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Going the Distance: The Diurnal Range of Cortisol and its Association with Cognitive and Physiological Functioning

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Abstract

Cortisol features prominently in theories describing how chronic stress wears away at physical and cognitive health. The current study examines composite measures of physiological and cognitive functioning in relation to two aspects of daily cortisol: total daily output and change in levels throughout the day. Participants (N=1001; aged 28–84 years-old) from the Midlife Development in the United States (MIDUS) study provided 4 daily saliva samples across four consecutive days and underwent a physical exam that provided information about six interrelated physiological systems that were combined into a measure of allostatic load. They also completed a phone-based battery of cognitive tasks, which provided a composite score combining memory, reasoning, and speed of processing performance. Total daily cortisol output was captured using area under the curve, with respect to ground (AUCg). Change in cortisol levels was assessed using two methods: slope, calculated through piecewise spline models, and dynamic range, calculated by the difference

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between the day's highest and lowest log-cortisol levels. Findings indicate that, when examined together, overall cortisol output was not associated with either outcome, but a greater range in cortisol throughout the day was associated with both lower allostatic load and higher cognitive functioning. Results emphasize the importance of dynamic daily processes, assessed either using slopes or dynamic range, to both physiological and cognitive functioning.

Keywords

cortisol; allostatic load; cognition; daily diary; dynamic range

1. Introduction

Cortisol, a hormone released by the hypothalamic-pituitary-adrenal (HPA) axis, is essential to the survival of an organism. Healthy HPA axis functioning is dynamic, responding to periods of sleep and wakefulness and adjusting to acute changes in the environment (Dmitrieva, et al., 2013). Circulating levels of cortisol are lowest when people are conserving energy and sleeping, then rise upon awakening and peak approximately 30 minutes later, an increase believed to prime the body for the demands of the day ahead (Fries et al., 2009). Cortisol then declines across the day to allow for surges when stressors are encountered, ultimately reaching a nadir in the evening or during the night (Dumbell et al., 2016).

Researchers frequently use slopes to capture change in cortisol levels across the day, often with one slope to capture the cortisol awakening response (CAR), defined as the post-awakening surge that occurs in the 30–40 minutes after awakening, and one or two slopes to capture changes from morning to evening over the waking day, referred to as the diurnal cortisol slope (DCS; for review, see Adam et al., 2017). Cortisol dynamic range (CDR), the distance between the estimated peak and the estimated nadir over the waking day has also been used, though not as frequently (e.g., Bandy et al., 1998; Karlamangla et al., 2013; Karlamangla et al., 2018).

Although critical for cognitive and behavioral functioning (Lupien et al., 2009), patterns of diurnal cortisol have also been related to high levels of chronic stress (Karlamangla, et al., 2013; Miller et al., 2017). Some researchers consider cortisol to be a primary pathway for the damaging effects of chronic stress (McEwen, 2019). The concept of stress-related circadian dysregulation (SCiD) describes how psychosocial stress leads to dysregulation across multiple circadian processes, including a flatter DCS, which in turn creates cascading physiological effects that ultimately result in poorer physical health. Cortisol SCiD is consistent with findings from a large meta-analysis showing that cortisol predicts physical health disorders, with the effect size of prospective studies similar to that of cross-sectional studies (Adam et al., 2017). Cortisol is hypothesized to be a primary mediator of allostatic load (McEwen and Seeman, 1999), which is a precursor to both morbidity (Seeman et al., 1997) and mortality (Karlamangla et al., 2006).

1.1 Cortisol and Allostatic Load

Allostatic load is a multiple biomarker measure designed to capture the cumulative "wear and tear" of multiple systems in the body that results from constant physiological adjustments to internal and external milieu (e.g., McEwen, 2007). Higher allostatic load places people at greater risk for morbidity and mortality (e.g., Kumari et al., 2011; McEwen, 2007). According to this model, cortisol is one of the primary mediators vital for maintaining allostasis, defined as an organism's ability to modulate physiological response to challenge. Over time, however, these constant fluctuations can lead to adverse cellular-level outcomes within multiple systems (McEwen and Seeman, 1999). Ultimately, these changes result in higher allostatic load, a secondary outcome of stress (Seeman et al., 2001). Higher levels of allostatic load, in turn, predict tertiary outcomes such as cardiovascular disease (e.g., Mattei et al., 2010), a higher number of functional limitations (e.g., Piazza et al, 2018), and greater risk for mortality (e.g., Hwang et al., 2014; Kumari et al., 2011). Thus, it is important to conduct research aimed at identifying points of intervention between the point of allostasis and allostatic load.

A large body of literature has linked flattened diurnal cortisol slopes (the primary mediator) with tertiary health outcomes, but no work to our knowledge has yet examined whether cortisol predicts allostatic load, the predicted secondary outcome. This question is important both theoretically and practically. Cortisol can be measured across days through salivary collection; in contrast, allostatic load is typically assessed during a clinic visit, as it requires collection of biomarkers via blood, saliva, and urine, as well as anthropometric measures (Gruenewald et al., 2012). Thus, diurnal cortisol may provide a proxy for underlying physiological processes that may otherwise be difficult to ascertain. A likely reason why the link between cortisol and allostatic load has not been tested is that measures of allostatic load include HPA axis biomarkers, including cortisol (e.g., Gruenewald et al., 2012). To empirically examine whether cortisol is a primary mediator of allostatic load, indicators of HPA functioning must be removed from composite allostatic load measures.

1.2 Cortisol and Cognitive Functioning.

Researchers posit that cortisol is a primary pathway explaining how chronic stress affects not only physical health, but cognitive functioning as well. (Marin et al., 2011). According to the gluocorticoid cascade hypothesis constant exposure to stressors leads to poorer regulation of cortisol (Sapolsky, et al., 1986). Over time, high levels of cortisol degrade hippocampal functioning, which in turn influences cognitive functioning. The original glucocorticoid cascade hypothesis emphasized the effects of chronically high levels of cortisol, but other researchers have emphasized the role of more dynamic markers of cortisol for cognitive functioning. For example, flatter cortisol slopes have been related to lower cognitive functioning (Stawski et al., 2011). More studies, however, are needed to assess which cortisol indicators predict cognitive outcomes.

1.3 The Current Study

Daily cortisol has been measured in several ways, including assessments of overall levels as well as by CAR, DCS, and CDR. The current study will examine how different indices of cortisol are related to both physiological (i.e., allostatic load) and cognitive functioning.

Specifically, the study will examine which aspect of cortisol – overall cortisol output versus more dynamic measures (DCS or CDR) – is most closely relate to these two health-related outcomes. Given the importance of adaptation to evolutionary theory, we predict that dynamic measures of cortisol will contribute more unique variance to cognitive and physiological functioning than will daily total cortisol output. In addition, we will examine how best to capture daily cortisol levels, by comparing models with slopes to models with daily dynamic range.

2. Material and Method

2.1 Participants and Procedures

The Midlife in the United States (MIDUS) study is a large, longitudinal examination of health and well-being in midlife and later adulthood that includes a telephone and mail-in survey, as well as multiple sub-studies. Participants in the current study completed the second wave of MIDUS (MIDUS II; 2004–2006) and three additional sub-studies: a phone-based battery of cognitive tasks (always conducted next after the MIDUS II survey); the second wave of National Study of Daily Experiences (NSDE II); and the Biomarker Project. Over one-third (38%) of participants completed the NSDE II before the Biomarker Project, and 62% completed the Biomarker Project first. The interval between assessments was included in all analyses, and the order of the testing for the NSDE and the Biomarker Project were included in the analyses with allostatic load. Results were unrelated to interval times or to test order.

Of the 5,555 participants who completed the MIDUS II telephone interview and written questionnaire, 4,445 participated in the phone-based cognitive battery, 2,022 respondents enrolled in NSDE II, and 1255 participated in the Biomarker Project. The NSDE II is a daily diary study that consisted of telephone interviews across eight consecutive days conducted 3–6 months after the MIDUS surveys (Almeida et al., 2009a). For the NSDE, participants started the interviews on different days of the week to stagger them across the week. On days 2–5, participants also provided saliva samples four times daily. Participants who provided useable daily cortisol on at least one day (86% of the sample (N = 1735); 843 male; 892 female) ranged in age from 28–84 ($Mean$ = 55.99, SD = 12.3), were primarily European-American (93%), and were fairly well-educated, with approximately half (48%) reporting at least 1–2 years of college. Those who provided saliva samples and those who did not were similar with respect to age (t(2020) = −1.38, $n.s.$), gender (χ^2(1, N = 2022) = 0.88), race (t(296) = − 1.43, $n. s.$), and education level (t(1896) = 1.06, $n.s$).

Of the 1735 participants who provided saliva, 1500 also completed the cognitive battery. Of these participants, 1,001 also participated in the MIDUS Biomarker Project. The Biomarker project included an overnight visit at one of three regional centers (Georgetown, DC; Los Angeles, CA; Madison, Wisconsin), and entailed a medical exam/history, assessments of physical health and physiological functioning and the collection of a wide array of biomarkers (Love et al., 2010). These participants were more highly educated than participants in MIDUS II (i.e., 42.1% college degree or greater versus 34.5%), but were comparable on demographic (age, race/ethnicity, marital status, income) and health

characteristics (e.g., self-rated health, number of health conditions, impairments in activities of daily living; see Love, et al (2010) for additional details).

2.2 Measures

Salivary cortisol collection and assessment.—Prior to their initial NSDE interview, participants received a Home Saliva Collection Kit, which included a detailed instruction sheet, and sixteen numbered and color-coded salivette collection devices (Sarstedt, Nümbrecht, Germany). Interviewers reviewed collection procedures with participants during the first interview, and saliva collection began the next day. Participants provided saliva samples four times a day on four consecutive interview days on days 2–5 of the NSDE 8-day study: immediately upon waking, 30 minutes after waking, before lunch, and before bed. Participants were instructed not to eat, brush their teeth or consume caffeine for 30 minutes prior to each sample's collection.

The saliva collection kit included a paper-pen log to record the sample collection time. Participants also reported the collection times during each nightly telephone interview. As a further compliance check, approximately 25% of respondents received salivette storage "smart boxes" (Cayuga Design, Ithaca NY) that contained a computer chip that recorded when the box was opened or closed. Intraclass correlations (ICCs) between times reported from the "smart box" and self-reported times were .60 for waking; .59 for 30 minutes after waking; .80 for afternoon; and .59 for bedtime collections. Following the four collection days, participants mailed their saliva kit to the laboratory in a pre-paid, addressed box (see Almeida, et al., 2009a for a description of the reliability and validity of this procedure). Cortisol concentrations were quantified with a commercially available luminescence immunoassay (IBL, Hamburg, Germany), with intra-assay and inter-assay coefficient of variations below five percent (Dressendörfer et al., 1992; Polk et al., 2005).

Allostatic load.—Consistent with previous work, the measure of allostatic load (AL) was designed to summarize dysregulation across multiple physiological systems (Gruenewald et al., 2012). Biomarkers were selected based on two major criteria: theory about the major regulatory systems; and information that could be collected within the logistical and financial constraints of the MIDUS project itself. Selection of subscale components was confirmed by results of factor analyses (Wiley et al., 2016). The six systems studied, and the biomarkers that comprised them, included: (1) cardiovascular functioning: resting systolic blood pressure, pulse pressure, and resting pulse rate; (2) sympathetic nervous system activity: overnight urinary epinephrine and norepinephrine; (3) parasympathetic nervous system activity: heart rate variability indicators (low frequency spectral power, high frequency spectral power); the standard deviation of RR (heartbeat to heartbeat) intervals, and the root mean square of successive differences; (4) inflammation: plasma C-reactive protein, fibrinogen, and serum measures of interleukin-6 and the soluble adhesion molecules E-selectin and intracellular adhesion molecule-1; (5) lipid/fat metabolism: high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides, body mass index, and waist hip ratio; and (6) glucose metabolism: glycosylated hemoglobin, fasting glucose, and insulin resistance. A seventh system that assesses hypothalamic pituitary adrenal axis activity (i.e., overnight urinary cortisol and a serum measure of the hormone

dehydroepiandrosterone sulfate) was collected but was NOT included in the current calculation of allostatic load to ensure that any association between the dynamic range of cortisol and allostatic load was not driven by diurnal salivary cortisol predicting overnight urinary cortisol.

For each system, a risk score was computed by calculating the proportion of biomarkers in that system falling into high-risk quartile ranges, defined as the upper or lower quartile of the biomarker distribution, depending on whether high or low values of the biomarker typically confer greater risk for poor health outcomes. For most biomarkers, high values indicated greater risk; those where lower scores were considered higher risk included high density lipoprotein cholesterol and all parasympathetic biomarkers. Proportion scores for each system were continuous and could range from 0 (none, low risk) to 1 (all, high risk) depending on number of biomarkers (ranging from 2 to 6 depending on the system) that fell into the high-risk range. System risk scores were computed for individuals with values on at least half of the system biomarkers. Missing data was low: 98% of participants had complete biomarker data for each system, with the exception of 92% for parasympathetic system, as a result of instrumentation failures and/or measurement difficulties.

Scores for the six risk scores used in the current study were summed to calculate allostatic load (possible range from 0 to 6; see Gruenewald et al., 2012, for overview). Allostatic load scores were computed for participants with information on at least 5 of the 6 systems, and over 90% of participants had data for all 6 systems. For those missing only parasympathetic scores, AL scores were imputed based on participants' scores on the other five systems and age, gender, and race, using a regression equation derived from those with complete biomarker data. For participants who were missing only one of the other six system scores, that score was computed as 0, which was the sample median for five of the six system scores. All those with imputed scores were flagged (9.4%), and the flag was included as a covariate in AL regressions. In addition, if participants indicated that they were taking medications to control clinical risk factors that are also biomarkers in three systems - cardiovascular, glucose metabolism, and lipid metabolism -- they were scored as being in the high-risk quartile for those biomarkers regardless of the measured biomarker values. This placed people using (a) antihypertensive medication in high-risk for systolic blood pressure; (b) heart rate reducing medications (e.g., beta blockers and atrio-ventricular nodal blockers) in high-risk for resting heart rate; (c) diabetes medications in high-risk for fasting glucose and glycosylated hemoglobin; (d) statins, cholesterol absorption inhibitors, niacin, and/or bile acid sequestrants in high risk for LDL cholesterol; and (e) those on fibrates at high-risk for serum triglycerides.

Cognitive functioning.—The Brief Test of Adult Cognition by Telephone (BTACT) was used to measure five domains of fluid cognition: episodic verbal memory, assessed through immediate and delayed recall; reasoning, assessed through a letter series; speed of processing, assessed through backward counting; and working memory span, assessed through backward digit span (Lachman et al., 2014). To obtain a standardized episodic verbal memory score, scores on immediate and delayed recall were summed and converted to z scores. The other three components (reasoning, speed of processing, and working memory span) were also each converted to z scores. Scores reflecting all four domains of

cognition were then averaged into one overall composite score of cognitive functioning (Stawski et al., 2011).

Covariates.—Additional variables that could potentially influence diurnal cortisol were obtained via daily telephone interviews on each day cortisol was collected, including length of sleep the previous night, morning waking time, bedtime, and whether it was a weekend day - a distinction made only for those who were employed (1 = weekend day; 0= week day). To capture the influence of too little sleep and too much sleep, we categorized the previous night's sleep time into three groups: <6 hours, 6–8 hours, and >8 hours. Waking time and bedtime were used to compute the length of the waking day, which was averaged over all eight diary days, to get average wake-day length for every participant.

Variables that may mediate the associations between allostatic load and daily cortisol trajectories were collected from questionnaire responses at the time of the Biomarker collection and included depression (yes/no), a count of chronic physical health conditions (range, 0 to 4 or more), body mass index (calculated from reported weight and height), and current smoking status (yes/no). Mean number of cigarettes smoked per day, mean physical activity (minutes per day), use of oral steroid medications (yes/no), and use of anti-anxiety or anti-depressant medications (yes/no) were collected in NSDE II.

2.3 Analytic Strategy

To obtain the cortisol parameters (AUC, CAR, DCS, and CDR), we used linear multilevel modeling to account for nesting in the current data (Snjiders and Bosker, 1999). This method has been used in previous analyses of these data to assess DCS, AUC, and CDR (e.g., Karlamangla et al., 2013; Stawski et al., 2011). The (ICC) revealed that 49% of the variance in allostatic load and 50% of the variance in cognitive functioning was due to family influences.

Multiple studies demonstrate that cortisol rhythms are driven by time elapsed since awakening and less by clock time (Clow et al., 2004; Fries et al., 2009; Kumari et al. 2011; Steptoe et al., 2003; van Couter, 1990), so we examined cortisol trajectories as a function of time since waking, after excluding measurements for days with extreme waking times (before 0400h and after 1100h) and extreme waking day lengths (longer than 20 hours). A model of these data, estimating log-cortisol over consecutive 15 minutes intervals in the complete study sample, consistently showed a morning peak 30 minutes after wakening, followed by a more gradual decline for about 10.5 hours, and then a plateau or an upturn. For this reason, we modeled the daytime trajectories of log cortisol as a piece-wise linear trajectory with four linear segments and three fixed knots at 0.5 hours, 4.5 hours, and 15 hours after waking (Karlamangla et al., 2013). Linear splines with fixed knots have been used previously to model diurnal cortisol rhythms (Dowd et al., 2009; Ranjit et al., 2005).

We used multi-level (four hierarchical levels), linear mixed-effects regression to model the log-cortisol growth curves and to account for within-day, within-person, and within-family correlations in cortisol measurements. All growth curve parameters were modeled using the following covariates: average wake-day length (individual-level), waking time (day-level), and weekend vs. workday status (day-level). To account for correlation between members of

the same family (twin pairs and siblings were included for a subset of participants), we included a random intercept at the family level. To account for correlations between repeated measurements in the same individual, we included random effects at the individual level for *all* growth curve parameters. To capture correlations (in an individual) between repeated cortisol measurements in the same day, we included a random intercept at the day level and either a random initial decline slope (for the linear spline and the linear-cubic specifications) or a random quadratic growth rate (for the quadratic spline specification).

The model estimates of mean intercept and slopes (fixed effects) were combined with corresponding random effects at the family level and individual level, to get individual-specific estimates for the five growth curve parameters to characterize the individual's intrinsic diurnal rhythm. These were then combined, using standard methods for piecewise-linear curves, to create individual-specific estimates of the log-cortisol morning peak, evening nadir, and AUC – the integrated area under the log-cortisol curve over the first 16 hours after waking; the latter was computed using the trapezoidal formula (Pruessner et al., 2003). The participant's intrinsic diurnal cortisol dynamic range (CDR) was calculated as log-cortisol peak minus log-cortisol nadir, which translates to log of the cortisol diurnal peak-to-nadir ratio (refer to Karlamangla et al., 2019 for a complete description). Figure 1 provides a visual graph of the CDR in two random samplings of participants to illustrate differences in range across the sample: one sampling of individuals who are at the lowest quartile for the CDR, and the other at the highest quartile. The estimates of linear splines were also used to calculate diurnal cortisol slopes. The first linear spline (waking to .5 hours) represents the CAR, the second linear spline represents the initial diurnal cortisol slope (DCS1) occurring .5 to 4.5 hours after waking, the third segment represents the subsequent diurnal cortisol slope (DCS2) occurring between 4.5 to 15 hours after waking (Karlamangla et al., 2013).

The current analysis compared the predictive utility of different parameters for quantifying the diurnal rhythm of cortisol. We compared two models. In the first, we quantified diurnal rhythm of cortisol with the CAR; DCS (both DCS1 and DCS2); and the AUC, including them in a model with covariates to examine its relationship with allostatic load (in one model) and cognitive functioning (in another model). We repeated these models, but instead we used the CDR instead of CAR, DCS1 and DCS2 to capture the diurnal pattern of cortisol. Values were standardized to allow comparison of the predictive utility of the two different parameterizations of daily cortisol. DCS1 and DCS2 were multiplied by −1 to aid in interpretation; higher values indicate better functioning consistent with the interpretation for CDR.

Gender (male=1 vs female = 0), age, current smoking status (non-smoking=0 vs. smoking=1), education level (college education = 1 vs. no college degree = 0), and ethnicity (Non-Caucasian= 0 vs. Caucasian = 1) were included as covariates. All continuous predictors and covariates were grand-mean centered. Pseudo-R^2 was calculated as an indication of the variance accounted for in the MLMs (Singer & Willet, 2003). To estimate the effect size of the cortisol parameters in relation to age, age equivalent effects were computed. To generate these values in each model, we identified the number of years in age

that equated the size of the effect of the cortisol parameter on the outcome to the size of the age effect on the outcome.

3. Results

Descriptive statistics and correlations among the continuous variables of interest appear in Table 1. Higher AL was related to a more compressed CDR. Conversely, higher cognitive functioning was related to a wider CDR. Higher cognitive functioning was also related to lower AL. As expected, older age was related to higher AL, lower cognitive functioning, greater AUC, and a more compressed CDR.

Relating our categorical covariates to the cortisol parameters and outcomes, we computed standardized differences between groups (i.e., Cohen's *d*). Results are displayed in Table 2. Using criteria provided by Cohen (1988), only gender differences on CAR, and education differences on CF met criteria for medium or large differences.

3.1 Allostatic Load and Cortisol

A baseline model including only covariates revealed that older age (compared with younger) and lower education (compared to higher) were significantly associated with higher AL. This set of covariates accounted for approximately 18% of the variability in AL (pseudo-R^2 = 0.183; Table 3, Model 0). The addition of AUC values in Model 1 revealed that AUC did not significantly predict AL (p = .397). Model 2 kept the AUC in the model along with all of the covariates but included the CDR parameters. CDR was a significant predictor of AL (b = −.244, SE = 0.047, p <.01; pseudo-R^2 = 0.193) with a wider CDR predicting lower AL. The effect of a more compressed CDR was equivalent to a 7-year age difference in the current sample. Model 3 examined the three diurnal slope parameters as predictors of AL in addition to the covariates and the AUC. As predicted, attenuated DCS slopes were related to higher AL (p's < .05; pseudo-R^2 = 0.196). The magnitude of these effects was equivalent to a 2- to 4-year age difference in the current sample.

3.2 Cognitive Functioning and Cortisol

The same multilevel modeling strategy was applied to examine the relationships of different cortisol parameters with cognitive functioning. Table 4 includes the results of the multilevel models for each set of predictors. Model 0 included just the covariates predicting cognitive functioning (pseudo-R^2 = .296). Model 1 added AUC to predict cognitive functioning. As with AL, AUC was not a significant predictor (p = .709). In Model 2, CDR was a significant predictor of cognitive functioning (b = .055, SE = 0.018, p < .01; pseudo-R^2 = .369), with the effect of a more compressed CDR equivalent to a 3-year age difference in the current sample. Finally, Model 3 used the three diurnal slope parameters instead of CDR as predictors of cognitive functioning. For this model, only the daily decline slope between lunch and bedtime was a significant cortisol predictor (b = −0.039, SE = 0.018, p = .03; pseudo-R^2 = 0.370). The effect of this slope was equivalent to a year and a half age difference in the current sample.

4. Discussion

Of all the hormones, cortisol is most often implicated in the damaging effects of stress on health and well-being (Miller et al., 2007). The current study examined both total output and change in levels of cortisol throughout the day (i.e., CAR, DCS1 and DCS2; and CDR) across four days in relation to indicators of overall physiological and cognitive well-being. Findings indicate that assessments capturing attenuated cortisol slopes (CAR; DCS1 and DCS2) and a more compressed range (CDR)--but not overall cortisol output--were related to higher levels of allostatic load and poorer cognitive functioning.

4.1 Dynamic Measures of Cortisol

Researchers have discussed the importance of physiological systems to adapt in response to short-term challenges, a process referred to as 'adaptive homeostasis' (Pomatto and Davies, 2017). Organisms evolved to be able to respond to a constantly changing environment, and those who were most adept at meeting the challenges of their environment were the most likely to survive (Gotthard and Nylin, 1995). For example, a cardiovascular system that can easily prepare for fight or flight, as indicated by heart rate variability, can mobilize the system quickly for action. A neurological system that quickly detects pain and mobilize reflexes to escape the pain-inducing elicitor may incur less damage. Similarly, researchers have posited that an HPA-axis that is responsive to threat is adaptive, but if it is elicited too often, too long or without reprieve, damage to the organism can occur, through dysregulation of an innate negative feedback loop mechanism (Sapolsky, 1986). This resulting damage could result in a "flattening" of the diurnal slope, which is indicative of reduced physiological flexibility.

The current study assessed cortisol change during the waking day using two methods: a measure of CDR; and three measures capturing the morning surge (CAR), change from morning to the afternoon (DCS1), and change from the afternoon to the evening (DCS2). These two different approaches yielded the same results both predicted higher allostatic load and lower cognitive functioning. However, the CDR may be preferred because the single parameter yields a more parsimonious statistical model, comprised of one score with effects quantifiable to age years, as opposed to three separate slope estimates.

4.2 Cortisol Levels and Allostatic Load

Daily cortisol levels often vary in response to environmental demands (Adam et al., 2006; Stawski et al., 2013). For example, one study found that overall levels of total cortisol output are higher, and diurnal slopes are steeper on days when stressors occur (Stawski et al, 2013). Other studies have found that cortisol slopes are flatter on days when people experience more anger and tension (Adam, et al., 2006) and higher levels of overall distress (Piazza et al., 2013). For some individuals, however, such as those diagnosed with an affective disorder or certain chronic physical health conditions, changes in cortisol (e.g., slopes) are flatter (e.g., Booij et al., 2013; Miller, et al., 2007; Wirtz et al., 2007). Individuals with conditions such as these have a more static picture of cortisol more akin to the concept of allostatic load. Greater damage, or load, makes quick adjustments in response to environmental demands less efficient and, in some cases, not possible. The current study used two methods

to assess daily changes in cortisol in relation to allostatic load, which is a more static measure of cumulative biological dysregulation.

We found that a greater compression of the CDR was similar to having aged seven years more than someone with a more robust CDR. This relationship can be interpreted in several ways. First, greater compression of the CDR could be interpreted as an indicator of a more permanent shift in functioning. In this interpretation, cortisol secretion is no longer able to adapt in response to physical and psychological demands, a loss which may be viewed as yet another indicator of allostatic load. Using this interpretation, findings indicate that cortisol serves as a useful biomarker that indicates not only change in the HPA axis, but also change across multiple physiological systems. Given that cortisol can be assayed from saliva samples mailed in by participants, it is easier to assess than allostatic load. As such, cortisol may be a useful proxy to infer the effects of stress on the physiological system. More research is needed, however, to ensure replicability of results in other large data sets.

Another interpretation of these findings is that greater compression of the CDR leads to further dysregulation in other physiological systems. Although we have no longitudinal evidence to test this hypothesis, these findings nonetheless raise questions as to the unique importance of cortisol and health. A growing number of studies have examined how diurnal patterns of cortisol predict changes in functional health and illness years later (e.g., Piazza et al., 2018; Sephton et al., 2013; Wrosch et al., 2009), so further studies can examine whether CDR predicts health outcomes as well. Although causal inferences cannot be made from the current cross-sectional results, findings do raise questions as to the extent to which changes in the dynamic range of cortisol play a causal role in the dysregulation of other physiological systems. Moreover, our findings support the hypothesis that cortisol may be one of the primary mediators linking allostasis with allostatic load (e.g., McEwen and Seeman, 1999).

4.3 Cortisol Dynamic Range and Cognitive Functioning

In addition to being related to allostatic load, CDR was also related to cognitive functioning, even after adjusting for all covariates. People who had a greater range in levels of daily cortisol had cognitive performances that were more similar to those three years younger than same-aged peers with a more restricted CDR. The glucocorticoid cascade hypothesis predicts that cortisol levels play a causal role in cognitive decline. According to this model, chronically high levels of cortisol lead to damage in the hippocampus, which in turn leads to poorer memory and performance in related cognitive tasks (Sapolsky et al., 1986). Research has supported this model, with studies indicating that levels of cortisol predict both hippocampal volume and memory deficits (e.g., Lupien et al. 1998). Additional studies have found that flatter daily slopes are also related to lower cognitive functioning (Stawski et al., 2011).

The current study replicates these prior studies and builds upon them in two ways. First, it shows that greater change in cortisol levels throughout the day– either using slopes or CDR – is related to higher cognitive functioning and better physiological functioning (i.e., lower allostatic load). Although both yield similar results, the single measure of CDR is arguably more parsimonious, and may convey the importance of overall range of cortisol across the course of the day more easily than three slope variables. Second, the study reinforces the

importance of examining change in cortisol in conjunction with cognitive and physiological functioning. Both daily change in cortisol (captured by either CDR or by the combination of CAR, DCS1 and DCS2) and a measure of cortisol output (AUC) were included in the models, yet only the indicators of dynamic change were associated with allostatic load and cognitive functioning. Results suggest that cortisol's dynamic range may be more predictive of health and cognitive outcomes than its overall level. Importantly, chronically high levels of cortisol are hypothesized to result in changes in diurnal patterns of cortisol (Miller et al., 2007), so additional work is needed to determine longitudinal effects in the association between dynamic indicators of cortisol and health outcomes.

4.4 Limitations and Future Directions

Researchers argue that CDR is a measure for how well the body responds to environmental demands and then recovers by the end of the day (Karlamangla, et al., 2013). The current study only examined one model for CDR, however. Other models exist, with different assumptions and measurement time points. The findings, therefore, need to be interpreted with that in mind. In addition, the current study examined one model of CDR but provided no information about the daily environment. We do not know the physical and psychological stressors that were encountered, and as such it is unclear whether or how cortisol levels varied in response to environmental demands. Establishing links between daily stressors (both physical and psychological) and fluctuations in cortisol will strengthen the underlying hypothesis that dynamic range represents adaptive response to daily challenge. Another possibility is that cortisol daily range is one of many physiological indicators that correlates with health and cognitive measures, but which plays no causal role in physiological or cognitive processes. CDR may even be the result of good physical and cognitive functioning. Longitudinal studies will need to examine these processes across long periods of time to establish how physiological systems and cognitive functioning relate to one another.

In addition, our study relied on daily cortisol assessments taken from saliva collected by the participants. As evidenced by the intraclass correlations from self-reports and smart-boxes, the timing of the cortisol collections is inexact. This poses a problem for all points of collection, but is most problematic for accurate assessment of CAR. In addition, the CAR that was collected does not meet the current measurement standards (Stalder et al., 2016). Accurate, objectively monitored, multiple morning assessments are critical for CAR, and the potential biases that occur without these standards most likely decreased its effect size in these analyses. Moreover, cortisol levels begin to rise before waking, and the capture of cortisol, with the first assessment after waking, fails to capture the full awakening response. This issue would also affect the CDR and DCS1, but the issue is most problematic for an accurate CAR.

Furthermore, information across four days of sampling was pooled together to capture a robust indicator of estimated CDR. This provided a more reliable index of CDR than one using only a single day of cortisol, yet the study provided no information about the optimal number of days of cortisol collection. Past research has showed variability across days on measures of cortisol (e.g., CAR: Almeida et al., 2009b). Future studies will need to examine the reliability of the CDR, and how many days would be best for its calculation. Data from

burst design studies may also provide interesting information and should be considered for future studies.

5. Conclusion

Despite these limitations, the current study uses a large ambulatory study to examine overall levels of daily cortisol output (AUC) and patterns of diurnal cortisol. Results emphasize the importance of change in cortisol when studying its association with physiological and cognitive measures. Moreover, findings indicate that the single measure of CDR has the same association with allostatic load and cognitive functioning as does a combination of slopes capturing the change in cortisol throughout the day (CAR and DCS). These findings suggest that health is perhaps best captured by the degree to which physiological processes exhibit dynamic changes in our daily lives.

Acknowledgments

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Highlights

- Cortisol dynamic range is the distance from the daily estimated daily peak to nadir.

- Cortisol dynamic range, but not total daily output, is related to allostatic load.

- Cortisol dynamic range is related to cognitive functioning, but total daily cortisol output is not.

- Cortisol dynamic range, as well as cortisol diurnal slopes, predict allostatic load

A. CDR for a random sampling of individuals at the lowest quartile

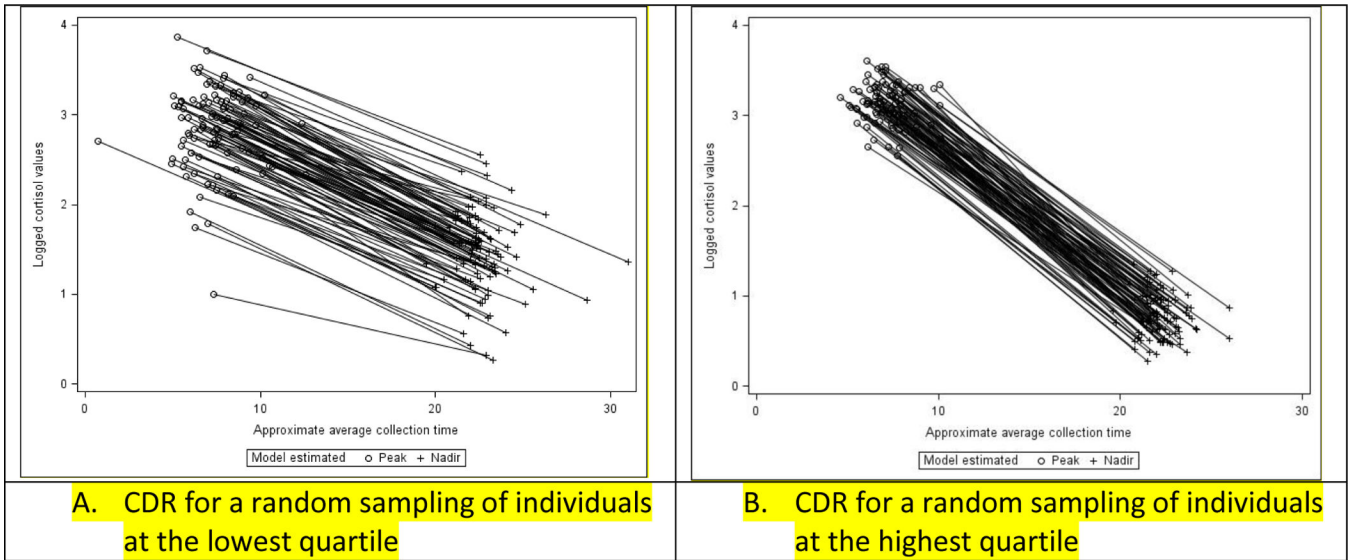B. CDR for a random sampling of individuals at the highest quartile

Figure 1 –.

Panels illustrating CDR for the lowest (panel A) and highest (panel B) quartiles in the current sample. Cortisol graphed in logged units for comparison to regression model results.

Table 1

Descriptive statistics and correlations for continuous variables

	AUCg	CDR	CAR	DCS 1	DCS 2	AL	CF	Age
AUCg								.257
CDR	−.350							−.179
CAR	.356	−.098						.165
DCS 1	−.317	.681	−.277					−.172
DCS 2	−.267	.899	−.037	.292				−.130
AL	.118	−.259	.159	−.211	−.209			.370
CF	−.110	.203	−.130	.192	.151	−.292		−.435
Mean	29.246	1.891	0.688	0.245	0.087	1.629	0.033	55.43
SD	5.778	0.415	0.139	0.047	0.030	1.079	0.682	12.44
Minimum	−1.367	0.119	0.215	0.063	0.060	0.000	−2.481	28
Maximum	56.166	2.924	1.210	0.406	0.181	5.067	2.489	84

Note. Correlations in italics are non-significant. All other correlations p < .05. AL = Allostatic load; AUC = Area under the curve; CDR=Cortisol Dynamic Range; CF = Cognitive functioning; CAR = Cortisol awakening response; DCS 1 = Diurnal cortisol slope 1 (30 post waking to lunch sample); DCS2 = Diurnal cortisol slope 2 (lunch sample to bedtime sample). DCS variables were reverse scored.

Table 2

Standardized differences between groups for cortisol parameters

	Gender differences	Education differences	Smoking Status differences	Ethnicity differences
AUCg	**0.24**	0.02	**0.16**	0.05
Diurnal CDR	−0.02	**0.24**	**−0.24**	**−0.43**
CAR	**−0.10**	**−0.13**	**0.18**	**0.19**
DCS 1	**−0.17**	**0.22**	**−0.27**	**−0.31**
DCS 2	0.07	**0.18**	**−0.14**	**−0.38**
AL	0.10	**−0.34**	**0.22**	0.01
CF	0.04	**0.83**	**−0.19**	**−0.40**

Note. AL = Allostatic load; AUC = Area under the curve; CDR=Cortisol Dynamic Range; CF = Cognitive functioning; CAR = Cortisol awakening response; DCS 1 = Diurnal cortisol slope 1 (30 post waking to lunch sample); DCS2 = Diurnal cortisol slope 2 (lunch sample to bedtime sample). DCS variables were reverse scored. Differences were calculated as: gender (male - female); education (college education - no college education); smoking status (smoker - non-smoker); ethnicity (African-American - Caucasian). Values in bold are significant, per Cohen's guidelines values below .2 are small, above .5 are medium, and above .8 are considered large.

Table 3

Multilevel models including chronic conditions predicting allostatic load

Predictor	Model 0 Covariates		Model 1 AUCg only		Model 2 AUCg with CDR		Model 3 AUCg with Diurnal slopes	
	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Intercept	1.652 *	0.083	1.641 *	0.095	1.648 *	0.093	1.638 *	0.093
Gender (ref = Female)	0.118 *	0.077	0.098	0.090	0.105	0.087	0.122	0.089
Age	0.359 *	0.042	0.369 *	0.051	0.366 *	0.049	0.360 *	0.049
Chronic conditions	0.134 *	0.023	0.129 *	0.029	0.119 *	0.028	0.117 *	0.028
Education (ref = No college education)	−0.232 *	0.077	−0.230	0.089	−0.186	0.088	−0.176	0.088
Smoking status (ref = Non-smoker)	0.106	0.077	0.123	0.090	0.095	0.088	0.086	0.088
Ethnicity (ref = Caucasian)	0.011	0.128	−0.162	0.157	−0.221	0.154	−0.241	0.154
AUCg	--	--	0.040	0.047	−0.033	0.048	−0.063	0.050
CDR	--	--	--	--	−0.244 *	0.047	--	--
CAR	--	--	--	--	--	--	0.084	0.046
DCS 1	--	--	--	--	--	--	−0.121 *	0.047
DCS 2	--	--	--	--	--	--	−0.187 *	0.048
Model pseudo-R^2	0.183		0.153		0.193		0.196	

Note.

*
p< .05. AUCg = Area under the curve relative to ground; CDR = cortisol dynamic range; CAR = Cortisol awakening response; DCS 1 = Diurnal cortisol slope (30 post waking to lunch sample); DCS 2 = Diurnal cortisol slope (lunch sample to bedtime sample). DCS variables were reverse scored.

Table 4

Multilevel modeling results predicting cognitive functioning

Predictor	Model 0 (Covariates only)		Model 1 AUCg only		Model 2 AUCg with CDR		Model 3 AUCg with Diurnal slopes	
	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Intercept	−0.105*	0.022	−0.017	0.034	−0.019	0.034	−0.019	0.037
Gender (ref = Female)	−0.027	0.020	−0.007	0.033	−0.006	0.033	−0.010	0.033
Age	−0.262*	0.011	−0.264*	0.018	−0.262*	0.018	−0.260*	0.018
Chronic conditions	−0.015*	0.006	−0.016	0.010	−0.014	0.010	−0.013	0.010
Education (ref = No college education)	0.433*	0.022	0.386*	0.034	0.376*	0.034	0.373*	0.034
Smoking status (ref = Non-smoker)	0.020	0.021	−0.055	0.034	−0.049	0.034	−0.045	0.034
Ethnicity (ref = Non-Caucasian)	−0.304*	0.033	−0.236*	0.061	−0.213*	0.061	−0.205*	0.061
AUCg	--	--	0.006	0.017	0.023	0.017	0.036†	0.019
CDR	--	--	--	--	0.055*	0.018	--	--
CAR	--	--	--	--	--	--	−0.030	0.018
DCS 1	--	--	--	--	--	--	0.033†	0.017
DCS 2	--	--	--	--	--	--	0.039*	0.018
Model pseudo-R^2	0.296		0.364		0.369		0.370	

Note.

*
p< .05,

†
p < .07.

AUCg = Area under the curve relative to ground; DR = dynamic range; CAR = Cortisol awakening response; DCS 1 = Diurnal cortisol slope (30 post waking to lunch sample); DCS 2 = Diurnal cortisol slope (lunch sample to bedtime sample). DCS variables were reverse scored.