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Stress-Related Trajectories of Diurnal Cortisol in Older Adulthood Over 12 Years

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A B S T R A C T

Objective: Although evidence shows that stress experiences can predict both hyper- and hypo-cortisol regulation, there is a lack of research examining these associations longitudinally. Our study assessed whether levels and increases in psychological stress experiences predicted 12-year changes in circadian cortisol levels (area under the curve; AUC) and cortisol slopes in a sample of community-dwelling older adults.
Methods: In 2004, 190 community dwelling older adults (57 to 94 years) started providing three days of diurnal cortisol and stress experience data every two years for a total of seven waves of data. All analyses controlled for relevant covariates including: SES, BMI, age, sex, cortisol-related medication, chronic illness, and smoking status.
Results: Growth-curve modeling documented that compared to participants who reported generally lower stress experiences (T-ratio = -5.57, $p < .01$), their counterparts with higher stress experiences showed significantly steeper declines in cortisol AUC over time (T-ratio = -9.23, $p < .01$). Higher stress experience was associated with generally flatter cortisol slopes. In addition, among participants with high and increasing stress experience over 12 years, cortisol slopes became increasingly flatter over time (T-ratio = 2.78, $p < .01$).
Conclusions: Among individuals with high, as compared to low, levels of chronic stress experience, cortisol levels displayed steeper declines across the study period. Moreover, cortisol slopes became increasingly flatter as a function of high and increasing stress experience. Implications for theory and research on the associations between stress experience and cortisol in the context of longitudinal observations are discussed.

1. Introduction

Stress involves both objective stressful events and their subjective experience (Lazarus & Folkman, 1984). Chronic stress experiences can trigger cortisol dysregulation of the circadian rhythm, the awakening response, or acute reactivity to a stressor (Russell & Lightman, 2019; Strueber, Strueber & Roth, 2014). Such processes of cortisol dysregulation are believed to increase vulnerability towards poor health outcomes (Cohen et al., 2007). Cortisol dysregulation is theorized to accelerate the wear and tear of specific homeostatic systems of the body (e.g., metabolism or immunity), a concept referred to as allostatic load (McEwen, 1998). As such, cortisol is considered an important biological intermediary in the link between stress experiences and the development of disease (Miller et al., 2007). These processes may be particularly important in old age, a life phase when people frequently experience an increase of age-related stressors and physical health declines (Heckhausen et al., 2019). Related to this possibility, aging has been associated with disturbances in cortisol regulation (Gaffey et al., 2016; Otte et al., 2005; Nater et al., 2013; Piazza et al., 2010) that can predict inflammation, functional limitations, frailty, and mortality (Johar et al., 2014; Kumari et al., 2011; Piazza et al., 2018).

When experiencing a threat, the human organism mobilizes energy by activating the autonomous nervous system, and the hypothalamic-pituitary adrenal (HPA) axis with its final product cortisol. Cortisol has a myriad of anabolic effects, allowing the organism to appropriately deal with an increase in demand (for a review, see, for example, Ulrich-Lai & Herman, 2009). Cortisol follows a distinct circadian rhythm and is involved in regulating alertness, metabolism, and immune function (Dallman et al., 1994).

Both acute and chronic or cumulative stress experiences can

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influence the HPA axis. The former has been shown to result in temporary increases in cortisol at any time of day, and therefore have been studied over time periods of 1-2 hours as a measure of acute biological stress reactivity (Kudielka et al., 2009). By contrast, to examine how chronic stress experiences influence diurnal cortisol secretion, metrics such as area under the curve (AUC; total daily secretion levels) and slope (the rate at which cortisol declines over the course of the day) are frequently employed.

Much theoretical work has explored how the build-up of stress experiences can lead to persistent alterations in the diurnal cortisol rhythm (Adam, 2012; McEwen, 1998; Del Giudice et al., 2013; Strüber et al., 2014). The exact nature of how chronic stress influences the diurnal cortisol rhythm over time, however, is less established. With regards to the rate of decline in cortisol across the day (i.e., cortisol slope), studies frequently observe that chronic stress is linked with flatter daily cortisol slopes in cross-sectional research or over short time periods (e.g., DeSantis et al., 2015; Ice et al., 2005; Sephton et al., 2000), which may confer a risk for poor health outcomes (Adam et al., 2017; Heim et al., 2000).

The associations between chronic stress and total daily cortisol output (AUC), however, have been less clear. Early conceptual frameworks hypothesized that such stress experiences can lead to elevated cortisol secretion, which in turn confers an increased risk for disease (McEwen, 1998). These theories were informed by findings from experimental (e.g., acute stress reactivity) and correlational studies, suggesting that stress experiences can increase HPA axis activity or prevent the normative down-regulation of cortisol secretion across the day (hyper-cortisolism; Heim et al., 2000). Other evidence, however, has pointed to an inverse association, whereby chronic stress is related to lower cortisol levels (hypo-cortisolism; Carroll et al., 2017; Heim et al., 2000; Vedhara et al., 2002). Hypo-cortisolism may thus also reflect long-term stress-related dysregulation of the HPA axis, and could play a role in the development of disease (Heim et al., 2000; Voellmin et al., 2015).

The extant literature is thus not clear on the diurnal cortisol pattern that is indicative of stress-related disruptions in the HPA axis regulation, which is also reflected in the theoretical contributions on that topic (Adam, 2012; Del Giudice et al., 2013; Strüber et al., 2014). One explanation for these inconsistent findings could be that differences in the chronicity or timing of a stressor could explain varying types of cortisol dysregulation. In this regard, a meta-analysis suggested that cortisol levels are elevated in samples that confronted more recent stressors, but levels are comparatively lower in samples that experienced a longer and chronic period of stress (Miller et al., 2007). It is difficult, however, to arrive at firm conclusions about links between recent and long-term stress and cortisol because much of the existing research is based on cross-sectional or short-term experimental studies. As such, there is a need for studies that follow stress-exposed populations over longer periods of time and examine the effects of both levels and changes in chronic stress on their long-term trajectories of cortisol secretion.

The present study sought to address this issue by examining the associations between chronic stress experiences and 12-year trajectories of cortisol functioning (i.e., cortisol AUC and slope) in a community-dwelling sample of older adults. Because stressful experiences may increase over time, particularly in older populations (Heckhausen et al., 2019), we chose to include both average long-term levels and long-term longitudinal changes in stress experiences as predictors of diurnal cortisol and tested their main effects and interaction for significance. Given that chronic stress experiences may result in reduced cortisol levels (Miller et al., 2007), we hypothesized that high and/or increasing levels of stress experiences over 12 years would predict a relative decline of levels of older adults' cortisol secretion (AUC). Further considering the previously discussed link between stress experiences and a person's inability to downregulate the slope of the diurnal cortisol rhythm, we hypothesized that high and/or increasing levels of stress experiences would predict progressively flatter cortisol slopes over time.

2. Methods

2.1. Participants

A total of 215 older adults were assessed at baseline as part of the Montreal Aging and Health Study (MAHS). This sample included older adults (age range = 57 to 94 years) from an age-normative sample of community-dwelling individuals living in Montreal, QC, Canada. Participants were initially recruited via newspaper advertisements in the Montreal area in 2004. To be eligible for inclusion into the study, participants had to be older than 60 years of age (we note that one included participant misreported his age during recruitment and was only 57 years old) and living the in the Montreal area. Since our interest was to examine changes in cortisol, we included only those participants into this study who provided cortisol data in at least two waves (25 participants of the original sample were excluded). The analytic sample therefore included 190 older adults. Following the first wave, participants were assessed every two years for a total of 7 waves (12 years; T2: N = 182; T3: N = 164; T4: N = 136, T5: N = 125; T6: N = 96; T7: N = 87). Study attrition was due to death (N = 49), lost contact (N = 20), refusing to participate (N = 26), sickness (N = 4), unable to follow directions (N = 3), or personal reasons (N = 1). Written informed consent was obtained from all participants prior to participation in the study, and the institutional review board of Concordia University approved the study. At baseline, the distribution of sociodemographic variables was within the normative range of older Canadians residing at home (National Advisory Council on Aging, 2006).

3. Materials

3.0.1. Diurnal Cortisol

At each wave diurnal cortisol was assessed on three non-consecutive days over the course of one week. Five saliva samples were collected each day using salivettes at awakening, 30 min after awakening, 2 PM, 4 PM, and at bedtime. The first sample was collected by the participants when they woke up, after which they set a timer to collect the 30-min sample. Research assistants contacted the participants at 2 PM and 4 PM to facilitate the afternoon sample collection. The final sample was collected by participants just before they went to bed. Collection times for each sample were recorded by the participants. Participants were instructed to not eat or brush their teeth prior to saliva collection to prevent contamination with food or blood. Salivettes were stored in refrigerators until returned to the lab where they were frozen at -20 degrees Celsius until analysis. University of Trier completed all cortisol analyses using a time-resolved fluorescence immunoassay with cortisol-biotin conjugate as a tracer. The inter-assay variability from these cortisol analyses was on average 4.88%, and the intra-assay variability in this laboratory is routinely below 10%.

Cortisol scores that deviated more than three standard deviations from the mean cortisol level for that time of day were excluded. Cortisol values were skewed and log-transformed to stabilize variance. Daily cortisol levels were calculated using the area under the curve with respect to ground (AUC) across each day separately, based on hours after awakening (Pruessner et al., 2003). AUC was only calculated if participants provided four useable cortisol scores on each day. The 30-min measure was excluded from AUC calculation because the awakening response has been shown to be independent from circadian regulation (Chida & Steptoe, 2009). Using these criteria, we were able to calculate cortisol scores for 95.70% to 98.44% of days on which participants collected saliva. Cortisol slope was calculated by regressing cortisol values on hours after awakening for each collection day (excluding the 30-min sample). At each wave, the three cortisol AUC and slope scores were averaged to obtain reliable indicators of average AUC and average

Table 1
Means, Standard Deviations, Frequencies and Zero-Order Correlations of Main Study Variables (N = 190) [a].

Construct	*Mean (SD) or %*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*
1 Average AUC	11.85 (1.95)													
2 Average Slope	−0.03 (0.01)	.17*												
3 Stress Levels	0.55 (0.53)	-.05	.12											
4 Stress Change	0.03 (0.12)	-.03	.06	.15*										
5 SES	0.00 (0.88)	.16*	.04	.02	.02									
6 BMI	25.55 (3.72)	.03	.12	.05	.03	-.09								
7 Female	51.1 %	-.25**	-.06	.13	-.02	-.15*	-.10							
8 Age	72.33(5.91)	.27**	.22**	-.16*	-.02	-.10	-.15*	.01						
9 Smoking	8.9%	.09	-.05	-.01	-.01	-.01	.00	-.10	-.17*					
10 Chronic Illness	2.52 (1.67)	.05	.01	.05	-.10	-.10	.21**	-.10	.06	.12				
11 Thyroid Med	16.3%	.15*	-.04	-.07	-.10	.02	.05	.23**	.01	.01	.13			
12 Estrogen Med	8.4%	-.11	.06	-.08	-.12	.05	-.03	.30**	-.04	-.03	.05	.07		
13 Cortico. Med	5.3%	-.14*	.11	.10	-.06	-.09	.10	-.01	-.05	.01	.14*	-.04	.01	
14 Other Heart Med	7.9%	.11	-.13	-.12	.04	.03	.09	-.14*	.08	.11	.32**	.14	-.09	-.07

* $p \leq .05$.
** $p \leq .01$.
[a] Data in this table are based on variables prior to mean-substitution and as such, some *N*s are slightly reduced for some variables.

slope. The three AUC (α = .75 - .91; *r*s = .42 - .83, *p*s < .01) and slope (α = .54 - .70; *r*s = .22 - .54, *p*s < .01) scores were positively correlated at each wave. The ICC for AUC was 0.24 (76% of the variance was located within-person), and the ICC for slope was 0.41 (59% of the variance was located within-person).

3.0.2. Chronic stress experiences

Daily stress levels were assessed at each wave on three non-consecutive days during one week. Towards the end of each day, participants were asked to report the extent to which they felt "stressed" during that day on a Likert scale ranging from *very slightly/not at all* (0) to *extremely* (4). Daily stress levels were comparable with other research on daily stress in older adulthood (e.g., Scott et al., 2013, see also Table 1). The three daily stress assessments were positively correlated at each wave (αs = .74 - .85; *r*s = .38 -.85, *p*s < .01). To obtain an indicator of chronic stress levels, the three daily stress values were averaged at each wave, and then averaged across all waves. Daily stress levels were significantly correlated across waves (*r*s > .30, *p*s < .01). To assess long-term changes in stress experiences, we conducted a hierarchical linear model, predicting variability in stress experiences across the study period by time in study (and a residual term), and saved the obtained individual slope coefficients for further analysis. Stress experiences significantly increased over the course of the study (*coefficient* = .016, *T-ratio* = 3.32, $p < .01$). The ICC for stress experiences was 0.41 (therefore 59% of the variance was located within-person).

3.0.3. Covariates

Demographic and health-relevant covariates were incorporated into the analyses. The covariates included SES, BMI, age, sex, cortisol-related medication usage, chronic illness, and smoking status. Socioeconomic status was indexed via two variables: income and education. These two variables were standardized and averaged to obtain a reliable indicator of SES (r = .47, $p < .001$). Our sample represented a diverse socioeconomic status, 28.9% completed high school, 29.5% completed college or a trade, 22.6% completed a bachelor's degree, and 10% completed a postgraduate education (approximately 5.8% did not provide education information, and 3.2% did not complete any schooling). 19.5% had an income less than $17,000, 35.3% of the sample had an income between $17,001 and $34,000, 30% had an income between $34,001 and 68,000, and 7.4% had an income greater than $68,000 ($CAD; 7.9% of the sample did not provide income information). Participants height and weight were self-reported and BMI was then calculated (M = 25.55, SD = 3.72). Sex was coded as 1 = *male*, 2 = *female* (51.1% female). Smoking status was coded as 0 = *No*, 1 = *Yes* (8.9% were smokers). Chronic illness was assessed at baseline using a 17-item checklist of different chronic illnesses used in previous research (e.g., cardiovascular problems, arthritis, cancer, diabetes, high blood pressure, Wrosch et al., 2007). The number of chronic illnesses reported was counted to represent a total score of chronic illness (M = 2.52, SD = 1.67).

To control for the possibility that certain medications may influence cortisol trajectories, we coded baseline data of medication usage into major categories of medication that could influence the HPA axis. Participants were coded as 0 (*taking zero medications*) or 1 (*taking one or more medications*) in a respective category. Medications were coded into the following categories: blood pressure-related medication (e.g., beta blockers, calcium-channel blockers, ACE inhibitors; 48.4%), non-narcotic pain medication (e.g., Acetaminophen, Ibuprofen, Naproxen; 46.3%), cholesterol-related medication (e.g., Statins; 36.8%), psychiatric medication (e.g., SSRIs, Benzodiazepines; 20.5%), thyroid-related medication (e.g., Synthroid; 16.3%), diuretic medication (e.g., Hydrochlorothiazide, Indapamide, 15.3%), diabetes medication (e.g., Metformin; 12.6%), estrogen and progesterone-related medication (e.g., Premarin; 8.4%), other heart-related medication (e.g., Lanoxin, Imdur, Nitroglycerin; 7.9%), corticosteroid medication (e.g., Symbicort, Flonase; 5.3%), narcotic pain medication (e.g., Valium; 1.6%), and other medication that may influence HPA axis but did not fit these major categories (11.6%).

3.1. Data analyses

Preliminary analyses were conducted by computing descriptive statistics of the main study variables and zero-order correlations among the main study variables (Table 1). The descriptive statistics of cortisol and stress variables across all waves are reported in Supplemental Table 1. The hypotheses were tested in two separate growth-curve models, predicting trajectories of AUC and slope over 12 years (using HLM 6.0, Raudenbush, 2004). The reported effects are based on models using restricted maximum likelihood estimation and robust standard errors. At Level 1, we estimated variance in participants' AUC and cortisol slope from T1-T7 as a function of an intercept, person-centered scores of time in the study, and a residual term. The intercept represented participants' average levels of AUC and averaged cortisol slope across T1-T7, while the time slope coefficient represents the yearly changes in AUC and cortisol slope from T1 to T7.

At Level 2, we predicted the intercept and slope of cortisol AUC and cortisol slope as a function of average stress levels (T1-T7), changes in

stress levels (T1-T7) and the covariates (SES, BMI, sex, age, medication, smoking). To reduce the number of medication-related covariates in our models, we conducted preliminary analyses in HLM predicting cortisol AUC and slope separately from each medication category. Based on these analyses, we included only those medication categories into the Level-2 models for predicting cortisol AUC (or cortisol slope) that were significantly associated with levels or changes in cortisol AUC (or cortisol slope). The preliminary analyses showed that taking thyroid and other heart-related medication was associated with higher cortisol AUC levels on average, while taking corticosteroid or estrogen and progesterone-related medication were associated with lower cortisol AUC (intercept effects; *T-ratios* > |1.94|, $p \leq .05$). Thyroid and corticosteroid medication significantly predicted increasingly flatter cortisol slopes over time (slope effects; *T–ratios* > 2.21, $p < .03$). In addition, other heart-related medication significantly predicted flatter average levels of cortisol slopes (intercept effect; *T-ratio* = -2.32, $p < .03$). None of the other medication categories were associated with either cortisol AUC or cortisol slope and thus not included in the respective models.

In subsequent models, we tested the interactions between levels and changes of stress experiences for significance. Level 2 main effect predictors were standardized prior to conducting the analyses. Significant interaction effects were followed up by calculating simple slopes of the effects of stress experiences on changes in AUC and cortisol slope over time at high (+1 SD) and low (-1 SD) stress levels and changes. Since HLM is capable of handling missing data at Level 1 (i.e., cortisol AUC and slope), missing data in the outcome variables were not replaced. There was a small amount of missing data of between-person predictors variables (SES: $N = 1$, changes in stress experiences = 4, BMI: $N = 2$, Smoking: $N = 2$), which were replaced with the sample mean (Tabachnik et al., 2013).

Given that any findings related to predicting a flatter cortisol slope across day could occur as a result of either decreasing morning levels and/or increasing evening levels, we also conducted a set of supplemental analyses. These analyses explored which aspect of the daily cortisol rhythm was associated with longitudinal changes in cortisol slopes. Morning cortisol levels reflected the first cortisol sample of the day, and evening cortisol levels represented the last cortisol sample of the day. To explore how changes in diurnal cortisol slope predicted changes in these specific cortisol measures, we saved the HLM time slope coefficients of the diurnal cortisol slope as an indicator of change in cortisol slope for each individual, and used this measure to predict levels and longitudinal changes in morning and evening cortisol levels at Level 1, controlling for the included covariates at Level 2.

4. Results

4.1. Predicting Cortisol Level (AUC)

The Level 1 intercept of cortisol AUC was significant, indicating that participants' average cortisol levels across waves were significantly different from zero (see Table 2). In addition, the time slope of AUC was significantly different from zero, indicating that cortisol levels significantly decreased over 12 years. Finally, results from the Level 1 model for AUC displayed significant variance around participants' average intercept, $\chi^2 = 616.47$, $df = 189$, $p < .001$, and time slope, $\chi^2 = 241.23$, $df = 189$, $p < .01$.

The Level 2 model predicted the observed variance in participants' intercepts and time slopes of AUC scores as a function of levels and changes in chronic stress experiences and the covariates. As documented in Table 2, higher SES, being male, and older age significantly predicted higher average AUC scores. Of the medication variables, thyroid medication was associated with higher average cortisol AUC scores, and taking corticosteroid medication was associated with lower cortisol AUC scores on average. None of the covariates were significantly associated with the time slope of AUC scores. Of importance, however, chronic stress levels significantly predicted the time slope of AUC scores. In contrast, chronic stress level changes did not predict the intercept of AUC scores (see Table 2). No significant interaction emerged between stress levels and changes in predicting the AUC intercept or time slope.

To illustrate the significant cross-level interaction between levels of stress experiences and the time slope, we used recommended growth-curve techniques (Preacher et al., 2006), plotting the trajectories of AUC scores over 12 years separately for those with low (-1 SD) and high stress experiences (+1 SD). Fig. 1 shows that AUC significantly declined across all participants over the 12 years. However, participants who reported higher chronic stress levels exhibited significantly steeper AUC declines over time (*T-ratio* = -9.24, $p < .001$), as compared to their counterparts who reported lower stress levels (*T-ratio* = -5.57, $p < .001$). Including levels of perceived stress in the model explained an additional 18.17% of variance in changes in AUC across waves, controlling for all covariates. In sum, these analyses indicate that higher levels of chronic stress over the 12-year observation period were associated with a stronger decline in AUC levels.

4.2. Predicting Cortisol Slope

The Level 1 intercept of cortisol slope was significant, indicating that the average cortisol slope across all participants was significantly different from zero (see Table 3). The time slope of cortisol slope was not significant, which suggests that, on average, daily cortisol slopes did not change over time among all participants. The Level 1 model for cortisol slope displayed significant variance around participants' average intercept, $\chi^2 = 869.51$, $df = 189$, $p < .001$, and time slope, $\chi^2 = 228.74$, $df = 189$, $p < .03$.

The Level 2 model predicted the variance in the intercepts and slopes of participants' daily cortisol slope scores as a function of levels and changes in chronic stress and covariates. Higher BMI and being older predicted significantly flatter average cortisol slopes across all waves, that is, lower morning and/or higher evening levels of cortisol. Of the medication variables, other heart-related medication predicted steeper cortisol slopes on average. In addition, thyroid and corticosteroid medication categories significantly predicted the time slope. Taking these medications were associated with increasingly flatter cortisol slopes over the course of the study. No other covariates significantly predicted the intercept or time slope. In addition, the main effects of changes in chronic stress did not significantly predict the intercept or time slope or daily cortisol slope values. Importantly, however, the analysis showed a significant Level-2 effect of stress levels in predicting the intercept (but not the slope) of cortisol slope scores (*T-ratio* = 1.97, $p \leq .05$). The stress level effect on the intercept indicated that higher stress experiences were associated with flatter average cortisol slopes. The addition of chronic stress levels to the model explained additional 1.47% of variance in the intercept of participants' cortisol slope scores, controlling for all covariates.

Finally, a significant interaction emerged between levels and changes of stress experiences in predicting changes over time in cortisol slope (*T-ratio* = 2.09, $p < .04$, see Table 3). To examine the cross-level, 3-way interaction of stress levels and stress changes on changes over time in cortisol slope, we plotted the trajectories of cortisol slope across waves for participants with high (+1 SD) and low stress levels (-1 SD) and increasing (+1 SD) and decreasing (-1 SD) stress (see Fig. 2). The calculation of the simple time slopes showed that cortisol slopes remained stable over 12 years among participants who experienced relatively low levels of stress regardless of whether stress decreased (*T-ratio* = 0.73, $p > .05$) or increased over time (*T-ratio* = -0.84, $p > .05$). Cortisol slopes also remained stable for those participants with high levels of stress experiences that decreased over time (*T-ratio* = -0.75, $p > .05$). By contrast, daily cortisol slopes became progressively flatter among participants with high stress levels that increased over time (*T-ratio* = 2.78, $p < .01$). The addition of the interaction between levels and changes in stress to the model explained additional 4.65% of

Table 2
Results of Growth-Curve Analysis Predicting Cortisol AUC Trajectories by Stress, and Covariates (N = 190).

	Cortisol AUC			
	Intercept (Average levels)		Slope (Time)	
Effects	Coefficient (SE)	T-ratio	Coefficient (SE)	T-ratio
Level 1 (β_0; β_1)[a]	11.7512 (0.1341)**	87.629	−0.2678 (0.0233)**	−11.486
Level 2:				
Stress Level	0.1252 (0.1195)	1.047	−0.0673 (0.0236)**	−2.848
Stress Change	−0.0431 (0.1535)	−0.281	0.0516 (0.0410)	1.258
SES	0.2490 (0.1268)*	1.964	0.0033 (0.0261)	0.126
BMI	0.1431 (0.1071)	1.336	−0.0219 (0.0239)	−0.918
Sex	−0.5208 (0.1337)**	−3.896	0.0318 (0.0263)	1.205
Age	0.5845 (0.1335) **	4.379	0.0343 (0.0263)	1.304
Smoke	0.2466 (0.1517)	1.625	−0.0354 (0.0300)	−1.182
Chronic Illness	−0.1077 (0.1454)	−0.741	0.0364 (0.0252)	1.445
Thyroid Med	0.3659 (0.1105)**	3.311	0.0026 (0.0247)	0.106
Estrogen Med	−0.0617 (0.1047)	−0.589	−0.0106 (0.0227)	−0.464
Corticosteroid Med	−0.2354 (0.1059)*	−2.223	0.0015 (0.0260)	0.057
Other Heart Med	0.0242 (0.1084)	0.223	0.0059 (0.0211)	0.281
Interaction: Stress				
Level X Change	−0.0857 (0.1362)	−0.629	0.0484 (0.0417)	1.162

* $p \leq .05$.
** $p \leq .01$. SE = standard error.
[a] The first parameter (e.g., β_0) estimated the intercept, which represents participants' average levels of cortisol AUC across T1 – T7, and the second parameter (e.g., β_1) estimated the slope, which represents the within-person associations between years in study from T1-T7 and participants' cortisol AUC. The Level 1 model had 189 *df*s, the Level 2 models had 177 *df*s, and the model including the stress level X change interaction term had 176 *df*s.

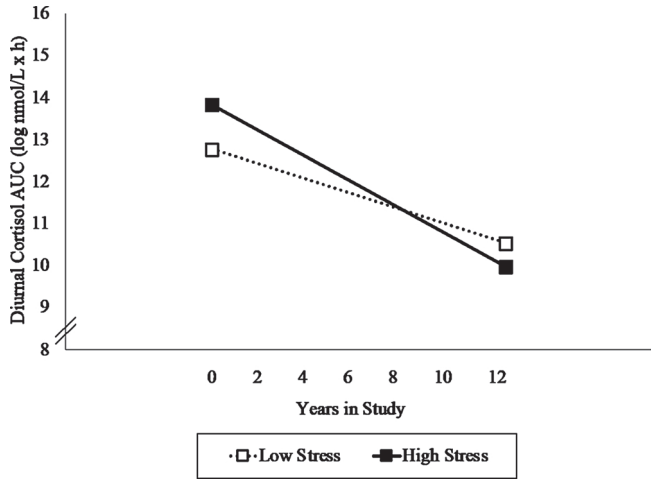

Fig. 1. Trajectories of diurnal cortisol AUC plotted as a function of participants' average levels of stress experiences. Trajectories were estimated one standard deviation above and below the mean of the moderator variable.

variance in the time slope of participants' cortisol slope scores, controlling for all covariates.

4.3. Cortisol Slope and Morning and Evening Cortisol

We conducted supplemental analyses to explore how longitudinal changes in cortisol slope were associated with changes in morning and evening cortisol levels. In two separate models, variance in the intercept and slope of morning and evening cortisol levels were estimated as a function of change in cortisol slope scores, controlling for covariates (SES, BMI, sex, age, cortisol medication [thyroid, corticosteroid, estrogen-progesterone, and other heart-related medication]) chronic illness and smoking status). Across all participants, morning (*T-ratio* = -8.28, $p < .001$) and evening (*T-ratio* = -6.52, $p < .001$) cortisol generally declined over the course of the study. Thyroid and corticosteroid medication significantly predicted the intercept of morning cortisol levels. Taking thyroid medication was associated with higher morning cortisol (*T-ratio* = 2.02, $p < .05$), while corticosteroids were associated with lower morning cortisol levels on average (*T-ratio* = -2.54, $p < .02$). No other covariates significantly predicted morning cortisol. For evening cortisol, being older (T-ratio = 5.43, $p < .01$), and having a higher SES (*T-ratio* = 2.29, $p < .03$), were associated with higher evening cortisol levels on average (intercept effect). In addition, thyroid medication predicted higher evening cortisol levels on average (intercept effect; *T-ratio* = 2.01, $p < .05$).

Table 3
Results of Growth-Curve Analysis Predicting Cortisol Slope Trajectories by Stress, and Covariates (N = 190).

	Cortisol Slope			
	Intercept (Average levels)		Slope (Time)	
Effects	Coefficient (SE)	T-ratio	Coefficient (SE)	T-ratio
Level 1 (β_0; β_1)[a]	−0.0317 (0.0008)**	−37.385	0.0002 (0.0001)	1.426
Level 2:				
Stress Level	0.0016 (0.0008)*	1.973	0.0001 (0.0001)	1.462
Stress Change	0.0007 (0.0009)	0.849	0.0003 (0.0002)	1.413
SES	0.0009 (0.0010)	0.957	0.0000 (0.0001)	0.276
BMI	0.0018 (0.0008)*	2.254	−0.0001 (0.0001)	−0.633
Sex	−0.0008 (0.0008)	−0.952	0.0000 (0.0001)	0.312
Age	0.0035 (0.0009)**	4.013	0.0000 (0.0001)	0.184
Smoke	0.0002 (0.0011)	0.216	0.0001 (0.0001)	0.922
Chronic Illness	−0.0004 (0.0009)	−0.401	0.0000 (0.0001)	0.304
Thyroid Med	0.0000 (0.0007)	0.038	0.0002 (0.0001)*	2.422
Corticosteroid Med	0.0011 (0.0008)	1.324	0.0002 (0.0001)*	2.365
Other Heart Med	−0.0017 (0.0007)*	−2.295	−0.0001 (0.0001)	−0.876
Interaction: Stress				
Level X Change	0.0004 (0.0009)	0.458	0.0004 (0.0002)*	2.092

* $p \leq .05$.
** $p \leq .01$. SE = standard error.
[a] The first parameter (e.g., β_0) estimated the intercept, which represents participants' average levels of slope across T1 – T7, and the second parameter (e.g., β_1) estimated the slope, which represents the within-person associations between years in study from T1-T7 and participants' slope. The Level 1 model had 189 *df*s, the Level 2 models had 178 *df*s, and the model including the stress level X change interaction term had 177 *df*s.

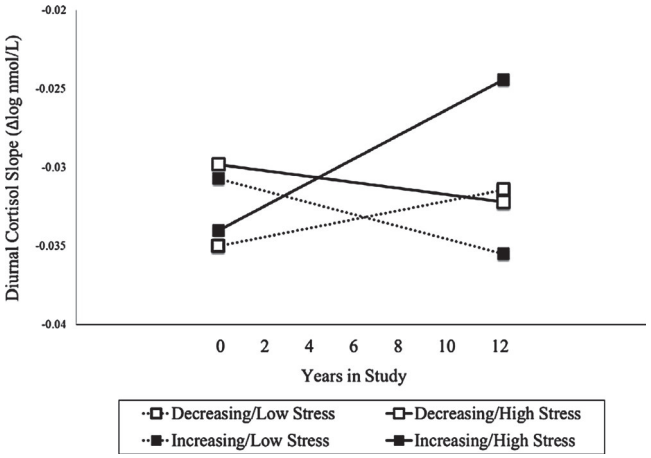

Fig. 2. Trajectories of diurnal cortisol slope as a function of participants' average levels and changes of stress experiences. Trajectories were estimated one standard deviation above and below the mean of the moderator variables. Only the slope for increasing and high stress experiences reached significance (*T-ratio* = 2.78, $p < .01$; all other *T-ratios* < |0.84|, *ps* > .05).

Of importance, the analyses further showed that change in cortisol slope significantly predicted the time slope of morning cortisol (*T-ratio* = -8.74, $p < .001$) and evening cortisol levels (*T-ratio* = 6.24, $p < .001$), but not the intercept of morning or evening cortisol. The effects of cortisol slope on the time slope of morning (left panel) and evening (right panel) cortisol levels are illustrated in Fig. 3. Simple slope analyses documented that changes in daily cortisol slope across the study period were associated with longitudinal changes in both morning and evening cortisol levels. Among participants whose daily slopes became progressively flatter (+1 SD) over time, morning cortisol levels significantly declined across the study period (*T-ratio* = -9.45, $p < .01$), while evening cortisol levels significantly increased (*T-ratio* = 3.32, $p < .01$). By contrast, among participants whose daily cortisol slopes became increasingly steeper across the study period (-1 SD), morning cortisol displayed significant increases over time (*T-ratio* = 5.65, $p < .01$), while evening cortisol levels became increasing reduced (*T-ratio* = -8.76, $p < .01$). Above and beyond the covariates, changes in cortisol slope across the study explained between 64.29% and 40.00% of variance in the time slope of participants' morning and evening cortisol scores, respectively.

5. Discussion

The present study showed that average levels and changes in chronic stress experiences predict longitudinal trajectories of older adults' diurnal cortisol output (AUC and daily slope). Across all participants, AUC levels – and thus total cortisol output – declined over the course of the 12 years. In contrast, diurnal slope – the decrease from morning to evening of cortisol – did not change on average. These trajectories were moderated by average levels, and changes, in chronic stress. Among older adults who perceived high, as compared to low, levels of chronic stress, AUC levels were relatively enhanced at the beginning of the study. However, the AUC levels of highly stressed participants exhibited significantly steeper linear declines over the subsequent 12 years, resulting in substantially reduced cortisol levels towards the end of the study period.

Levels of stress experienced also increased over time (see Methods) and higher stress levels predicted generally flatter daily cortisol slopes across the study period. The results further showed that participants who perceived high and increasing levels of chronic stress exhibited progressively flatter diurnal cortisol slopes over time. To this end, supplemental analyses revealed that progressively flatter cortisol slopes were associated with a reduction in morning cortisol levels and an increase in evening cortisol levels. Note that the observed effects of stress experiences were substantial, explaining between 4.65% and 18.17% of the variance in cortisol change, and the results were independent of covariates that have shown significant effects on cortisol in previous research (i.e., age, sex, BMI, smoking, chronic illness, and cortisol-related medication; Nater et al., 2013).

These findings document that the trajectories of older adults' diurnal cortisol levels (AUC) and daily cortisol slopes differed markedly as a function of chronic stress experiences. Higher chronic stress levels predicted an accelerated decline in cortisol levels over time. By contrast, cortisol slopes became progressively flatter over time as a function of both high and increasing levels of chronic stress. As such, cortisol AUC and slope displayed differential patterns, which points to the potential independence of different aspects of the diurnal cortisol rhythm (Ice, 2005; Vedhara et al., 2006). In support of this possibility, cortisol AUC and slope only exhibited a modest correlation in our study (r = .17; see Table 1).

On the one hand, these results could be interpreted to mean that chronically high and increasing stress experiences progressively degrade the ability of the body to regulate the HPA axis, contributing to flatter cortisol slopes over time. Indeed, researchers have theorized that the negative feedback loop that governs the regulation of cortisol secretion may be impaired and underlie the emergence of flatter cortisol slopes (Kumari et al., 2010). On the other hand, chronic stress may have different effects on daily cortisol levels (AUC). Consistent with meta-analytic findings (Miller et al., 2007), our results suggest that during earlier exposure to chronic stress experiences, HPA activation is peaking. The continued exposure to prolonged stress however may then create a counter-regulatory response, downregulating the HPA axis and resulting in below normal levels of cortisol in the long-term.

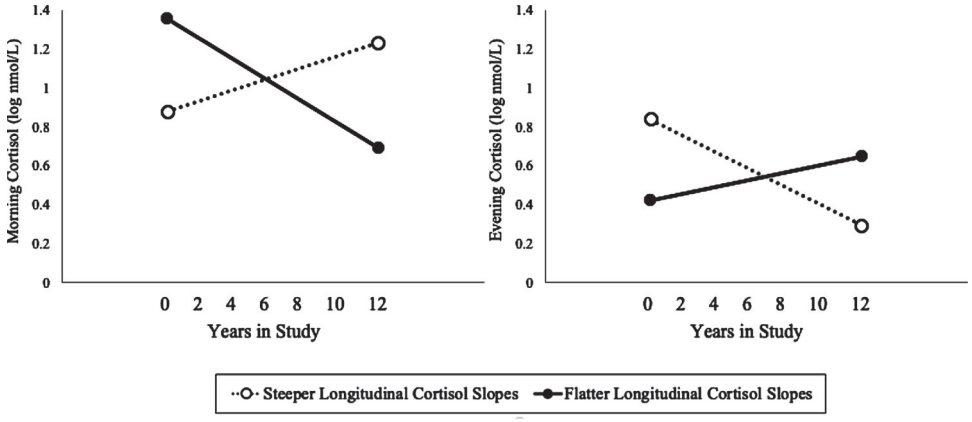

Fig. 3. Trajectories of morning cortisol levels (left panel) and evening cortisol levels (right panel) as a function of participants' changes in cortisol slopes across the study period. Trajectories were estimated one standard deviation above and below the mean of the moderator variable.

A corollary of the previous discussion is that research examining cortisol dysregulation may require more detailed assessment of the aspects associated with stress experiences. In our study, the obtained patterns related to both high levels and/or changes in stress experiences over a relatively long period of time, and as a consequence, point to the importance of examining chronicity and timing of stress experiences in relation to cortisol output (AUC). These findings suggest that it may be critical for researchers to consider the length and changes related to stress experiences to determine whether cortisol is dysregulated.

With respect to cortisol slope, our findings are consistent with previous research linking chronic stress to flatter cortisol slopes (Ice et al., 2005; Sephton et al., 2000). These results advance the literature by documenting that both levels and changes in stress experiences predicted cortisol slope trajectories, whereas cortisol levels were related only to levels of stress experiences. In addition, they could imply that cortisol slope may be more sensitive than cortisol levels to the cumulative effects of increasing stress levels. These findings further suggest that cortisol slope is a promising construct to consider in research on stress and health, given that there is less uncertainty about the relationship between stress experiences and cortisol slopes.

We also conducted supplemental analyses to explore whether flatter cortisol slopes were associated with changes in morning and/or evening cortisol. The results showed that participants who exhibited progressively flatter cortisol slopes over time secreted both reduced morning levels and increased evening levels of cortisol. These findings replicate earlier research, linking flatter cortisol slopes to lower morning levels, higher evening levels, or both (Bower et al., 2005; Pruessner et al., 1999; Sephton et al., 2000). In addition, they may imply that as daily cortisol slopes become flatter the entire diurnal rhythm is affected. While the underlying mechanisms of this process requires further study, it is for example possible that a stress-related disruption of the circadian rhythm, associated with sleeping problems or general HPA axis dysfunction, could explain the obtained pattern of findings (McEwen, 1998; Sephton et al., 2000). Regardless of the underlying mechanisms, the observation that a flatter diurnal slope is systematically associated with chronic stress is an important observation that is currently understudied.

Our study also sheds light on how cortisol may generally change in aging populations. Previous research has reported mixed associations between age and cortisol levels, with some studies finding positive associations (Adam et al., 2006; Dmitrieva et al., 2013; Evans et al., 2011; Gaffey et al., 2016; Nater et al., 2013), and others documenting negative associations (Brandtstädter et al., 1991; Evans et al., 2011; Heaney et al., 2012). The cross-sectional findings from our study revealed that being older was associated with generally higher cortisol levels and flatter diurnal cortisol slopes (see Table 1). However, our longitudinal analyses showed that, on average, cortisol slope remained relatively stable and cortisol levels declined over time.

These patterns point to inconsistencies between cross-sectional and longitudinal data (for methodological considerations, see Sliwinski, & Buschke, 1999). Although more research is clearly needed to shed light on these inconsistencies, we suggest two preliminary explanations for the obtained pattern. First, it should be noted that longitudinal time range (12 years) was much narrower than the cross-sectional age range at study entry (more than 35 years, as described in the Methods). As such, it is possible that we could have observed progressively flatter cortisol slopes, matching the cross-sectional age effects, if our study had continued following participants past the 12-year period. Second, even though cortisol levels may have declined in the entire sample as a function of increasingly chronic stress experiences, such an effect may not rule out the possibility that cortisol levels could still be elevated in advanced, as compared to early, old age. Diurnal cortisol levels have been shown to be enhanced during the onset of new stressors and for uncontrollable stress experiences (Miller et al., 2007), and the prevalence and frequency of such experiences may increase particularly in advanced old age (Heckhausen et al., 2019). Cortisol levels could thus be relatively higher in advanced, as compared to early, old age, but still decline over time in both age segments as stress experiences become more chronic.

A final implication of the current research relates to the potential clinical consequences on the health of older adults. Aging populations are at risk of experiencing disturbances in HPA axis function (Gaffey et al., 2016; Nater et al., 2013; Nicolson et al., 1997; Otte et al., 2005). Research has also demonstrated that HPA axis disruption could play a role in cognitive decline or neurodegeneration (Conrad & Bimonte-Nelson, 2010), depression (Murri et al., 2014), morbidity, and mortality (Heim et al., 2000, Kumari et al., 2011). Since both enhanced and reduced of cortisol output is likely to increase vulnerability to physical disease (Björntorp & Rosmond, 1999; Heim et al., 2000), future research should examine whether the documented effects of stress experiences on cortisol dysregulation forecast long-term health outcomes. We feel that research along these lines is warranted and has the potential to contribute to our understanding of how stress experiences can shape pattern of physiological and physical health outcomes across the human lifespan.

6. Limitations and Future Directions

Although this study has many strengths, including the analysis of 12-year longitudinal biomarkers in a normative sample of community dwelling older adults, it also has several limitations. First, our sample size was not as large as it could have been, and as a result, the reported findings may not be generalizable to all older adults. In addition, we observed significant attrition over the course of our study. However, we note that we conducted supplemental analyses using only the 85 participants that participated at T7. Although these analyses are difficult to compare to the reported results, the effects of stress experiences on cortisol AUC remained consistent. The effects on cortisol slope (intercept and time slope), however, were not significant in these supplemental analyses, indicating that participants who reported high and increasing stress experiences and flatter cortisol slopes dropped out before the last wave of the study.

Second, our stress measurement was limited to daily stress experiences at each wave on three different days. As such, it will be important for future research to examine chronic stress experiences over longer periods of time and more thoroughly capture different features of the stress process. These aspects may include the onset and conclusion of stress experiences, the chronicity of different stress experiences, as well as the nature of the stressor itself (e.g., controllability; Miller et al., 2007). Note that although the original goal of our study was to test associations between stress and cortisol, it was not designed to examine the full complexity of stress experiences. As a result, a more comprehensive assessment of stress experiences could help future research to address important remaining questions regarding cortisol dysregulation. For example, it will be important to examine how long stress-related cortisol levels tends to stay elevated, and at what point they shift from elevated to blunted cortisol dysregulation.

Third, while old age is an important life phase to study HPA axis functioning, we were unable to examine whether the documented effects of stress experiences on cortisol output extend across the entire lifespan. Future research should therefore attempt to replicate the reported findings among samples that cover the entire lifespan. Fourth, some research has shown that older adults may be more likely to display inconsistent cortisol patterns across days (e.g., Ice et al., 2004). While three days of cortisol assessment is considered sufficient to produce good reliability for cortisol AUC at each wave, research has suggested that more than three days can produce more reliable measures of cortisol slope (Segerstrom et al., 2014). Future research should therefore measure cortisol over more days to ensure the assessment of reliable cortisol slopes.

Finally, we acknowledge that some psychiatric conditions have been known to be associated with dysregulation of the HPA axis (e.g.,

depression; Pariante & Lightman, 2008). While our study did not include any psychiatric diagnoses, it incorporated a baseline measure of depressive symptoms, which can function as a screening instrument for clinical depression (i.e., CESD-10; Andresen et al., 1994). In our original conceptualization, we did not consider this variable as a covariate, since the negative mood associated with depressive symptoms could represent an important pathway linking stress experiences and cortisol regulation (Cohen et al., 2007). As such, controlling effects of stress experiences for depressive symptoms could remove important variance from the stress-cortisol link. Nonetheless, we note here that both the interaction between average stress levels and the time slope in predicting cortisol AUC, and the interaction between stress levels and increases in predicting change in cortisol slope over time, remained significant if baseline levels of depressive symptoms were added to the models. However, the main effect of average stress levels predicting the intercept of cortisol slope became marginally significant after controlling for depressive symptoms ($p < .09$).

7. Conclusions

The present study identified stress-related trajectories of diurnal cortisol secretion over 12 years among a community-dwelling sample of older adults. Among individuals with high, as compared to low, levels of chronic stress experiences, cortisol levels displayed steeper declines across the study period. Cortisol slopes across days, by contrast, became increasingly flatter over time as a function of high and increasing stress levels (which reflected both longitudinal declines in morning cortisol and increases in evening cortisol). These findings have important implications for theory and research on stress, cortisol, and health by shedding light on the stress-related conditions that predict patterns of hyper- and hypo-cortisolism.

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