life stress was indexed by the LES score at age 37 years (when diurnal cortisol was assessed). The remaining scores were grouped into four developmental periods (Farrell et al., 2017): early childhood (1–5 years; 7 assessments; $\alpha = .83$), middle childhood (Grades 1, 2, 3, and 6; 4 assessments; $\alpha = .66$), adolescence (ages 16 and 17; 2 assessments; $r = .46$), and early adulthood (age 23–age 34; 5 assessments; $\alpha = .76$). To test the cumulative model, we summed all coded responses across all the time periods (1–37 years; 19 assessments, $\alpha = .81$). Figure 1 shows target participants' life-stress trajectories and a box plot for each assessment.

Diurnal cortisol. At age 37 years, participants provided five saliva samples on each of two consecutive days by passively drooling through a straw into labeled vials. Specifically, they were instructed to provide samples upon waking, 30 min after waking, 1 hr after waking, in the afternoon, and just before going to bed. MEMS track caps (Aardex Group, Seraing, Belgium) were used to confirm when the saliva samples were provided and to corroborate self-reported sample times. When the self-report and track-cap times differed, the track-cap time stamp was used. The vast majority of participants provided samples within the designated windows (i.e., ± 15 min of the three morning samples), but some did not comply with the instructions (see the Supplemental Material available online). Those who did not comply with instructions were not deleted from the sample because our target outcome was diurnal cortisol slope and not the cortisol awakening response. Because invalid morning samples can still be used to model cortisol slopes during the day, we retained them to minimize missing data. Critically, the results of our analysis did not change when we removed invalid morning samples.

Participants mailed their 10 samples back to the University of Minnesota, where the samples were stored in an industrial freezer at -20 °C. The samples were then shipped to the University of Trier, Germany, for assaying using time-resolved fluorescence immunoassay (dissociation-enhanced lanthanide fluorescent immunoassay, or DELFIA). Each sample was assayed in duplicate, and results of the two assays were averaged.

All cortisol data were log transformed prior to analyses, to correct for positive skew. The log-transformed measures showed the typical diurnal rhythm across each day. After transforming the data, we winsorized values 3 or more standard deviations above the mean. Five cortisol values met this threshold.

Results

Data-analytic approach

The primary outcome was the pattern of diurnal cortisol release each day. We used mixed modeling given the nested structure of the data across days and participants. For all analyses, the slope variable was time since awakening (TSA), how many hours after waking each sample was collected. We analyzed cortisol release over an 18-hr period, assuming that most individuals sleep at least 6 hr per night under typical circumstances. Most participants provided their final cortisol sample much earlier than this benchmark (mean TSA = 14.6 hr, $SD = 2.78$), but 11 cortisol samples (< 2% of all samples) were provided more than 18 hr after awakening. These extreme samples were removed prior to the analyses. All 90 participants, however, were still represented in

the final analyses. Results did not change when these 11 samples were included (see the Supplemental Material for the analyses using the full range of TSA).

In order to analyze cortisol slopes, we necessarily had to assess the intercepts, or cortisol levels at awakening. Although our focus is on the slopes, the intercepts provide additional information, as a flat slope with a high intercept has different biological significance than a flatter slope with a low intercept. Therefore, we fitted mixed models with random intercepts and slopes (i.e., TSA) nested within the two consecutive days of each participant's data. All models tested the fixed effects of both a linear and a quadratic slope; that is, each model tested the effect of TSA and TSA-squared on cortisol. We also entered the following covariates into all models: gender (male = -1 , female = 1), ethnicity (White/non-Hispanic = -1 , all others = 1), a variable reflecting the number of medications currently being taken that could have affected the cortisol pattern (Granger, Hibel, Fortunato, & Kapelewski, 2009), and whether or not the participant reported currently having the flu or cold symptoms (6 participants reported having cold-like symptoms, but no fever). There were no effects of these covariates in any of the models reported.

Primary analyses

Cumulative stress. The cumulative model predicts that individuals exposed to more stress across their entire lives (summed across ages 1 through 37 in this study) should have a flatter diurnal cortisol pattern, with cortisol levels declining at a slower rate across the day (i.e., a flattened diurnal cortisol slope) compared with individuals exposed to less total life stress. To test this possibility in our analysis, we entered the fixed effect of total (accumulated) life stress and the interaction between total life stress and TSA to determine whether total stress moderated the slope of diurnal cortisol across each day. Both the linear and the quadratic slope significantly predicted cortisol levels across the day (see Table 1). However, total life stress did not predict cortisol output across the day, nor did it interact with the linear or quadratic slope term.

Biological embedding. The biological-embedding model predicts that individuals exposed to more early life stress (during the first 5 years) should have a flatter diurnal cortisol pattern compared with those exposed to less early life stress. To test this prediction, we entered the main effect of early life stress and the interaction between early life stress and the linear and quadratic slopes into the mixed model. The linear and quadratic TSA terms predicted cortisol output across the day (see Table 1).

Table 1. Results for the Linear Mixed Models

Term	Cumulative model		Biological-embedding model		Sensitization model	
	β	95% CI	β	95% CI	β	95% CI
TSA	-1.06**	[-1.21, -0.91]	-1.06**	[-1.21, -0.91]	-1.09**	[-1.24, -0.94]
TSA ²	0.38**	[0.24, 0.52]	0.38**	[0.24, 0.52]	0.41**	[0.26, 0.55]
Early stress			0.01	[-0.12, 0.15]	0.02	[-0.12, 0.16]
Current stress					-0.12	[-0.26, 0.02]
Cumulative stress	-0.07	[-0.2, 0.07]				
Early Stress \times Current Stress					-0.04	[-0.18, 0.1]
Early Stress \times TSA			0.04	[-0.16, 0.24]	0.03	[-0.17, 0.23]
Current Stress \times TSA					0.18	[-0.01, 0.37]
Cumulative Stress \times TSA	0.13	[-0.07, 0.32]				
Early Stress \times TSA ²			-0.02	[-0.18, 0.15]	-0.01	[-0.17, 0.15]
Current Stress \times TSA ²					-0.08	[-0.24, 0.08]
Cumulative Stress \times TSA ²	-0.05	[-0.22, 0.11]				
Early Stress \times Current Stress \times TSA					0.26*	[0.07, 0.46]
Early Stress \times Current Stress \times TSA ²					-0.23*	[-0.39, -0.07]

Note: CI = confidence interval; TSA = time since awakening.

* $p < .01$. ** $p < .001$.

However, there was no main effect of early life stress, and early life stress did not moderate the effect of either the linear or the quadratic slope.

Sensitization. The sensitization model predicts that individuals who experienced higher levels of stress early in life (during the first 5 years) and are currently experiencing higher stress in adulthood (at age 37 in the present case) should have a flatter diurnal cortisol pattern. The effect of early life stress, therefore, should be moderated by current life stress, such that the two variables interact to predict the diurnal cortisol pattern. To test this prediction, we entered two three-way interactions into our mixed model. The first interaction included early life stress, current stress, and the linear slope; the second included early life stress, current life stress, and the quadratic slope. All lower-order two-way interactions and main effects were also entered into the model. There were no main effects or two-way interactions (see Table 1). However, both three-way interactions were significant, indicating that diurnal cortisol output was dependent on both early life stress and current life stress. As Figure 2 shows, when early life stress was low (1 *SD* below the mean), diurnal cortisol patterns did not differ between individuals exposed to high (1 *SD* above the mean) levels of current life stress and those exposed to low (1 *SD* below the mean) levels of current life stress. But among individuals exposed to high early life stress (1 *SD* above the mean), those experiencing high current life stress had consistently flatter cortisol slopes across the day than did those experiencing low current life stress.

Exploratory analyses

Life stress across other periods. Thus far, the main focus of our analyses has been to test the cumulative, biological-embedding, and sensitization models' predictions for diurnal cortisol slopes. However, it is possible that life stress experienced in other developmental periods, such as middle childhood or adolescence, also predicts diurnal cortisol slopes. For example, recent models propose sensitive periods beyond early childhood (Del Giudice, Ellis, & Shirtcliff, 2011; Lupien et al., 2009). The prospective, longitudinal design of this study included 19 measurements of life stress across 37 years, which allowed us to test the influence of life stress during other developmental periods. Therefore, we tested three additional exploratory models using the same mixed-modeling approach and covariates as in our three confirmatory analyses. The first exploratory analysis examined the effect of life stress during middle childhood (from Grade 1 through Grade 6), the second one examined adolescent stress (from age 16 to age 17), and the third one examined stress in early adulthood (from age 23 to age 37). As described in the Supplemental Material, there were no consistent effects revealed in any of these exploratory analyses. In addition, stress during these time periods did not interact with current stress to predict diurnal cortisol patterns.

Socioeconomic status. SES has been studied widely in relation to stress and physiology, and it has been a key predictor in past research. However, SES is most often treated as a proxy for stress because studies often lack

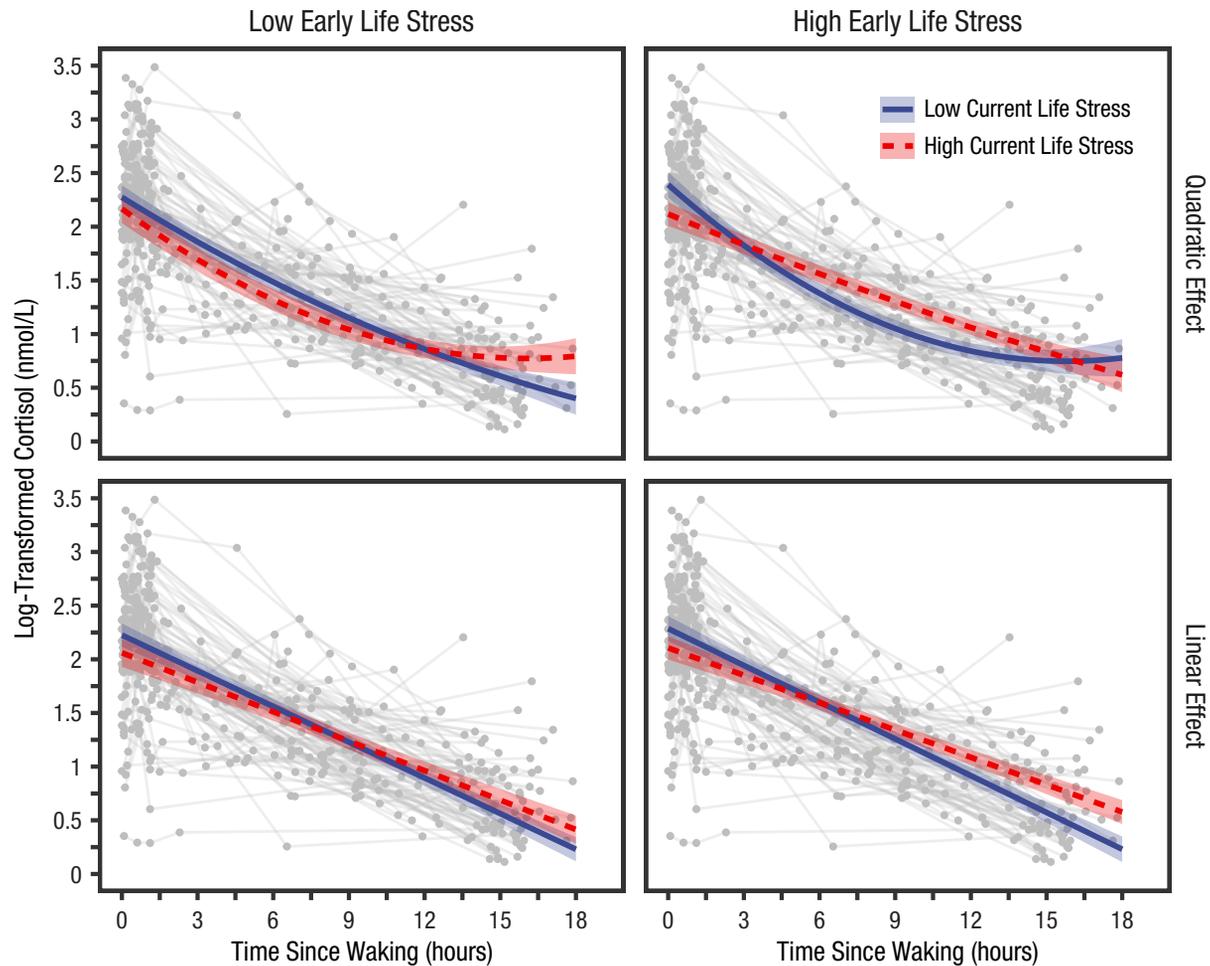


Fig. 2. Log-transformed diurnal cortisol as a function of time since waking. The colored lines show results from the mixed model testing the sensitization model of stress, which predicts that current life stress moderates the effect of early life stress on the diurnal cortisol pattern. The gray points and lines represent the raw data (note that these data are the same across all four panels). The panels in the left column depict the results for individuals who experienced low early life stress, and the panels in the right column depict the results for individuals who experienced high early life stress. The panels in the top row depict quadratic effects of time since waking, and the panels in the bottom row depict linear effects. For both early and current life stress, high and low refer to values 1 standard deviation above and below the sample mean, respectively.

direct measures of stress; that is, in the absence of direct measures, SES is used as the next best variable to quantify stress exposure. For this study, we had direct measures of stress (i.e., the LES data), which was a key construct in all of the models we tested. Therefore, we did not control for SES in our primary analyses.

Nonetheless, it is important to understand how the potential effects of early and current SES compare with the effects of life stress, so we ran a set of exploratory analyses in which both early SES and current SES were included. In the first 5 years of life, there were two assessments of SES: at birth and at age 42 months. At both time points, the Duncan Socioeconomic Index (Duncan, 1961) was used to measure occupational prestige of the mother and income. The two Duncan scores were averaged to create an early-life SES score. For

current SES at age 37, target participants were interviewed regarding their yearly income.

To explore the effects of early and current SES, we first reran our main analysis for the sensitization model (which included the interaction of early and current life stress), this time controlling for the main effects of both early and current SES. This analysis did not reveal any main effects of SES. However, adding early and current SES as main-effect covariates in a mixed model controlled only for the effect of SES on cortisol intercepts. To control for potential slope effects of SES, we next ran three separate mixed models using the same covariates as in our focal analyses. The first tested for effects of early SES on intercepts and slopes. The second tested for effects of current SES on intercepts and slopes. The final analysis examined the interactive effect of early

SES and current SES on cortisol slopes. This final analysis paralleled the sensitization model for life stress by testing whether early SES influenced cortisol slopes differentially when current SES was low versus high.

Importantly, none of these analyses revealed effects of SES. Specifically, there were no effects of either early or current SES on cortisol intercepts or slopes. Furthermore, for the SES sensitization model, there were no interactive effects of early and current SES on cortisol intercepts or slopes (see the Supplemental Material for more details).

Discussion

Prolonged stress exposure affects HPA functioning negatively, but the relative impact of stress experienced at different life stages has not been definitively established in humans. We compared three theoretically relevant models that describe how exposure to stress at distinct life stages could be related to HPA dysregulation in adulthood: the cumulative model (Karatsoreos & McEwen, 2013; McEwen, 1998, 2008) the biological-embedding model (Hertzman, 1999; Lupien et al., 2009; Miller et al., 2011; Power & Hertzman, 1997; Shonkoff et al., 2009), and the sensitization model (Daskalakis et al., 2013). The cumulative model posits cumulative life stress as the key factor predicting HPA dysregulation. The biological-embedding model suggests that early life stress is the critical factor because the HPA axis is still developing during the first several years of life. The sensitization model suggests that the influence of early life stress on HPA functioning in adulthood should be most evident when current life stress is also high.

We did not find support for the cumulative or the biological-embedding model in this study. That is, neither greater cumulative stress nor greater stress during the first 5 years of life alone predicted flatter diurnal cortisol patterns at age 37. We did, however, find support for the sensitization model. Specifically, individuals exposed to greater early life stress had flatter diurnal cortisol patterns, but only when they were also experiencing relatively high current stress (at age 37). When current life conditions were not stressful, the diurnal cortisol patterns of individuals exposed to greater early life stress did not differ from those of individuals exposed to less early life stress. These findings suggest that early life stress may serve a sensitizing role by calibrating later responses to stressful conditions in adulthood. In other words, early childhood may be a sensitive period during which important biological systems are particularly responsive to external influences, such as life stress. Such calibrations may influence how the stress response system reacts to future stressful experiences, remaining latent until the system is

challenged by concurrent life stress. Our exploratory analyses did not reveal any effects of stress during other developmental periods on later diurnal cortisol patterns.

These findings need to be replicated in other samples. Studies of early life stress using samples of children and adults who were reared in orphanage-like institutions in infancy have found significant impacts on the HPA axis, specifically, the cortisol awakening response, diurnal rhythm, and stress response to psychosocial challenges (Koss et al., 2016; Kumsta et al., 2017; McLaughlin et al., 2015). However, so far, none of this work has examined whether individuals institutionalized in infancy show dysregulated HPA functioning when experiencing high current stress in adulthood.

There are clear parallels between the sensitization and diathesis-stress models. In both models, particular psychological or biological factors are conceptualized as risk factors. These risk factors make certain individuals more likely to develop certain pathologies or health problems, especially in combination with environmental stressors, such as exposure to major trauma or very stressful events. The sensitization model can be framed as a special case of a diathesis-stress model in that early life stress is construed as a risk factor and current life stress is construed as an environmental stressor. In other words, stress early in life puts individuals at risk of dysregulated HPA functioning, which is manifested when stressful experiences occur later in life. It is important to note, however, that the sensitization model is a developmentally informed model for two reasons. First, it targets exposure to life stress during a specific developmental period that should be especially sensitive to “programming” effects of major external stressors. Second, it proposes that exposure to stressful early life experiences shapes how the HPA system functions during exposure to stressful events later in life.

The current study has some limitations. First, diurnal cortisol and life stress were measured concurrently at only one time point (age 37), limiting our ability to make inferences about HPA functioning at other time points. Nonetheless, the MLSRA measured life stress at 19 prior time points, giving us a unique opportunity to compare the cumulative, biological-embedding, and sensitization models using the same measures and same sample of participants. Second, the current sample is of modest size. Third, our findings may generalize only to initially at-risk samples whose demographic characteristics are similar to those of the current sample. In addition, though we adjusted for obvious confounds, other unmeasured factors (e.g., environmental pollutants, allelic variation, perinatal complications) may have contributed to the associations we observed. Finally, diurnal cortisol slope is only one measure of HPA functioning, and although cortisol slopes have been linked to health disparities, other aspects of HPA functioning,

such as cortisol reactivity, and other biological systems, such as the immune, metabolic, and sympathetic nervous systems, remain critically important in the study of stress and its impact on health. Despite these limitations, the MLSRA's prospective, longitudinal design spanning more than 37 years, along with its in-depth interview measures of life stress, provided a very rare, if not unique, data set for studying developmental processes and HPA functioning.

In summary, we examined three theoretically derived models of exposure to life stress and HPA dysregulation in adults. By comparing the impact of life stress at different time points across 37 years, we were able to assess the relative influence of stress exposure in distinct developmental periods on diurnal cortisol slopes at age 37. Consistent with the sensitization model, our findings revealed that the interaction between exposure to more life stress during the first 5 years of life and higher current life stress in adulthood was associated with the prototypical flat diurnal cortisol slope known to predict many negative health outcomes. These findings are important because they suggest that targeted interventions should be developed to ameliorate the negative effect of early life stress or, when that goal is not feasible, to at least reduce the negative effect of current stress in adulthood, especially for individuals who were exposed to relatively high levels of early life stress. Our findings suggest that measuring and modeling stress both early in life and concurrently may be essential to fully understanding how biological stress response systems become dysregulated.

Action Editor

Bill von Hippel served as action editor for this article.

Author Contributions

J. A. Simpson, M. M. Englund, and E. A. Carlson designed the study. E. S. Young and A. K. Farrell helped with data collection. E. S. Young performed all the analyses, produced the figures and table, and wrote the manuscript. J. A. Simpson helped write the manuscript; A. K. Farrell, E. A. Carlson, M. M. Englund, and G. I. Roisman provided comments, and M. R. Gunnar and G. E. Miller provided critical revisions. J. A. Simpson provided supervision over the analysis and writing of the manuscript.

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Declaration of Conflicting Interests

The author(s) declared that there were no conflicts of interest with respect to the authorship or the publication of this article.

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Supplemental Material

Additional supporting information can be found at <http://journals.sagepub.com/doi/suppl/10.1177/0956797619833664>

Open Practices

All data and materials can be obtained from the corresponding author. The design and analysis plans were not preregistered.

References

- Adam, E. K., & Kumari, M. (2009). Assessing salivary cortisol in large-scale, epidemiological research. *Psychoneuroendocrinology*, *34*, 1423–1436. doi:10.1016/j.psyneuen.2009.06.011
- Adam, E. K., Quinn, M. E., Tavernier, R., McQuillan, M. T., Dahlke, K. A., & Gilbert, K. E. (2017). Diurnal cortisol slopes and mental and physical health outcomes: A systematic review and meta-analysis. *Psychoneuroendocrinology*, *83*, 25–41. doi:10.1016/j.psyneuen.2017.05.018
- Daskalakis, N. P., Bagot, R. C., Parker, K. J., Vinkers, C. H., & de Kloet, E. R. (2013). The three-hit concept of vulnerability and resilience: Toward understanding adaptation to early-life adversity outcome. *Psychoneuroendocrinology*, *38*, 1858–1873. doi:10.1016/j.psyneuen.2013.06.008
- Del Giudice, M., Ellis, B. J., & Shirtcliff, E. A. (2011). The Adaptive Calibration Model of stress responsivity. *Neuroscience & Biobehavioral Reviews*, *35*, 1562–1592. doi:10.1016/j.neubiorev.2010.11.007
- Duncan, O. D. (1961). A socioeconomic index for all occupations. In J. Scott (Ed.), *Class: Critical concepts* (Vol. 1, pp. 388–426). New York, NY: Free Press.
- Farrell, A. K., Simpson, J. A., Carlson, E. A., Englund, M. M., & Sung, S. (2017). The impact of stress at different life stages on physical health and the buffering effects of maternal sensitivity. *Health Psychology*, *36*, 35–44. doi:10.1037/hea0000424
- Granger, D. A., Hibel, L. C., Fortunato, C. K., & Kapelewski, C. H. (2009). Medication effects on salivary cortisol: Tactics and strategy to minimize impact in behavioral and developmental science. *Psychoneuroendocrinology*, *34*, 1437–1448. doi:10.1016/j.psyneuen.2009.06.017
- Gunnar, M., & Quevedo, K. (2007). The neurobiology of stress and development. *Annual Review of Psychology*, *58*, 145–173. doi:10.1146/annurev.psych.58.110405.085605
- Heim, C., Ehler, U., & Hellhammer, D. H. (2000). The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. *Psychoneuroendocrinology*, *25*, 1–35. doi:10.1016/S0306-4530(99)00035-9
- Hertzman, C. (1999). The biological embedding of early experience and its effects on health in adulthood. *Annals of the New York Academy of Sciences*, *896*, 85–95.
- Karatsoreos, I. N., & McEwen, B. S. (2013). Annual research review: The neurobiology and physiology of resilience and

- adaptation across the life course. *Journal of Child Psychology and Psychiatry*, *54*, 337–347. doi:10.1111/jcpp.12054
- Koss, K. J., Mliner, S. B., Donzella, B., & Gunnar, M. R. (2016). Early adversity, hypocortisolism, and behavior problems at school entry: A study of internationally adopted children. *Psychoneuroendocrinology*, *66*, 31–38. doi:10.1016/j.psyneuen.2015.12.018
- Kumari, M., Badrick, E., Chandola, T., Adam, E. K., Stafford, M., Marmot, M. G., . . . Kivimaki, M. (2009). Cortisol secretion and fatigue: Associations in a community based cohort. *Psychoneuroendocrinology*, *34*, 1476–1485. doi:10.1016/j.psyneuen.2009.05.001
- Kumari, M., Shipley, M., Stafford, M., & Kivimaki, M. (2011). Association of diurnal patterns in salivary cortisol with all-cause and cardiovascular mortality: Findings from the Whitehall II study. *Journal of Clinical Endocrinology & Metabolism*, *96*, 1478–1485. doi:10.1210/jc.2010-2137
- Kumsta, R., Schlotz, W., Golm, D., Moser, D., Kennedy, M., Knights, N., . . . Sonuga-Barke, E. (2017). HPA axis dysregulation in adult adoptees twenty years after severe institutional deprivation in childhood. *Psychoneuroendocrinology*, *86*, 196–202. doi:10.1016/j.psyneuen.2017.09.021
- Levine, S. (2005). Developmental determinants of sensitivity and resistance to stress. *Psychoneuroendocrinology*, *30*, 939–946. doi:10.1016/j.psyneuen.2005.03.013
- Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience*, *10*, 434–445. doi:10.1038/nrn2639
- McEwen, B. S. (1998). Protective and damaging effects of stress mediators. *New England Journal of Medicine*, *338*, 171–179. doi:10.1056/NEJM199801153380307
- McEwen, B. S. (2008). Central effects of stress hormones in health and disease: Understanding the protective and damaging effects of stress and stress mediators. *European Journal of Pharmacology*, *583*, 174–185. doi:10.1016/j.ejphar.2007.11.071
- McLaughlin, K. A., Sheridan, M. A., Tibu, F., Fox, N. A., Zeanah, C. H., & Nelson, C. A. (2015). Causal effects of the early caregiving environment on development of stress response systems in children. *Proceedings of the National Academy of Sciences, USA*, *112*, 5637–5642. doi:10.1073/pnas.1423363112
- Meaney, M. J. (2001). Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. *Annual Review of Neuroscience*, *24*, 1161–1192. doi:10.1146/annurev.neuro.24.1.1161
- Miller, G. E., Chen, E., & Cole, S. W. (2009). Health psychology: Developing biologically plausible models linking the social world and physical health. *Annual Review of Psychology*, *60*, 501–524. doi:10.1146/annurev.psych.60.110707.163551
- Miller, G. E., Chen, E., & Parker, K. J. (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*, 959–997. doi:10.1037/a0024768
- Miller, G. E., Chen, E., & Zhou, E. S. (2007). If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. *Psychological Bulletin*, *133*, 25–45. doi:10.1037/0033-2909.133.1.25
- Power, C., & Hertzman, C. (1997). Social and biological pathways linking early life and adult disease. *British Medical Bulletin*, *53*, 210–221.
- Reuben, A., Moffitt, T. E., Caspi, A., Belsky, D. W., Harrington, H., Schroeder, F., . . . Danese, A. (2016). Lest we forget: Comparing retrospective and prospective assessments of adverse childhood experiences in the prediction of adult health. *Journal of Child Psychology and Psychiatry*, *57*, 1103–1112. doi:10.1111/jcpp.12621
- Roisman, G. I., Susman, E., Barnett-Walker, K., Booth-LaForce, C., Owen, M. T., & Belsky, J., . . . The NICHD Early Child Care Research Network. (2009). Early family and child-care antecedents of awakening cortisol levels in adolescence. *Child Development*, *80*, 907–920. doi:10.1111/j.1467-8624.2009.01305.x
- Ross, K. M., Murphy, M. L. M., Adam, E. K., Chen, E., & Miller, G. E. (2014). How stable are diurnal cortisol activity indices in healthy individuals? Evidence from three multi-wave studies. *Psychoneuroendocrinology*, *39*, 184–193. doi:10.1016/j.psyneuen.2013.09.016
- Rubin, D. C., Rahhal, T. A., & Poon, L. W. (1998). Things learned in early adulthood are remembered best. *Memory & Cognition*, *26*, 3–19. doi:10.3758/BF03211366
- Shonkoff, J. P., Boyce, W. T., & McEwen, B. S. (2009). Neuroscience, molecular biology, and the childhood roots of health disparities: Building a new framework for health promotion and disease prevention. *Journal of the American Medical Association*, *301*, 2252–2259. doi:10.1001/jama.2009.754
- Smyth, J. M., Ockenfels, M. C., Gorin, A. A., Catley, D., Porter, L. S., Kirschbaum, C., . . . Stone, A. A. (1997). Individual differences in the diurnal cycle of cortisol. *Psychoneuroendocrinology*, *22*, 89–105. doi:10.1016/S0306-4530(96)00039-X
- Sroufe, L. A., Egeland, B., Carlson, E. A., & Collins, W. A. (2005). *The development of the person: The Minnesota study of risk and adaptation from birth to adulthood*. New York, NY: Guilford Press.
- Stone, A. A., Schwartz, J. E., Smyth, J., Kirschbaum, C., Cohen, S., Hellhammer, D., & Grossman, S. (2001). Individual differences in the diurnal cycle of salivary free cortisol: A replication of flattened cycles for some individuals. *Psychoneuroendocrinology*, *26*, 295–306. doi:10.1016/S0306-4530(00)00057-3