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Diurnal Dynamic Range as Index of Dysregulation of System Dynamics. A Cortisol Examplar using Data from the Study of Midlife in the United States

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Summary

We discuss the importance of including measures of dysregulated system dynamics in the operationalization of allostatic load. The concept of allostatic load, as originally proposed by McEwen and Stellar, included dysregulation not only in the resting state of physiological systems, but also in system dynamics. We describe previous work on cortisol diurnal dynamic range (peak to nadir spread) as an index of the health of the hypothalamic-pituitary-adrenal axis, with compression of dynamic range being a marker of dysregulation. In particular, we review the evidence for a) diurnal dynamic range compression in people from disadvantaged backgrounds, b) cross-sectional association of cortisol diurnal dynamic range compression with dysregulation in other systems' resting states, and c) cross-sectional association of cortisol diurnal dynamic range compression with lower scores on cognitive testing. Then, we present new data from the Study of Midlife in the United States (MIDUS) on longitudinal associations of cortisol dynamic range compression with subsequent cognitive decline and all-cause mortality. Briefly, each standard deviation decrement in cortisol diurnal dynamic range is associated with adjusted mortality hazard ratio of 1.35 (95% confidence interval: 1.19, 1.54). Among those who scored at median or lower in executive functioning at baseline and survive, each standard deviation decrement in cortisol dynamic range is associated with 1% greater decline in executive functioning over a decade (95% confidence interval: 0.4%, 2.0%). We conclude that including measures of system dynamics like diurnal dynamic range in the next generation of allostatic load measurement will likely advance understanding of the cumulative physiological burden of chronic stress and life experiences, and improve the prediction of future health consequences.

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Keywords

Cortisol diurnal peak and nadir; allostatic load; HPA axis dysregulation; cortisol area under the curve; cognitive decline; all-cause mortality

1. Introduction

The ability of our physiological systems to respond to new challenges is critical to the maintenance of our health. The capacity to respond to challenges is key to the success of every organizational structure, including not only the individual human, but also communities of people, biological species, entire ecosystems, and even business enterprises (Lasker, 1969). While homeostasis refers to the constancy of key physiological parameters maintained by negative feedback systems, the adaptation of physiological systems to changing external demands is called allostasis (Sterling & Eyer, 1988). The body's response to a stressor - an adverse event or challenging life experience - includes both emotional and physiological changes, together referred to as the stress response (Epel et al., 2018). While stress is the umbrella term that covers both stressors and the stress response, allostasis refers in particular, to the physiological component of the stress response. The McEwen and allostatic load thesis is that when demands are excessive – too frequent, protracted, and/or severe, it leads to gradual dysregulation of the physiological systems of the stress response apparatus. This dysregulation is manifest as both alteration in resting states and disruption in system dynamics, in the form of diminished reactivity to new challenges and slowed recovery after the challenge has passed (McEwen & Stellar, 1993). Such dysregulation is postulated to be the fundamental mechanism by which life stresses and the psychosocial environment get under the skin to affect one's health in the long term (McEwen, 1998).

Both kinds of physiological dysregulation – in system statics (altered resting levels) and in system dynamics (blunted reactivity and delayed recovery) – have been repeatedly documented in chronically stressed individuals. Changes in system dynamics have been well demonstrated in the neuroendocrine systems that are the primary mediators of allostasis - the sympathetic and parasympathetic neuro-hormonal systems and the hypothalamic-pituitary-adrenocortical (HPA) axis (Carpenter et al., 2007; Goldmann-Mellor et al., 2012; Kudielka et al., 2006; Lovallo et al., 2012; Matthews et al., 2001; Ockenfels et al., 1995; Ouellet-Morin et al., 2011). Repeated exposure to stressors over the life course causes exhaustion and burn out in the physiological systems of the stress response apparatus, and result in a reduction in their ability to mount a robust response to new stressors (Chida & Hammer, 2008; Juster et al., 2011; Kudielka et al., 2006; Lennartsson et al., 2015). Blunting of the adaptive capacity (allostatic reserve) of a system can be quantified as a reduction in the system's *dynamic range* - the difference between the maximal attainable level under stress and the minimal level at rest. In usual aging, as the effects of a lifetime of stressors accumulate, nearly every physiological and organ system exhibits reductions in dynamic range, a phenomenon that has been called *homeostenosis* in the literature on aging (Arbeev et al. 2011, Navaratnarajah and Jackson 2013).

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Both kinds of dysregulation – altered resting levels and reduced dynamic range - have also been linked to adverse downstream health outcomes. Elevated resting levels of the primary stress response mediators, cortisol and catecholamines, independently predict incident cognitive impairment, progression of dementia, and incident osteoporotic fractures (Csernansky et al., 2006; Greendale et al., 1999; Karlamangla et al., 2005a; Karlamangla et al., 2005b). Low resting heart rate variability, a biomarker of parasympathetic tone, predicts incident strokes, independent of the usual clinical cardiovascular risk factors (Binici et al 2011). Similarly, reduced cortisol and catecholamine dynamic range has also been linked to poor health and cognitive impairment (Carroll et al., 2009; De Rooij 2013; Heponiemi et al., 2007).

Despite the mounting evidence for dysregulation of system dynamics in relation to both history of adversity / stressors and future downstream health, nearly every attempt, to date, to operationalize allostatic load as a comprehensive summary of dysregulation across multiple systems, has focused exclusively on alterations in resting levels of systems. Allostatic load measures that have incorporated heart rate variability (a dynamic measure of parasympathetic tone) have also only used resting levels of heart rate variability, and not its reactivity and recovery to acute stressors (Gruenewald et al., 2012). This may, at least partly, be attributed to the difficulty of standardizing acute stressors/challenges across a large, diverse study sample, in order to assess reactivity to a uniform level of perceived stress.

Examining the diurnal rhythm, which most (though not all) physiological systems exhibit, may provide an alternate and more accessible window into dysregulation of system dynamics. Fortunately, changes in diurnal rhythm mimic changes in system's dynamic response to stressors

1.1 Diurnal Rhythms: The Importance of Diurnal Dynamic Range

The neuroendocrine systems that constitute the primary mediators of the stress response apparatus, the HPA axis and the sympathetic and parasympathetic neurohormonal systems, follow a circadian rhythm, with increased activity during the day and nadirs overnight (Turton & Deegan, 1974). Such diurnal rhythms are seen, for instance in levels of cortisol (Steptoe et al., 2003), catecholamines (Linsell et al., 1985), and heart rate variability – a measure of parasympathetic tone (Huikuri et al., 1994). Consequently, there are similar diurnal rhythms in the secondary mediators of allostasis, such as blood pressure and heart rate (Baschieri et al., 2019; Smolensky et al., 2017). Disruptions of these rhythms are seen in people who have experienced more life adversities. In particular, the amplitude of the rhythm; i.e., the dispersion from peak to nadir, is smaller or more compressed in those who report more life stressors. This phenomenon has been documented, for instance, in the diurnal rhythms of cortisol (Karlamangla et al., 2019), catecholamines (Rief et al., 2010), and blood pressure (Spruill et al., 2009).

The peak-to-nadir dispersion, or the magnitude of *nocturnal dipping*, has also been linked to subsequent health, with less dipping or smaller peak-to-nadir dispersion being related to adverse cardiovascular (Hower et al., 2018; Portaluppi et al., 2012) and neurodegenerative outcomes, such as Parkinson's and Alzheimer's disease (Spruill et al., 2009). Taken

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together, this body of evidence suggests that the diurnal peak-to-nadir dispersion has the potential to provide high-value information about the health of physiological systems, which would substantially enrich future measures of allostatic load. The diurnal peak-nadir dispersion is referred to as the *diurnal dynamic range*, which borrows from the engineering literature, where it is used in the context of audio amplifiers and speakers, cameras, display devices, and measurement instruments.

Here we focus on the diurnal rhythm of circulating levels of cortisol as an examplar, to illustrate how *compression of diurnal dynamic range* can be both a signature of life stresses and a predictor of adverse health outcomes, thus demonstrating the need for its incorporation in future operationalization of allostatic load. Changes in cortisol diurnal rhythm seen in individuals from socioeconomically disadvantaged groups and in people who report adversity include blunting or heightening of the morning peak (Bennett et al., 2004; Carlson & Earls, 1997; Dowd et al., 2011; Hajat et al., 2010; King et al., 2001; Meinischmidt & Helm, 2005) and elevated levels in the late evening nadir (Cicchetti et al., 2010; Cohen et al., 2006). Both kinds of changes are thought to be part of the biological pathway by which chronic or frequent life stressors affect physical health (Lundberg, 2005; Cohen et al., 2007) and mortality (Kumari et al, 2011). A compression of the diurnal dynamic range is necessarily accompanied by a flattening of the cortisol recovery trajectory (from morning peak to evening nadir). Studies that have examined the slope of this recovery curve have consistently found cross-sectional associations of flatter recovery with both chronic stressors (Miller et al., 2007) and poorer health and functioning, including poorer performance on cognitive testing (Fiocco et al., 2006; Stawski et al., 2011) and more frailty (Varadhan et al., 2008).

We start by reviewing recent findings from the second wave of the National Study of Daily Experiences (NSDE) that relate diurnal cortisol dynamic range to recalled life adversities and cross-sectionally to biology (specifically, a traditional measure of allostatic load based on static measures only) and health (specifically, cognitive functioning assessed over the telephone).

1.2 Life Adversity and Diurnal Cortisol Dynamic Range

Participants in the second wave of NSDE (N=1,733), a sub-study of the Midlife in the United States Study (MIDUS), collected four saliva samples per day (one upon waking, one around 30 minutes after waking, one before lunch, and one at bed time) on four consecutive days, including one weekend day (Almeida et al., 2009). After a visual examination to confirm consistency of the cortisol daytime trajectories across sub-groups of the population, we modeled natural-log-transformed cortisol values across the day as a piece-wise linear spline function of time since waking, with four linear segments and three fixed knots at 0.5 hours, 4.5 hours, and 15 hours after waking. We used linear mixed-effects regression to model the log-cortisol growth curves, with random effects to account for within-day, within-person, and within-family correlations. Growth curve parameters (intercept and four slopes) were modeled to vary with covariates. Model estimates of mean intercept and slopes (fixed effects) were combined with the random effects to create individual-specific estimates of the morning peak, the nightly nadir, and the integrated total log-cortisol exposure over 16

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hours, or area under the log-cortisol curve (AUC) by the trapezoidal rule – see Karlamangla et al. (2013) for details.

Cortisol diurnal dynamic range was computed for each individual as the peak of log (cortisol) minus the nadir of log (cortisol), which translates to the natural log of the ratio of the cortisol diurnal peak to its nadir. We found after adjusting for age and gender, that non-Whites - a group composed predominantly of African Americans (67.5%), but also included Hispanics, Native Americans, and people of mixed race/ethnicity - had 0.42 smaller diurnal dynamic range than non-Hispanic Whites (which translates to 34% reduction in the peak to nadir ratio), and those with some college education but without a college degree had 0.08 smaller diurnal dynamic range than college graduates, a 7.7% smaller peak to nadir ratio. While the difference in dynamic range between Whites and non-Whites was due to both higher nadirs and lower peaks, the difference between college graduates and those with college education but no college degree was due to a smaller peak only. Of note, the AUC was not statistically different by race/ethnicity nor by education level (Karlamangla et al., 2013).

In a separate analysis, we examined the associations of recalled early childhood adversity with cortisol diurnal dynamic range and AUC in the same sample. We created two indices of childhood adversity: Economic adversity in childhood was indexed by recalled parental education, family welfare dependence, and perceived financial status (range, 0–3); and childhood social adversity by parental separation, death, and abuse (range, 0–3). Adjusted for age, gender, and race/ethnicity, both kinds of childhood adversity were strongly associated with smaller diurnal cortisol dynamic range in adulthood, but not with cortisol daytime AUC. When adult income, education, and social strain were added to the models, the associations with childhood adversity diminished in magnitude by about one third, and only the association of dynamic range with total childhood adversity (sum of economic and social adversity indices; range 0–6) remained marginally statistically significant, at −0.018 (or 1.8% reduction in peak-to-nadir ratio per unit increment in adversity score; p=0.08). More adult social strain and lower levels of adult education were significantly associated with smaller dynamic range of cortisol in the full models, but not related to cortisol daytime AUC. Social strain in adulthood (range, 0–3) was calculated as the mean rating over 14 responses about 3 potential sources of strain (spouse/partner, other family members, friends) to questions regarding how often (range, 0–3) the source causes strain. Per increment in the social strain scale, the dynamic range was 0.053 smaller (or 5.2% smaller peak to nadir ratio). There was a clear dose response with level of education: While those with some college education but without a college degree had 0.052 smaller diurnal dynamic range (or 5.1% smaller peak-to-nadir ratio) than college graduates, those with high school or less education had 0.087 smaller dynamic range (or 8.3% smaller peak-to-nadir ratio) (Karlamangla, et al. 2019).

1.3 Cortisol Diurnal Dynamic Range and Dysregulation in Other Systems

If exposure to life stressors does indeed result in diurnal dynamic range compression, then one would expect range compression to be correlated with dysregulation in other allostatic systems. To test this hypothesis, we examined the correlations of diurnal cortisol dynamic

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range (and AUC) with allostatic load, operationalized using static system measures, which were measured in the MIDUS Biomarker Project. 1001 participants in the second wave of NDSE also participated in the MIDUS II Biomarker Project, which entailed an overnight visit to a MIDUS study site, with overnight urine and morning fasting blood collections, and measurements of blood pressure, resting heart rate, and heart rate variability (Love et al., 2010). Static (resting) measures of dysregulation across 6 physiological systems, cardiovascular (systolic blood pressure, pulse pressure, heart rate), sympathetic (overnight urinary epinephrine and norepinephrine, normalized by urinary creatinine), parasympathetic (four indices of heart rate variability), inflammation (five cytokines), lipid metabolism (serum low and high density cholesterol levels, fasting serum triglycerides, body mass index, and waist hip ratio), and glucose metabolism (fasting blood glucose, insulin resistance, and glycosylated hemoglobin) were combined to create a comprehensive single measure of allostatic load. The seventh system, HPA axis, which was assessed in the Biomarker Project using overnight urinary cortisol, was not included in the allostatic load score for this analysis of correlation with diurnal cortisol dynamic range (and daytime cortisol AUC). As described in greater detail in Gruenewald et al. (2012), a risk score was computed for each of the other 6 physiologic systems as the proportion of biomarkers that fell in the high-risk quartile of the biomarker's distribution; the 6 system-level risk scores (range, 0–1) were summed to create a multi-system allostatic load score (range, 0–6). After adjusting for age, gender, number of chronic conditions, education, smoking status, and race/ethnicity, greater cortisol diurnal dynamic range was associated with smaller allostatic load; conversely smaller dynamic range was associated with greater allostatic load. Cortisol daytime AUC was not associated cross-sectionally with allostatic load (Charles et al., 2020).

1.4 Cortisol Diurnal Dynamic Range and Cognitive Functioning

To assess the potential health consequences of dynamic range compression, we examined the cross-sectional association of cortisol diurnal dynamic range (and AUC) with performance on a telephone-based assessment of cognitive functioning in 1500 NDSE II participants who also completed the MIDUS II cognition battery (Lachman et al., 2014). Four domains of cognitive functioning were assessed using the Brief Test of Adult Cognition by Telephone (BTACT): 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 (assessed through backward digit span). Scores on all 4 domains were converted to z scores and averaged into a single composite score. Adjusted for age, gender, number of chronic conditions, education, smoking status, and race/ethnicity, greater cortisol diurnal dynamic range was associated with better composite scores of cognitive functioning, but AUC was not related to cognitive functioning score (Charles et al., 2020).

Of note, static measures of the HPA axis in MIDUS II were not cross-sectionally associated with cognitive functioning. An HPA axis dysregulation score (values 0,1,2) created from measurements of overnight urinary cortisol (normalized by urinary creatinine) and serum level of dehydroepiandrosterone sulfate (DHEA-S) in MIDUS II Biomarker Project participants, was not associated with either episodic memory or executive functioning

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(Karlamangla, et al., 2014), highlighting the importance of going beyond static measures of physiological systems to assess dysregulation that may be relevant to health outcomes.

These and other data support a possible role for cortisol diurnal dynamic range compression as a biological marker of exposure to life stresses and potentially as a predictor of adverse health consequences. The objective of the new analyses that we present here, is to extend the evidence base linking diurnal cortisol dynamic range to health by leveraging longitudinal data to evaluate the extent to which cortisol diurnal dynamic range is a significant predictor of future health, going beyond cross-sectional associations to an examination of longitudinal outcomes. To this end, we combine data on cortisol measurement in the second wave of MIDUS with data on cognition from both the second and third waves, and data from MIDUS mortality follow up. Specifically, we examine the extent to which cortisol diurnal dynamic range and AUC predict all-cause mortality and, among those who survive, cognitive decline over 9–10 years.

2. Methods

MIDUS is a national study initiated in 1995 to determine how social, psychological, and behavioral factors over the life course influence health and well-being in midlife and older adulthood. English-speaking, non-institutionalized, 25 to 74 year-old adults residing in the contiguous 48 states were recruited, with oversampling of five metropolitan areas, twin pairs, and siblings (Brim et al., 2004). A decade later, 5,555 participated in the second wave of data collection (2004–09), which included a new sample of 592 African Americans living in Milwaukee, WI, to increase the representation of urban African Americans (Radler and Ryff, 2010; Slopen et al., 2010). As part of NSDE II, a random sub-sample (n= 2,022) of the MIDUS II sample also completed a daily telephone diary study about their experiences over eight consecutive days and collected four saliva samples per day (for cortisol assessments) on four consecutive days, starting from day 2 of the diary study (Almeida et al., 2009).

2.1. Study Samples

The NSDE II sample was similar to the complete MIDUS II sample, but slightly better educated and with fewer minority respondents (Almeida et al., 2009). Of the 2,022 NSDE II participants, 1,736 (86%) collected saliva, up to 16 times over 4 consecutive days. Of the 27,776 possible saliva samples (1,736 × 16), around 3% (874) were unusable, because the sample was missing, had insufficient volume to measure cortisol, or could not be linked to a specific day or time of collection. An additional 1.5% of cortisol measurements were excluded because they were outliers (>60 nmol/L; note that the standard deviation of cortisol across all samples was 10 nmol/L and the mean diurnal peak cortisol was 18.7 nmol/L) that may reflect the effect of medications such as corticosteroids; this left us with 1,733 participants who had at least one cortisol sample linked to sampling time, over a total of 6,883 days. Because cortisol diurnal rhythms are disrupted by early and late wakeup times and late bedtimes, we dropped data from 130 days when participants awoke before 4 am, an additional 104 days when the 3rd cortisol sample was 10 nmol/L or more higher than the 2nd sample (since this might reflect a time-recording error for one of the saliva samples or saliva sample contamination with food), 49 days when respondents woke after 11am, and an

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additional 28 days for respondents who were awake more than 20 hours on a given day. This left us with a potential sample of 1,697 participants (from 1,411 families) with 6,334 days of data, and 24,452 cortisol samples.

Of the 5,555 MIDUS II participants, 4,512 (81%) completed a telephone cognition assessment. Of them, 2,712 completed a second cognition assessment, approximately 9–10 years later, at the third wave of MIDUS data collection in 2014–15. As is typical in longitudinal studies, those who participated in the third wave were younger, better educated, had better self-rated health at MIDUS II, less likely to be from non-White race/ethnicity groups, and scored better on cognition testing in MIDUS II (Hughes et al., 2018). Of the 1,697 participants who had MIDUS II diurnal cortisol rhythm data for calculation of diurnal dynamic range, 1,250 (74%) completed cognition assessments in both MIDUS II and III. After excluding those who were missing covariates (race/ethnicity: 1, primary language:19, education level: 9, neurological conditions: 2, depression and diabetes: 22, body mass index [BMI]: 44), we were left with an analysis sample of 1,153 for analysis (from 974 distinct families) of cortisol diurnal dynamic range and future cognitive decline.

Of the 1,697 participants with MIDUS II cortisol diurnal dynamic range, we excluded those who were missing covariates needed for the mortality analysis (race/ethnicity: 1, education: 14, depression, diabetes, and other chronic conditions: 54, BMI: 65), leaving us with a mortality analysis sample of 1,578 from 1,317 distinct families.

2.2. Measurements

2.2.1. Cortisol Diurnal Dynamic Range and AUC—Prior to day 1 of the 8-day diary study, NSDE II participants received an in-home saliva collection kit by mail. Interviewers reviewed collection procedures with participants during the day 1 telephone call, and saliva collection began the next day (day 2) and continued for 4 consecutive days (through day 5). Participants collected four saliva samples each day: one upon waking, one around 30 minutes after getting out of bed, one before lunch, and one at bed time. Data on the exact time of each saliva sample were obtained from nightly telephone interviews by study staff and on a paper-pencil log sent with the collection kit. Salivettes were frozen (at –60 °C) for storing and shipping. Cortisol concentrations were measured with a commercially available luminescence immunoassay (IBL, Hamburg, Germany).

Additional variables that could potentially influence the daily cortisol trajectory were obtained for every day of the cortisol measurement from the participant during the nightly telephone interviews, and included the length of sleep the previous night, morning waking time, night bedtime, and whether or not it was a weekend day - a distinction that was made only for those who were employed.

As described in greater detail in Karlamangla et al. (2013), we used multi-level, linear mixed-effects regression to account for within-day, within-person, and within-family correlations in cortisol measurements, and model the log-cortisol growth curves as a linear spline with three fixed knots at 0.5 hours, 4.5 hours, and 15 hours after waking. There was considerable right-sided skew in the distribution of cortisol whereas the distribution of the logarithm of cortisol is closer to a Gaussian which is preferred to mitigate the influence of

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extreme values. Further, a piece-wise linear growth curve fit the daytime trajectory of log (cortisol + 1 nmol/L) substantially better than it fit the trajectory of raw cortisol (R-squared of 55.6% vs. 42.4%). We therefore used linear splines to model the trajectories of log (cortisol + 1 nmol/L) over the waking day. All five growth curve parameters (intercept and four slopes) were modeled to vary with the following covariates: average wake-day length (individual-level, averaged over all 8 days), waking time (day-level), previous night's sleep time (day level) and weekend vs. workday status (day-level). Model estimates of mean intercept and slopes (fixed effects) were combined with corresponding random effects at the family level and individual level to create individual-specific estimates for the five growth curve parameters. These were then combined to create individual-specific estimates of the log-cortisol diurnal peak and nadir values and AUC - the area under the log-cortisol curve over the first 16 hours after waking. Cortisol diurnal dynamic range was calculated as log-cortisol peak minus log-cortisol nadir, which is mathematically equivalent to the log of the cortisol peak-to-nadir ratio.

2.2.2. Cognitive Decline—After a brief hearing check, cognition was assessed over the telephone using the BTACT (Lachman, Agrigoroaei, Tun, & Weaver, 2014) and the Stop and Go Switch Task (SGST), a test of task switching and inhibitory control processes, designed to be especially sensitive to early changes in cognitive functioning (Lachman & Tun, 2008). The BTACT measures 6 key domains of cognitive aging: episodic memory (immediate and delayed word list recall), working memory (digits backward), executive function and semantic memory (category fluency), reasoning (number series completion), and speed of processing (backward counting). The SGST provides both accuracy and latency measures of cognitive function. In order to assess response latencies while ensuring that participants were performing the task as directed, the latencies data were filtered to exclude individuals who did not meet 75% or better accuracy criteria on each task condition; for more details, see Tun & Lachman (2006) and Tun & Lachman (2008).

Both exploratory and confirmatory factor analyses were conducted on MIDUS II measures, and two factors were identified (Lachman et al., 2014): Episodic memory (composed of immediate and delayed word recall) and Executive functioning (based on five subtests - backward counting, digit span backward, number series, category fluency, and the SGST mixed-mode latency measure). The 2 summary scores, episodic memory and executive functioning, were computed as the mean of standardized (to mean 50 and standard deviation 10) scores of component items, using the means and standard deviations from MIDUS II to standardize component items at both waves (Hughes et al., 2018).

We calculated the annualized percentage change in both episodic memory and executive functioning between MIDUS II and MIDUS III, as 100*(MIDUS III score – MIDUS II score) / (MIDUS II score * years between exams).

2.2.3. All-cause Mortality—Mortality of MIDUS participants is tracked in 3 ways. One, the University of Wisconsin Survey Center, which fields the MIDUS surveys, conducts a closeout interview with informants of suspected decedents, when they are made aware of a participant's passing during the fielding of the next wave of data collection. The second mechanism is by formal searches of the National Death Index (NDI) through December

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31, 2016. The third mechanism is via longitudinal sample maintenance activities of the MIDUS Administrative Core, which routinely sends birthday cards and newsletters to MIDUS participants, and receives information about decedents from family and friends of decedents, and searches online obituaries, grave listings, and funeral home websites.

2.2.4 Covariates—Age, race/ethnicity, gender, highest level of educational attainment, primary language spoken at home when growing up, chronic conditions, body height and weight, and smoking status, were all self-reported in the MIDUS II survey questionnaire. We categorized age in three groups of similar size: <50 years old, 50–64 years old, and 65 years of age or older. Race/ethnicity was self-identified as White, Black/African-American, Other, or Multi-racial. Because the number of participants in the Other and Multi-racial groups was small (75 in the mortality sample, 51 in the cognitive decline sample), for the purposes of this analysis, we combined them with the African American group, and denoted the combined group Non-White. Education was analyzed as a three-category variable indicating whether the respondent had completed high school or less; had some college education but not completed it; vs. had completed a college education. Body mass index (BMI) was created from self-reported height and weight. We created a binary indicator for diabetes mellitus (based on the response to question about 'diabetes or high blood sugar') and one for depression (based on the response to a question about 'anxiety, depression, or other emotional disorder'). For the cognition score change analysis, we created a created a binary indicator variable for neurological conditions (combined from separate questions about stroke, serious head injury, Parkinson's disease and other serious neurological condition). For the mortality analysis, we created a count (range, 0–15) of other major chronic conditions (not including diabetes), as described previously in Piazza et al. (2013), but excluded diabetes from the count.

2.3. Statistical Analysis

We used mixed effects linear regression to model the annualized percentage change in episodic memory and executive functioning scores between MIDUS II and MIDUS III as a function of cortisol diurnal dynamic range and AUC, adjusted for age (continuous, linear and quadratic terms), gender, race/ethnicity, primary language (English vs. not English), education (3 levels), smoking status (past smoker, current smoker vs. never smoker), BMI (continuous), depression (yes/no), diabetes (yes/no), neurological conditions (yes/no), and cognition score at baseline (MIDUS II). We included a random intercept at the family level, to allow for correlations between individuals from the same family. Separate models were run for episodic memory and executive functioning outcomes. We included adjustment for cognition score at baseline, because the same value of the dependent variable (percent change per year in cognition score) translates to a larger absolute change per year in people who start at a higher baseline than in people who start at a lower baseline.

Those who start at a lower level of cognitive functioning are more susceptible to further declines (Mazzeo et al, 2019); vascular disease for instance has a smaller impact on cognitive decline in those with higher cognitive reserve (Pinter, et al., 2015). Lower levels at study baseline may reflect ongoing decline from a prior peak level of functioning and increased susceptibility to decline, while those who start higher may still be functioning

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at their peaks, and test ceiling effects may mask their declines. To test for the possibility that the association of cortisol diurnal biomarkers with change in cognition scores may be different in people who start at low vs high baseline scores, we added two interaction terms between baseline cognition score and a) cortisol diurnal dynamic range and b) cortisol AUC. If the interaction test was statistically significant ($p<0.1$), we conducted stratified analyses in strata defined by baseline cognition score being below or above the median baseline score in the MIDUS II Cognition Sample. We used a higher p-value threshold (i.e., allowed a higher Type I error rate) for assessing the significance of interactions to reduce the failure rate in detecting a key hypothesized interaction (Type II error rate), given that there is generally less statistical power to detect interactions than to detect main effects (McClelland & Judd, 1993).

To examine the association of cortisol diurnal parameters with subsequent all-cause mortality, we conducted proportional hazards regressions of time to death as a function of cortisol diurnal dynamic range and AUC, adjusted for age (continuous, linear and quadratic terms), gender, race/ethnicity (White vs. non-White), education (3 levels), smoking status (past smoker, current smoker vs. never smoker), BMI (continuous), depression (yes/no), diabetes (yes/no) and a count of other major chronic conditions (excluding diabetes) at MIDUS II. We used the marginal model approach of Wei et al. (1989) to account for correlations between individuals from the same family. We first ran a base model with only the demographic variables and smoking status, and in the next step, added the chronic condition count and cortisol diurnal biomarkers, to determine how much of the mortality associations with demographic and behavioral variables is explained by chronic conditions and cortisol diurnal biomarkers.

In supplementary analyses, we explored the possibility of a non-linear relationship between diurnal dynamic range and all-cause mortality, by using linear splines for dynamic range, with knots fixed at quintile cutoffs. SAS 9.4 statistical software was used for all analyses.

3. Results

Mean age at MIDUS II was 56 years in both analysis samples, and men constituted 43% of both analysis samples (Table 1). To be in the cognitive decline sample, participants had to have survived until MIDUS III. As shown in the third column of the table, 14% of the respondents had died by December 31, 2016. Comparing columns 1 and 2 of the table, White participants and those who had completed college were more likely to have survived and participated in cognition testing in MIDUS III; there were fewer non-Whites in the cognitive decline sample than in the mortality analysis sample (12% vs. 14%), and a larger fraction of the cognitive decline sample had completed college (44% vs. 40%). Current smokers and diabetics were less likely to survive to MIDUS III and participate in cognition testing; MIDUS II prevalence of current smoking and diabetes was lower in cognitive decline sample than in the mortality analysis sample: 10.6% vs. 12% for current smoking and 8.2% vs. 10.1% for diabetes. Those who survived to MIDUS III and participated in MIDUS III cognition testing also had healthier cortisol diurnal rhythms – larger dynamic range (1.91 vs. 1.85, which translates to raw cortisol peak-nadir ratios of 6.75 vs. 6.36) and smaller AUC (28.7 vs. 29.1). The model-predicted (and inverse log transformed) mean

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cortisol diurnal rhythm in the sample is shown in Figure 1. Correlation between diurnal dynamic range and AUC was modest, −0.30 in the mortality sample and −0.25 in the cognitive decline sample. Correlations between diurnal dynamic range and other more traditional measures of diurnal rhythm (such as awakening response, recovery slope, etc.) in this sample have been previously published (Charles, et al., 2020).

Cognition score mean decline rates in the Cognitive Decline Sample were 0.1% per year in episodic memory scores and 0.5% per year in executive functioning scores. For someone who started with a baseline score of 50 and experienced mean declines, episodic memory would have declined by 0.5 and executive functioning by 2.5 over one decade. There was twice as much variability over the cohort in episodic memory decline rate than in executive functioning decline rate, as evidenced by standard deviations of 1.93% per year and 0.93% per year, respectively (Table 1). There were 237 deaths in the mortality analysis sample; mean follow up time was 10.1 years (standard deviation, SD, 2.1 years) and median 10.8 years (interquartile range, 9.2 to 11.6 years).

3.1 Associations with Cognitive Decline Rates

As expected, older participants experienced faster declines in both episodic memory and cognitive functioning, and there was an acceleration of the age effect at older ages, as evidenced by significantly negative quadratic age associations (Table 2). Thus, while people who were 56 years of age at MIDUS II experienced, on average, 0.88% more decline in episodic memory and 0.58% more decline in executive functioning over a decade than those who were 54 years of age at MIDUS II, relative to those 64 years old, those who were 66 years old at MIDUS II experienced 1.28% and 0.74% more decline over a decade in episodic memory and executive functioning, respectively. Men experienced faster decline in episodic memory than women, and those with high school or less education experienced faster declines in both episodic memory and executive functioning than college graduates. Those who scored higher on cognition testing at MIDUS II declined more on average than those who scored less (Table 2).

Cortisol diurnal dynamic range was not associated with cognition score decline rates, but a larger total cortisol exposure (i.e., larger AUC) was associated with faster decline in episodic memory (Table 2). Per SD increment in AUC (SD=5.2), episodic memory decline was 0.1% faster per year, which is more than twice the age effect on decline rate in an individual at the median age of the cohort: 0.088% faster annual decline for each year one is older. In interaction testing, there was no evidence of effect modification by baseline performance (in MIDUS II) for episodic memory decline rate; the effect sizes (and p values) for MIDUS II score interactions with dynamic range and AUC were −0.012 (p=0.55) and 0.0007 (p=0.52), respectively. However, there was evidence that baseline performance modifies dynamic range association with executive functioning decline rate; the effect sizes (and p values) for MIDUS II score interactions with dynamic range and AUC were −0.022 (p=0.08) and −0.0008 (p=0.57), respectively. We therefore, conducted further stratified analyses for the executive functioning decline outcome in two strata defined by MIDUS II scores on executive functioning: low (at or below median of 49.2) and high (above median).

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Among those who scored high on executive functioning at baseline, associations with decline rates were similar to those seen in the whole sample, and neither cortisol diurnal dynamic range nor AUC were associated with decline rates (Table 3). Among those who scored low on executive functioning at baseline, only age and baseline score were associated with decline rates, and there was no acceleration of the age effect at older ages. In this group, a larger cortisol diurnal dynamic range meant smaller annual % decline in executive functioning ($p=0.046$). Per SD increment in diurnal dynamic range (SD=0.4), executive functioning decline was 0.1% slower per year. This is comparable to the average reduction in decline rate in an individual who is 3 years younger.

3.2 Associations with All-cause Mortality

As expected, all-cause mortality rate increased significantly with age, was greater in men than in women, in those with less education, in those with history of smoking, and in current smokers (Table 4). These associations diminished but were not fully explained by the addition of chronic condition count and measures of diurnal cortisol rhythms. Larger cortisol diurnal dynamic range was significantly associated with less mortality; adjusted hazard ratio 0.74 per SD increment in dynamic range (SD=0.42); 95% confidence interval [0.65, 0.84] ($p<0.0001$). This survival advantage is comparable to the average benefit conferred by being 3.5 years younger. Cortisol daytime AUC was not independently associated with all-cause mortality (Table 4).

To explore the possibility that cortisol diurnal dynamic range may have a non-linear relationship with mortality hazard, we modeled dynamic range as a linear spline with knots fixed at the quintile cutoffs in its distribution:1.53, 1.80, 2.00, and 2.21 log (nmol/L). None of the spline terms were statistically significantly associated with mortality hazard, even after backward pruning to a single spline term, suggesting that the underlying relationship is essentially linear, with a 51% reduction in mortality hazard for every unit log (nmol/L) increment in diurnal dynamic range.

4. Discussion

Using longitudinal data from a large-scale national survey of adults, this study provides evidence of the added value in leveraging information about the dynamics of diurnal cortisol patterns to predict subsequent health and cognitive performance. We have established that cortisol diurnal dynamic range, the natural logarithm of the ratio of the morning cortisol peak to the evening cortisol nadir, is a significant predictor of both all-cause mortality and cognitive decline in some survivors. Individuals with compressed dynamic range are at substantially increased risk of all-cause mortality over the next 7–12 years; if they survive and had been performing below average on executive functioning at baseline, they experience faster declines in executive functioning. Conditional on diurnal dynamic range, cortisol AUC, a measure of total daytime cortisol exposure, does not predict mortality. But in those who survive, larger AUC predicts faster decline in episodic memory.

Diurnal dynamic range has advantages over other measures used to characterize cortisol diurnal rhythms. First, it provides a single, simple and intuitive summary of cortisol variation over the day, the ratio of cortisol peak to nadir. Second, because changes in

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slope over any fixed time interval are necessarily accompanied by changes in starting and/or final levels, dynamic range will reflect changes in other metrics that have been used to characterize the cortisol diurnal rhythm, such as awakening response, peak level, recovery slope, and nadir level. Third, in this and previous studies of cortisol diurnal dynamic range, the associations of dynamic range (with both prior adversities and current and future health) are independent of AUC, which reflects the average cortisol level over the waking day. This suggests that in addition to the absolute level of circulating cortisol, diurnal dynamic range is as, if not more, susceptible to life stressors and critical to health. Finally, we investigated the shape of the relationship between cortisol diurnal dynamic range and all-cause mortality by re-estimating the model with a linear spline and knots at each 20^{th} percentile of the dynamic range distribution. None of the spline terms was individually or jointly significant, implying a linear relationship and underscoring the parsimony benefits of the dynamic range measure.

With regard to cognitive decline in survivors, there was significant variability in the rate of decline even after accounting for age differences in the sample. While the mean decline over a decade was 1% in episodic memory and 5% in executive function, decline rates one SD above mean translates to 20% and 15% declines in episodic memory and executive function over one decade. Cortisol diurnal rhythms relate to some of this variability in future cognitive decline among survivors. Total cortisol exposure over the day, as indexed by AUC, is related to the rate of decline in episodic memory. This is consistent with previous work on cortisol's damaging effects on the hippocampus, a key brain region for memory functioning (Kim et al., 2015).

However, for executive functioning, it was not AUC but compression of the diurnal dynamic range that was implicated in faster decline, although only for those who start with lower levels of executive functioning. Previous studies of cortisol and executive functioning have found mixed results (Shields et al., 2016); our findings suggest that a robust cortisol diurnal dynamic range may be protective specifically in people who are already performing at a relatively lower level of executive functioning. The prefrontal cortex, a key brain region for executive functioning, has been found to be particularly sensitive to the effects of chronic stress, more so than to acute stress (Arnsten, 2009). Compression of cortisol diurnal dynamic range, which is also related to chronic, not acute, stress, may be mediating the effects on the prefrontal cortex and executive functioning decline.

Work by Rosmond et al. (1998) has demonstrated the importance of a robust cortisol diurnal dynamic range in preventing the development of obesity and metabolic abnormalities, which have been tied strongly to both mortality and cognitive decline in multiple studies in humans. In a rat model of diet-induced obesity, obese rats show deficits on cognitive tasks requiring the prefrontal cortex, and the cognitive deficits are accompanied by decreased dendritic spine density and synaptic marker expression in the region (Bocarsly et al., 2015), hinting at one potential pathway through which cortisol diurnal dynamic range compression might lead to faster declines in executive functioning. A more direct effect of diurnal dynamic range compression on cognitive functioning is suggested by experiments by Liston et al. (2013) in mouse models, which found that a high morning cortisol peak is critical

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for post-synaptic dendritic spine formation in the brain cortex, while a low cortisol evening nadir is needed to stabilize newly formed spines.

In addition to the direct and indirect (via obesity and metabolic abnormalities) effects of cortisol diurnal dynamic range compression on health and mortality, diurnal range compression may also be a marker of diminished capacity of the HPA axis to respond to acute stressors, or reduction in HPA axis allostatic reserve. Such reduction in allostatic reserve in physiological systems is a hallmark of aging (Arbeev et al., 2011; Navaratnarajah & Jackson, 2013) and it has been linked to the reduced ability of older adults to bounce back from illnesses and hospitalizations (Hadley et al., 2017; Oken et al., 2015). Diminished adaptive capacity is also a consequence of exposure to chronic and severe stresses (Koolhaas et al., 2011), but how well diurnal dynamic range compression reflects the magnitude of diminution in adaptive capacity remains to be determined. That the two are tightly interrelated is apparent from the findings of Rosmond et al. (1998) that cortisol reactivity to a standardized laboratory challenge is associated with adverse health *only* in individuals with compressed cortisol diurnal dynamic range, and not in individuals with robust diurnal cortisol variation.

4.1 Implications

Regardless of the ability of diurnal dynamic range compression to reflect diminution of allostatic reserve, by virtue of its demonstrated strong associations with life adversity and subsequent health and survival, diurnal range compression belongs in future operationalizations of allostatic load. Compression of diurnal dynamic range has been evidenced in all primary mediators of allostasis in relation to both chronic stresses (Rief et al., 2010) and aging (Toutou & Haas, 2000). It also represents a target for manipulation by behavioral and pharmaceutical interventions. In particular, restoring of the diurnal dynamic range in blood pressure by bedtime administration of anti-hypertensive medications has unequivocal and large benefits over simply reducing average blood pressure, with more than 50% reductions in the rates of major cardiovascular events and cardiovascular mortality demonstrated in a large randomized clinical trial (Hermida et al., 2020). Behavioral changes that restore the circadian rhythms of metabolic hormones, such as restricted time eating with extended nightly fasting intervals, also appear to have the potential to improve health (Manoogian & Panda, 2017; Świątkiewicz et al., 2021).

4.2 Limitations and Strengths

The main limitations of our study are its observational design which hampers definitive causal inference, over-representation of non-Hispanic whites (86% of the sample), inaccuracies in measuring cognitive decline rates from two measurements of cognitive functioning 10 years apart, lack of longitudinal data on diurnal dynamic range, and inability to determine which life stressors contributed to compression of the diurnal cortisol dynamic range. Cognitive decline rate estimation from cognitive functioning measurements at only two time points compounds measurement errors; more frequent measurements would have provided more reproducible estimates and allowed discrimination between early and late declines.

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Although the allostatic load hypothesis is that dysregulation of stress response physiology, including of the cortisol diurnal rhythm, is the biological signature of adversity over the life course, this study does not shed light on the causes of cortisol diurnal dynamic range compression. In addition to psychosocial adversity, chronic conditions and ill health are also stressors that can dysregulate the HPA axis, and the cortisol diurnal rhythm in particular. We include chronic conditions as covariates in multivariable regression to control for the role of ill health in cortisol dynamic range compression.

It is also possible however, that poor cognitive functioning is itself a stressor that further compresses cortisol dynamic range. Longitudinal studies with repeated measurement of cortisol diurnal dynamic range will be needed to tease apart any such bidirectional pathways between HPA axis dysregulation and cognitive functioning. Finally, information on pregnancy status at the time of the cortisol collection was not available. However, premenopausal women comprised less than 6% of the MIDUS sample.

This study also has major methodological strengths, such as multiple days of cortisol collection including one weekend day, longitudinal assessment of outcomes, control for total daytime cortisol exposure (the AUC), and accounting for within-family correlations.

4.3 Conclusions

With these study strengths and limitations in mind, the findings reported here add to the growing body of evidence on diurnal dynamic range compression as a key mechanism by which life stressors impact health. We therefore posit that the next generation of allostatic load scoring needs to include the diurnal dynamic range of primary mediators of allostasis. The concept of allostatic load, as originally proposed by McEwen and Stellar (1993), included dysregulation not only in the resting state of physiological systems, but also in system dynamics; however, most researchers operationalize allostatic load solely with static system (resting state) measures. We contend that diurnal dynamic range compression offers an innovative way to asses dysregulation of system dynamics. Our findings show that compressed cortisol diurnal dynamic range predicts both all-cause mortality and cognitive decline in some survivors, specifically those who had scored below average on executive functioning at the time of cortisol measurement. We conclude that including measures of system dynamics like diurnal dynamic range in the next generation of allostatic load measurement will likely advance assessment of the cumulative physiological burden of chronic stress and life experiences, and improve the prediction of future health consequences.

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Abbreviations

AUC	Area under the curve (used here for area under the log-cortisol curve over 16 hours, start from time of waking)

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MIDUS	Midlife in the United States
NSDE	National Study of Daily Experiences

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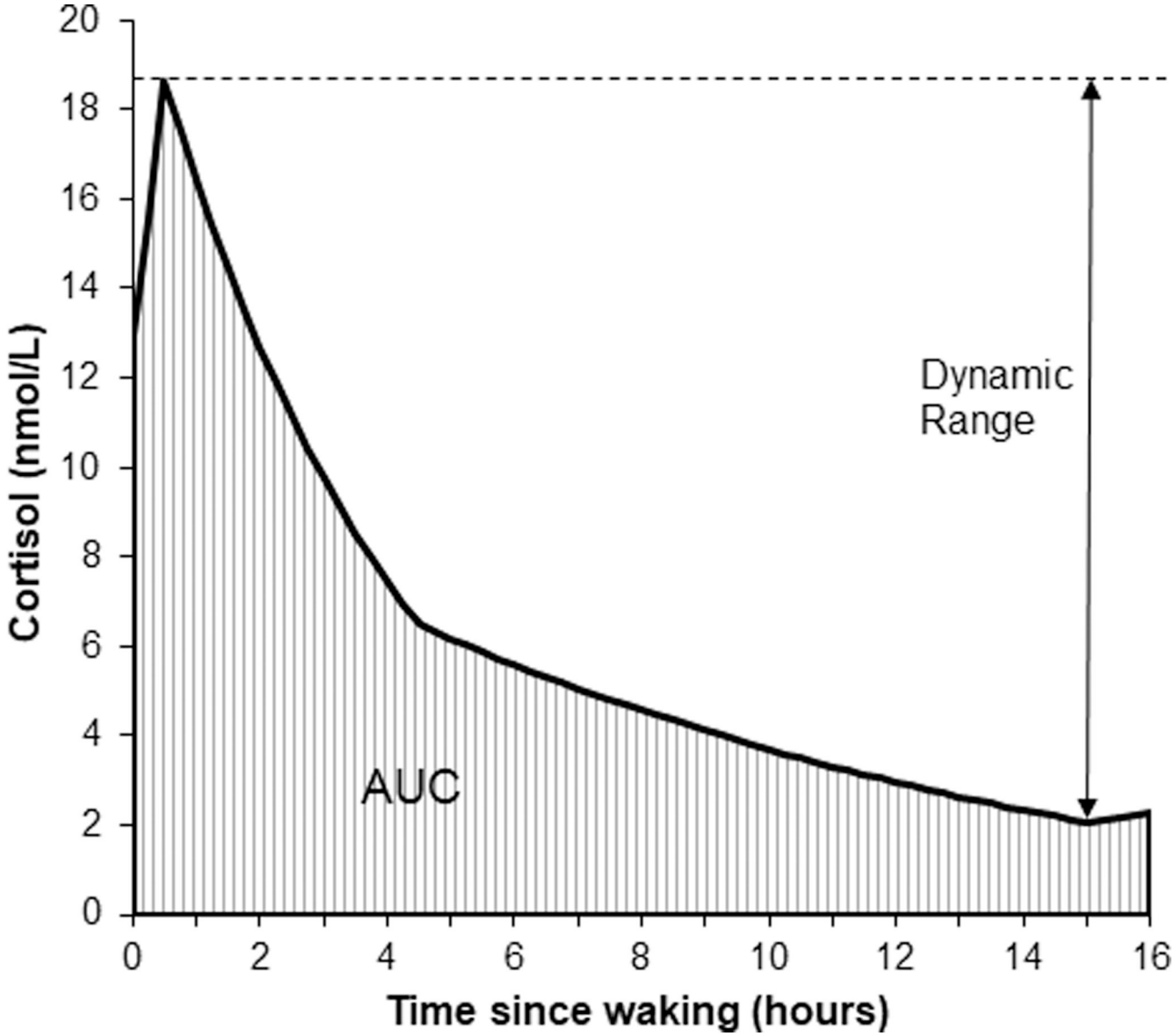

Figure 1.

Mean cortisol trajectory in the sample, constructed from growth curve intercept and slopes estimated from a mixed-effects, multi-level, linear spline model of log-transformed cortisol data collected over four consecutive days. Individual-level diurnal cortisol parameters, area under the log-cortisol curve (AUC) and dynamic range (log of the cortisol peak-to-nadir ratio), were calculated for each study participant.

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Table 1.

Descriptive Statistics[1] for Cognitive Decline and Mortality Samples

	Cognitive Decline Sample N = 1,153	Mortality Sample[2] N = 1,578
Demographics/Medical History		
Age at MIDUS II (years)	55.5 (11.2)	56.4 (12.0)
Male	493 (42.8%)	673 (42.7%)
Non-white	135 (11.7%)	217 (13.8%)
Non-English Speaker	23 (2.0%)	--
Education		
Some College	335 (29.1%)	466 (29.5%)
Completed College or More	507 (44.0%)	633 (40.1%)
Smoking Status at MIDUS II		
Past Smoker	371 (32.2%)	509 (32.3%)
Current Smoker	122 (10.6%)	189 (12.0%)
Depression at MIDUS II	193 (16.7%)	286 (18.1%)
Body mass index at MIDUS II (kg/m^2)	28.0 (5.6)	28.2 (5.9)
Diabetes mellitus at MIDUS II	94 (8.2%)	159 (10.1%)
Neurological Condition at MIDUS II	89 (7.3%)	--
Other Chronic Condition Count; MIDUS II	--	0.79 (0.81)
Cortisol Measures at MIDUS II		
Dynamic Range (log nmol/L)	1.91 (0.40)	1.86 (0.42)
AUC (log(nmol/L)-hour)	28.8 (5.2)	29.1 (5.7)
Cognition Scores at MIDUS II		
Executive Function	51.0 (6.4)	--
Episodic Memory	50.7 (8.9)	--
Cognition Change by MIDUS III		
Episodic Memory (% per year)	−0.10 (1.93)	--
Executive Function (% per year)	−0.51 (0.99)	--
Mortality by December 31, 2016	--	237 (14.1%)

[1]Descriptive statistics provided for predictors, outcomes, and covariates used in each analysis. Statistics provided are number (%) for categorical variables, and mean (standard deviation) for continuous variables

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Table 2.

Adjusted Associations[1] of Cortisol Diurnal Dynamic Range and AUC in MIDUS II with Rate of Change in Cognition Scores from MIDUS II to MIDUS III

	Episodic Memory (% per year)	Executive Functioning (% per year)
Age at MIDUS II (per decade) [2]		
Age	**−0.44** (−0.54, −0.33)	**−0.28** (−0.34, −0.23)
Age squared	**−0.11** (−0.18, −0.04)	**−0.04** (−0.08, 0.00)
Male	**−0.67** (−0.88, −0.46)	+0.08 (−0.03, +0.19)
Non-white	−0.08 (−0.42, +0.25)	−0.17 (−0.38, +0.03)
Non-English Speaker	+0.14 (−0.50, +0.78)	+0.03 (−0.30, +0.36)
Education		
High school or less	**−0.49** (−0.74, −0.24)	**−0.20** (−0.36, −0.04)
Some College but not Graduate	−0.18 (−0.41, +0.06)	−0.10 (−0.24, +0.03)
Smoking Status at MIDUS II		
Past Smoker	−0.05 (−0.27, +0.17)	−0.06 (−0.19, +0.06)
Current Smoker	−0.25 (−0.56, +0.06)	−0.15 (−0.34, +0.04)
Depression at MIDUS II	−0.23 (−0.49, +0.03)	−0.07 (−0.22, +0.09)
Body mass index at MIDUS II (kg/m ^{2})	+0.01 (−0.01, +0.02)	+0.00 (−0.01, +0.01)
Diabetes mellitus at MIDUS II	−0.02 (−0.43, +0.40)	−0.02 (−0.25, +0.21)
Neurological Condition at MIDUS II	−0.14 (−0.50, +0.23)	−0.04 (−0.32, +0.23)
Cognition Score at MIDUS II	**−0.11** (−0.13, −0.10)	**−0.04** (−0.06, −0.03)
Cortisol Measures at MIDUS II		
Dynamic Range (log nmol/L)	+0.05 (−0.21, +0.32)	+0.07 (−0.08, +0.22)
AUC (log(nmol/L)-hr)	**−0.02** (−0.04, 0.00)	0.00 (−0.01, +0.02)

[1] Estimated associations (and 95% confidence intervals) are from mixed effects linear regressions with all tabulated variables included as fixed effects, and a random intercept at family level. Associations are presented as increment in annualized change rate (% per year) in episodic memory score and executive functioning score per unit increment in continuous predictors/covariates or compared to reference group of categorical covariates

[2] Age is centered at 55 years

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Table 3.

Stratified, Adjusted Associations[1] of Cortisol Diurnal Dynamic Range in MIDUS II with Rate of Change in Executive Functioning Score from MIDUS II to MIDUS III

Stratum:	Executive Functioning at MIDUS II	
	Low baseline	High baseline
Age at MIDUS II (per decade) [2]		
Age	**−0.32** (−0.41, −0.23)	**−0.29** (−0.36, −0.22)
Age squared	−0.00 (−0.07, +0.06)	**−0.09** (−0.15, −0.03)
Male	+0.03 (−0.16, +0.23)	+0.11 (−0.02, +0.24)
Non-white	**−0.32** (−0.62, −0.03)	+0.10 (−0.12, +0.33)
Non-English Speaker	+0.21 (−0.20, +0.61)	−0.35 (−0.81, +0.11)
Education		
High school or less	−0.17 (−0.44, +0.10)	**−0.26** (−0.44, −0.08)
Some College but not Graduate	−0.04 (−0.30, +0.21)	−0.14 (−0.30, 0.01)
Smoking Status at MIDUS II		
Past Smoker	−0.15 (−0.36, +0.05)	+0.03 (−0.12, +0.19)
Current Smoker	−0.11 (−0.46, +0.23)	−0.14 (−0.35, +0.06)
Depression at MIDUS II	−0.13 (−0.38, +0.12)	−0.03 (−0.22, +0.16)
Body mass index at MIDUS II (kg/m ^{2})	+0.01 (−0.01, +0.02)	−0.01 (−0.02, +0.01)
Diabetes mellitus at MIDUS II	+0.03 (−0.26, +0.31)	−0.05 (−0.42, +0.31)
Neurological Condition at MIDUS II	−0.09 (−0.49, +0.30)	+0.05 (−0.31, +0.40)
Executive Functioning at MIDUS II	**−0.06** (−0.10, −0.03)	**−0.04** (−0.06, −0.03)
Cortisol Measures at MIDUS II		
Dynamic Range (log nmol/L)	**+0.26** (0.01, +0.50)	−0.05 (−0.24, +0.13)
AUC (log(nmol/L)-hr)	+0.01 (−0.01, 0.02)	0.00 (−0.01, +0.01)

[1] Strata defined by median split of executive functioning score at baseline (MIDUS II). Estimated associations (and 95% confidence intervals) are from mixed effects linear regressions with all tabulated variables included as included as fixed effects, and a random intercept at family level. Associations are presented as increment in annualized change rate in executive functioning score (% per year) per unit increment in continuous predictors/covariates or compared to reference group of categorical covariates

[2] Age is centered at 55 years

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Table 4.

Adjusted Associations[1] of Cortisol Diurnal Dynamic Range and AUC in MIDUS II with Subsequent All-cause Mortality Rate

	Adjusted hazard ratio (95% CI)	
	Base Model	**Full Model**
Age (per decade) [2]		
Age	**2.59** (2.14, 3.13)	**2.37** (1.95, 2.92)
Age squared	1.07 (0.98, 1.17)	1.06 (0.96, 1.16)
Male	**1.35** (1.04, 1.79)	1.23 (0.92, 1.64)
Non-white	1.21 (0.82, 1.79)	0.91 (0.59, 1.41)
Education		
High school or less	**1.49** (1.07, 2.07)	1.37 (0.96, 1.96)
Some College but not Graduate	**1.49** (1.07, 2.07)	1.44 (0.99, 2.10)
Smoking Status		
Past Smoker	**1.46** (1.11, 1.92)	1.26 (0.94, 1.70)
Current Smoker	**2.94** (1.93, 4.47)	**2.53** (1.61, 3.96)
Depression		1.11 (0.78, 1.59)
Body Mass Index (kg/m ^{2})		1.01 (099, 1.04)
Diabetes mellitus		**1.59** (1.10, 2.31)
Other Chronic Condition Count	--	**1.25** (1.09, 1.44)
Cortisol Measures		
Dynamic Range (log nmol/L)	--	**0.49** (0.36, 0.67)
AUC (log(nmol/L)-hr)	--	1.00 (0.97, 1.02)

[1] Estimated hazard ratios (and 95% confidence intervals) are from multivariable proportional hazards regressions with all tabulated variables included as predictors/covariates, and accounts for clustering within families. The primary predictors and all covariates were assessed at the MIDUS II. Base model includes only demographics and smoking status. Full models additionally include depression, body mass index (continuous), diabetes, a count of other major chronic conditions (not including diabetes) and cortisol diurnal. Hazard ratios are presented per increment in one unit of continuous predictors/covariates or as compared to reference group of categorical covariates

[2] Age is centered at 56.5 years