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Diurnal cortisol profiles, inflammation and functional limitations in aging: Findings from the MIDUS study

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Abstract

Objective: The current study examined the association between diurnal cortisol profiles, inflammation, and functional limitations, among adults ranging in age from 34-84 years.

Methods: Participants ($N = 799$) completed Waves 2 (between 2004-2006) and 3 (between 2014-2016) of the Midlife Development in the United States Survey. At Wave 2, participants provided saliva samples across four consecutive days, from which cortisol was assayed. Previously-validated diurnal cortisol profiles (i.e., normative, flattened, or elevated) were examined in relation to concurrent inflammation risk burden and to predict long-term changes in functional limitations.

Results: Compared to participants with normative profiles across all interview days, participants with dysregulated profiles across all interview days (i.e., all days elevated, flattened, or a combination of elevated and flattened) showed greater concurrent inflammation risk burden and more functional limitations at follow-up. Regions of significance testing indicated that the association was significant beginning at age 60 for inflammation risk burden and beginning at age 66 for functional limitations. Variable profiles (i.e., a mix of normative and flattened and/or elevated across the four days of assessment) were not significantly associated with these health indices.

Conclusions: Findings, consistent with the theoretical model of Strength and Vulnerability Integration, illustrate the importance of considering age when examining cortisol and its association with other health indices.

Keywords

Cortisol; HPA-axis; age; inflammation; functional limitations

A substantial body of literature indicates that stressors are associated with health problems, including functional limitations (Lantz, House, Mero, & Williams, 2005), chronic conditions (Piazza, Charles, Sliwinski, Mogle, & Almeida, 2013), and disease progression (Cohen, Janicki, & Miller, 2007). To identify causal mechanisms for this link, researchers have incorporated the use of biomarkers into their studies, with several focusing on the hormone cortisol (for review, see Piazza, Almeida, Dmitrieva, & Klein, 2010). Cortisol exhibits a diurnal pattern, with levels rising in the first 30-45 minutes after waking and declining thereafter (Lovallo & Tomas, 2000). Although robust, this pattern is prone to deviations for multiple reasons, including stressor exposure. Deviations in the diurnal pattern, in turn, have been linked with adverse psychological and physical health outcomes, and could be one mechanism linking stressors and health (for review, see Adam et al, 2017). Importantly, the link between stressors and health may vary across the lifespan. According to the model of Strength and Vulnerability Integration (SAVI), stressors exert a greater influence with increasing age because older adults have a more difficult time recovering from the physical changes that occur when a stressor is experienced (Charles, 2010). The current study examines whether diurnal cortisol profiles predict inflammation risk burden and functional limitations, and tests whether, as SAVI predicts, these associations increase in magnitude with age.

The importance of cortisol's diurnal pattern.

Cortisol is essential for human survival. The diurnal oscillation of cortisol, with a steep morning rise and a steady decline thereafter, plays a vital role in ensuring synchronization of physiological processes with an organism's behavior throughout the day. For example, the sharp increase of cortisol in the first 30-45 minutes after waking prepares the body for the day; oscillations throughout the day aid in maintaining vital physiological processes; and the daily decline prepares the body for rest (Dumbell, Matveeva, & Oster, 2016). Through a series of downstream processes, the hypothalamic-pituitary-adrenal (HPA) axis releases cortisol in response to environmental and psychological challenges, which can lead to deviations in the diurnal pattern (Oster, et al., 2016). Although homeostatic mechanisms allow the body to recover from these deviations, excessive cortisol release can compromise the HPA's ability to recover from future stressors, which could ultimately result in adverse health outcomes (e.g., Hackett, Kivimaki, Kumari, & Steptoe, 2016).

Aging and the diurnal pattern of cortisol.

The model of Strength and Vulnerability Integration (SAVI) posits that older adults are more vulnerable to the physiological effects of stress than are younger adults (Charles & Luong, 2013; Charles & Piazza, 2009). SAVI basis this prediction on research findings and theories of biological aging that seek to explain cellular aging and the higher prevalence and incidence of disease with age. For example, researchers find that cells accumulate damage over time, which leads to a cascade of decreased adaptability, defective structures, and cell destabilization (e.g., Terman & Brunk, 2006). In the case of cortisol, research based on the glucocorticoid cascade hypothesis of aging indicates that chronic exposure to high levels of cortisol impairs cellular functioning, making neurons of older adults, relative to those of younger adults, more vulnerable to insults (Porter & Landfield, 1998), which could lead to

adverse health-related outcomes. For these reasons, the effects of dysregulated cortisol (i.e., a diurnal pattern that deviates from the typical morning rise and daily decline) may have greater physical health consequences in later life.

Distinct classes in diurnal cortisol trajectories.

Cortisol dysregulation appears to manifest in either a hyperactivated or a hypoactivated pattern (Adam et al., 2017). To identify individual diurnal patterns, recent studies have used mixture modeling, such as group-based trajectory modeling or growth mixture modeling (Dmitrieva, Almeida, Dmitrieva, Loken, & Pieper, 2013; Kumari et al., 2010; Lasikiewicz et al., 2008). These approaches parsimoniously assess how multiple components of the diurnal pattern (e.g., overall output, cortisol awakening response (CAR), diurnal slope, evening level) co-occur within a day, and distinguish between distinct day-level patterns within the same person. One recent study, for example, identified commonly-occurring cortisol profiles in 1,101 individuals who provided 2,894 days of data (Dmitrieva et al., 2013). In addition to a normative cortisol profile (73% of days characterized by a robust CAR, a steep negative diurnal slope, and a low awakening and bedtime level), two dysregulated cortisol profiles emerged: an elevated profile and a flattened profile. The elevated profile (20% of days) was characterized by higher cortisol values throughout the day, especially at awakening; and the flattened profile (7% of days) was characterized by the weakest CAR, the flattest diurnal slope, and the highest bedtime levels (see Figure 1). Compared to the normative profile, the elevated and flattened profiles were more common among older adults and cigarette smokers. The flattened profile was also more common among males, medication users, and those reporting poor health. There was also substantial within-person variability in diurnal cortisol profiles: Among participants who provided valid samples across all four days, 52.3% consistently exhibited one type of profile across all four days, and 47.7% exhibited variability in profiles across days.

Intra-individual variability in cortisol profiles.

Because relatively few studies have examined the link between diurnal cortisol variability and other health indices (Segerstrom, Sephton, & Westgate, 2017), it is unclear if variability (i.e., some normative days and some dysregulated days) reflects a healthy HPA axis that is effectively responding to the challenges of life (e.g., Adam et al., 2006), or one that is beginning to show signs of wear (Yehuda, Teicher, Trestman, Levengood, & Siever, 1996). Studies examining this question indicate that diurnal cortisol variability is related to worse mental (e.g., Sannes, Mikulich-Gilbertson, Natvig, Simoneau & Laudenslager, 2016) and physical health outcomes (Herriot, Wrosch, Gouin, & Miller, 2016). Additional studies are needed, however, to test associations between diurnal cortisol variability and other health indices, particularly the prospective effects of cortisol on subsequent health outcomes.

Dysregulated cortisol, inflammation and functional limitations.

The current study examines how day-centered cortisol profiles relate to two indices of physical health: inflammation risk burden and functional limitations. Research on inflammation has gained significant traction in recent years, demonstrating that chronic

inflammation is related to diseases that are strongly linked to disability and death, including asthma, type 2 diabetes, and atherosclerosis (Kotas & Medzhitov, 2015). The stress response triggers a heightened immune response (such as an increased production of cytokines) as well as a cortisol response (Black & Barbutt, 2002). Cortisol and cytokines share a complex, interactive relationship. Cortisol is a known immune suppressant, and blunted cortisol levels are sometimes related to higher levels of cytokines (e.g., Kunz-Ebrecht, Mohamed-Alis, Feldman, Kirschbaum, & Steptoe, 2003). Yet, increases in cytokines also signal the system to increase levels of cortisol (e.g., Steensberg, Fischer, Keller, Moller, & Pedersen, 2003), so higher levels of cortisol can also be associated with higher levels of cytokines. Thus, consistent dysregulation of diurnal cortisol, manifested in a hypoactive or a hyperactive pattern, could be related to higher inflammation risk burden.

The second outcome in the current study is functional limitations, which refer to an individual's limitations in their ability to perform daily physical tasks, such as walking a city block or climbing a flight of stairs (U.S. Department of Health and Human Service, 2015).

Several behavioral factors increase a person's risk for functional limitations (e.g., Pahor et al., 2014; Mankowski, Anton, & Aubertin-Leheudre, 2015), and dysregulated diurnal cortisol may be an underlying neurobiological mechanism mediating these associations. For example, dysregulated cortisol is associated with metabolic changes that could lead to weight gain, as well as heightened inflammation that could lead to increased pain for musculoskeletal conditions (such as osteoarthritis), which may, ultimately, limit physical activity. Obesity and lack of physical activity, in turn, are two well-known predictors for functional decline (e.g. Mankowski, Anton, & Aubertin-Leheudre, 2015; Pahor et al., 2014). Although cross-sectional studies have identified a link between cortisol and functional limitations (e.g., de Sousa Alberquerque et al., 2017; Kumari et al., 2010; Peeters et al., 2007), few longitudinal studies have examined this question, and those that have, primarily focused on plasma cortisol (e.g., Baylis et al., 2013; Reynolds et al., 2005). Only one study to our knowledge has examined the association between salivary cortisol and subsequent functional limitations. In a sample of 164 older adults, ages 64-94 years, Wrosch and colleagues found that higher levels of cortisol, measured by area-under-the-curve with respect to ground (AUC_G), predicted functional disabilities four years later, but only among participants who did not report engaging in adaptive control strategies (Wrosch, Miller, & Schulz, 2009). Although the investigators collected salivary cortisol from participants for three days, AUC_G was averaged across all study days; thus, the effects of diurnal cortisol variability on functional disabilities was not examined, nor were dynamic fluctuations of cortisol levels within each day. This is an important area of inquiry, as relatively high AUC_G levels can manifest in multiple ways, including higher morning values coupled with relatively low evening values, or higher evening values coupled with an overall flat profile.

The current study examines whether diurnal cortisol profiles are associated with concurrent inflammation risk burden and long-term changes in functional limitations. Based on SAVI, which posits that physiological perturbations have greater downstream effects for older adults, we hypothesize the following: Compared to people with consistently normative profiles, people with dysregulated and variable profiles will show greater inflammation risk

burden and more functional limitations, but this association will be most pronounced with increasing age.

Method

Participants and Procedures

Midlife Development in the United States Survey.—Data for the current study is from the Midlife Development in the United States Survey (MIDUS), which consists of multiple projects collected across three longitudinal waves. The initial MIDUS Survey began in 1995, with the goal of understanding factors related to health and well-being in midlife. Participants, between the ages of 25 and 74 years, were asked to complete a phone interview and a battery of self-administered questionnaires (SAQ). Approximately ten years later, when participants were between the ages of 34 and 83, they completed Wave 2 of MIDUS, answering the same battery of questionnaires ($n = 4,963$). Wave 3 of MIDUS was collected between 2013 and 2014 on 3,294 of the original participants, now between the ages of 43 and 92. The current study uses data from Waves 2 and 3 of MIDUS, which we will refer to as baseline (Wave 2) and follow-up (Wave 3). For a complete description of MIDUS, please see Radler, 2014.

National Study of Daily Experiences (NSDE).—NSDE II is the daily diary portion of MIDUS and is one of four sub-projects that were conducted at baseline. Participants were recruited from a random sample of 3,600 MIDUS participants and asked to complete eight consecutive daily interviews. During each interview, participants were asked about the events of their day, their affective state, and any physical symptoms they experienced. Of the 3,600 MIDUS participants contacted, 2,022 participated, for a response rate of 78% (Almeida, McGonagle, and King, 2009). NSDE II participants provided saliva samples four times per day (upon waking, 30 minutes after waking, before lunch and before bed) on four out of eight interview days, using a Home Saliva Collection Kit. The kit included detailed instructions and 16 numbered and color-coded salivettes (Sarstedt, Nümbrecht, Germany). On participants' first interview day, trained interviewers reviewed collection procedures, and saliva collection began the next day (Day 2). Participants were instructed not to brush their teeth, eat, or consume caffeine for 30 minutes prior to providing each sample. Participants mailed their completed samples back to the laboratory, and cortisol was assayed, using a commercially available luminescence immunoassay (IBL, Hamburg, Germany), with intra- and inter-assay coefficient of variations below 5% (Dressendörfer, Kirschbaum, Rohde, Stahl, & Strasburger, 1992). In total, 1,736 participants returned the saliva collection kit. Data collection for MIDUS and NSDE was approved by the University of Wisconsin's and the Pennsylvania State University's Institutional Review Boards.

Estimation of diurnal cortisol profiles.—Of the 1,736 participants who provided cortisol, 1,101 were retained for analyses estimating diurnal cortisol profiles (Dmitrieva et al., 2013). The smaller sample size was due to the application of strict exclusion criteria, in keeping with previous work on salivary data collection rigor and participant compliance (e.g., Kudielka, Gierens, Hellhammer, Wüst, & Schlotz, 2012). Reasons for exclusion included, but were not limited to: samples with implausibly high values (i.e., > 60 nmol/L);

samples indicating atypical sleep timing (e.g., waking time > 11:00am); first waking samples characterized by a delay in saliva collection of > 15 minutes after waking; and second samples of the day collected earlier than 15 or later than 45 minutes after waking (for a full list of exclusion criteria and a detailed description of the analytic strategy used to identify cortisol profiles in this sample, see Dmitrieva et al., 2013). Of the 1,101 participants with baseline cortisol profiles, 801 completed the followup assessment (both the phone interview and SAQ's) and were thus eligible for inclusion in the current study.

The MIDUS Biomarker Project.—At baseline, a subset of MIDUS participants, who were healthy enough to travel ($n = 1255$), underwent an extensive physical exam at one of three possible General Clinical Research Center's (UCLA; University of Wisconsin-Madison; or Georgetown University). Testing lasted for two days - beginning in mid-afternoon (Day 1) and ending by noon the next day (Day 2) – and included a complete medical history, multiple blood draws, and urine collection. All biomarkers were collected during the overnight visit (5:00 PM – 11:00 AM). Anthropometrics, fasting blood samples, and overnight urine samples were collected and processed according to standardized instructions (for details regarding participant recruitment and sample information, see Love, Seeman, Weinstein, & Ryff, 2010).

Measures

Functional Limitations.—At baseline and follow-up, participants indicated on a fourpoint scale, ranging from 1 “a lot” to 4 “not at all,” the extent to which their health limited their ability to do each of the following tasks: bathing or dressing; walking one block; climbing one flight of stairs; lifting or carrying groceries; climbing several flights of stairs; bending, kneeling or stooping; walking more than a mile; walking several blocks; engaging in moderate activity; and engaging in vigorous activity. Scores were reverse-coded and averaged across each of the 10 items, with lower scores indicating less impairment. The questions are from the SF-36 (Ware & Sherbourne, 1992), but the scaling was modified for the MIDUS survey. This modified scaling has been used in several studies (e.g., Friedman, Christ, & Mroczek, 2015; Goodwin & Devanand, 2008; Grzywacz, Segal-Karpas, & Lachman, 2016) and shows high internal consistency ($\alpha = .94$: baseline; $\alpha = .95$: follow-up). Two people failed to answer half of the questions at follow-up and were thus excluded from analyses. For the remaining 799 participants, the average score for baseline limitations was 1.54; follow-up limitations score was 1.78. Age was positively associated with functional limitations at baseline, $r(798) = .28, p < .001$, and at follow-up, $r(798) = .40, p < .001$.

Inflammation.—We used a composite measure of inflammation risk burden as opposed to examining separate markers of inflammation, based on the theoretical underpinnings of the model of allostatic load (McEwen, 1998). According to this model, individual differences exist in how people respond physiologically to stress, so the specific biomarker influenced by stress may vary across individuals. In addition, poor functioning in one biomarker may be compensated by effective functioning in other areas, so examining one biomarker may not accurately depict overall physiological functioning and how well the body is responding to stress. In contrast to studying single measures, composite measures allow for a profile of overall functioning. A greater number of biomarkers with values indicating dysregulation

suggests that compensation for poor functioning in one area by another is less likely. The more biomarkers affected, the more difficulties a system will encounter when anticipating and responding to stress (Juster, McEwen, & Lupien, 2010).

Our composite measure of inflammation includes IL-6, C-Reactive Protein (CRP), soluble E-selectin, Intracellular Adhesion Molecule (ICAM), and Fibrinogen. For details regarding laboratory protocol, assay techniques and coefficient of variances, see Cohen, Granger, & Fuller-Thomson, 2015. Because clinical cut off values only exist for CRP (which we discuss below), the common standard for calculating the inflammation component of allostatic load is to use a count strategy, whereby biomarkers falling into the highest quartile in the group under investigation are considered to reflect poorer functioning (i.e., higher load).

Prior to creating composite scores, participants with CRP values higher than 10 ug/l were excluded from analyses ($n = 11$), as such values may be indicative of acute infection (Boylin & Ryff, 2013). Inflammation risk burden scores were then computed by dividing each of the five biomarkers into quartiles. For each biomarker, participants were given a 1 if their score fell into the highest quartile and a 0 if it did not. Scores for all five biomarkers were then added together, for an inflammation risk burden score that ranged from 0 to 5 (Yang, Schorpp, & Harris, 2014). This method that has been used successfully in a number of previous studies (e.g., Politt et al., 2007; Ransome, Slopen, Karlsson, & Williams, 2017; Yang, Gerken, Schorpp, Boen, & Harris, 2017).

To ensure consistency among our subsamples, the inflammation subsample was drawn from the 799 individuals from whom functional limitations data and cortisol profiles could be derived. Of these participants, 462 completed the Biomarker subproject, and 451 (which reflects the 11 who were excluded due to high CRP scores) were retained in our analyses. Inflammation risk burden scores for the 451 participants were as follows: 176 (39%) scored zero; 144 (31.9%) scored one; 73 (16.2%) scored two; 37 (8.2%) scored three; 15 scored four (3.3%) and 6 scored five (1.3%).

Demographic variables.—We statistically adjusted for several demographic variables in our models, including sex (coded male or female), race (coded White or other, due to the small number of minorities in the sample) and education (higher numbers reflecting more years of education). We also included covariates that have been associated with inflammation and functional limitations in previous research, including body mass index (BMI); history of smoking (“yes” or “no”), medication use (“yes” or “no”), and number of chronic health conditions (Marmot, Ryff, Shipley, & Marks, 1997), which were combined into 21 categories, summed, and winsorized at six or more. Chronic condition categories included: cancer; heart disease; lung conditions; digestive conditions; bone-related conditions; HIV/AIDS; autoimmune diseases; high blood pressure; diabetes; neurological problems; stroke; problems with gums, mouth or teeth; thyroid conditions; hay fever; bladder problems; gall bladder problems; migraines; thyroid conditions; hernia; anxiety or depression; and sleep problems.

Missing Data.: Some participants were missing data on BMI ($n = 54$), functional limitations at baseline ($n = 7$) and/or medication use ($n = 3$). For BMI and functional limitations at

baseline, missing data was replaced using mean imputation. For baseline medication use, logistic regression was used to predict probability of belonging to a medication use class.

Descriptive Statistics

Sample Characteristics.—Table 1 presents sample characteristics for the full MIDUS II sample ($n = 4,963$), the NSDE II subsample with functional limitations data ($n = 799$), and the Biomarker subsample with inflammation data ($n = 451$). Compared to the full MIDUS II sample, the subsamples were less diverse, more highly educated, and reported more chronic health conditions. The two subsamples, however, did not differ from one another on these variables.

Cortisol profiles—For data analysis, participants were placed into one of three groups: normative profiles across all interview days; dysregulated profiles (i.e., flat or elevated) across all interview days; and variable profiles across interview days (i.e., a combination of flat, elevated, and/or normative). Of the 799 participants in the final sample, 54.32% had normative cortisol profiles across all days sampled ($n = 434$), 13.64% had dysregulated profiles across all days sampled ($n = 109$); and 32.04% had variable profiles across all days ($n = 256$). Results of a One-Way ANOVA, with cortisol profile category as the independent variable and age as the dependent variable, revealed a trend: the group with dysregulated cortisol profiles was marginally older than the other two groups, $F(2, 798) = 2.94, p = .054$.

Results

Statistical Plan.

To maximize power, but to avoid dependency in the data (due to the inclusion of siblings and twins), analyses were conducted using Generalized Estimating Equations (GEE) in Proc Gen Mod (Liang & Zeger, 1986). Predictor variables included age, cortisol profiles (categorized as either normative, dysregulated or variable), and their interaction. Covariates (all assessed at baseline) included sex, race, education, BMI, history of smoking, chronic conditions, and medication use. For analyses predicting follow-up functional limitations, baseline functional limitations was also included as a covariate. Tests for normality indicated that both inflammation risk burden and follow-up functional limitations were skewed, and were thus transformed using square-root transformation. Because results remained unchanged when using transformed data, findings are presented using the original, non-transformed data, for ease of interpretation.

Inflammation.

We first examined whether cortisol profiles were associated with the composite inflammation risk burden score. The final model revealed a significant age by cortisol profile interaction (See Table 2). Age differences in inflammation risk burden were significant for participants with dysregulated cortisol patterns, but not for participants with normative or variable patterns (see Figure 2). Regions of significance were calculated, using Preacher's online calculator (Preacher, Curran, & Bauer, 2006), revealing that the lower-bound limit was out of the age range of the current sample and the upper-bound limit was 60. Simple slopes were significant outside of this region, indicating that the association between cortisol

dysregulation and inflammation risk burden begins at age 60 for participants in our study. To illustrate this difference, we calculated the percentage of individuals in each group (those with dysregulated cortisol and those with normative cortisol) who had three or more high risk inflammatory markers. Adults age 60 and over with normative profiles were less likely to have three or more high risk inflammatory markers (10%) than were adults age 60 and over with dysregulated profiles (17%).

Functional Limitations.

We hypothesized that compared to participants with normative profiles, participants with dysregulated and variable cortisol profiles at baseline would report significantly more functional limitations at follow-up, an association that would be most pronounced among older participants. Results revealed a main effect of age, indicating that functional limitations were higher with increasing age. This effect, however, was qualified by an age by cortisol profile interaction, indicating that, at follow-up, age differences in functional limitations were greater for participants with dysregulated profiles compared to participants with normative profiles. Age differences in functional limitations for variable profiles, however, did not significantly differ from those with normative profiles (See Table 2). Regions of significance were once again calculated using Preacher's online calculator. Results indicated that the upperbound region of significance was 66 years, while the lower-bound region of significance was 37.4 years. (see Figure 3) This indicates that consistently dysregulated cortisol profiles at baseline predicted an increased number of limitations at follow-up among people aged 66 years and older. Cortisol dysregulation was not associated with long-term changes in functional limitations for people between the ages of 37.4 and 66 years. Unexpectedly, dysregulated cortisol profiles prior to 37.4 years predicted fewer functional limitations at follow-up. We examined those individuals who were 37.4 years-old and younger in our sample ($n = 41$) to understand this finding. There were two people with dysregulated cortisol in this group; for these individuals, functional limitations did not increase over time. Two people with normative cortisol profiles in this group, however, had large increases in functional limitations across the two time-points. When the latter two outliers were removed, cortisol profile type was no longer associated with change in functional limitations among individuals younger than 37.4 years.

To illustrate the differences among individuals in the upper-bound region of significance (those age 66 and over), we calculated the percentage of individuals in each group (those with dysregulated cortisol and those with normative cortisol) who reported at least "some" functional limitations. The number of individuals with dysregulated profiles reporting at least "some" functional limitations (29.7%; scoring at least a 3), was nearly twice as many (16.5%) as those with normative profiles.

We also examined whether cortisol profiles were associated with concurrent functional limitations (i.e., both variables assessed at Wave 2). Results indicated that although cortisol profiles were predictive of future functional limitations, they were not associated with concurrent functional limitations (variable profiles: $b = -.0004$, $p = .92$; dysregulated profiles: $b = .008$, $p = .11$).

Exploratory Analyses

Flat or Elevated vs. Elevated Profiles.

Exploratory analyses were conducted to examine whether the link between dysregulated cortisol and health outcomes was due to flattened or elevated profiles. The cortisol profile variable was recoded so that instead of three groups (normative ($n = 435$), dysregulated ($n = 109$), variable ($n = 256$)), four groups were compared: all normative days ($n = 435$), all flattened days ($n = 23$), all elevated days ($n = 86$), and a mix of flattened and elevated days ($n = 33$). Results of two GEE's (the first examining inflammation risk burden as an outcome; the second examining functional limitations as an outcome) revealed that elevated profiles were marginally related to higher inflammation risk burden ($b = .022$, $p = .081$) and more functional limitations at follow-up ($b = .016$, $p = .0013$). Due to the small sample size for all flattened days, however, findings should be interpreted cautiously.

Cortisol sensitivity analyses.

Studies examining the link between diurnal cortisol and health outcomes typically rely on traditional formulations of diurnal cortisol, including area under the curve, with respect to ground (AUC_G), cortisol awakening response (CAR), and daily decline (Adam et al., 2017). The current study is among the first to use cortisol profiles as predictors of health indices. Thus, in exploratory analyses, we examined whether our results replicated when using more traditional formulations of diurnal cortisol. In keeping with previous research (e.g., Wrosch et al., 2009), AUC_G, CAR, and daily decline since peak (DCSP) were averaged across all interview days and used to predict inflammation risk burden and functional limitations. Results indicated that cortisol profiles were more sensitive in predicting health outcomes than standard measures of cortisol (see Table 3). Specifically, apart from DCSP significantly predicting functional limitations, no other significant associations were detected.

Inflammation risk burden and functional limitations.

Although dysregulated cortisol patterns predicted functional limitations for older adults, an alternative possibility could be that inflammation was responsible for the increases in limitations. To test this possible explanation, we ran another GEE with functional limitations at follow-up as the criterion variable and inflammation risk burden as the predictor. We ran the model with and without the covariates mentioned above; in both cases, inflammation risk burden did not significantly predict functional limitations at follow-up, either as a main effect ($b = -.018$, $p = .44$). or in an interaction with age ($b = -.001$, $p = .64$).

Discussion

The current study revealed that a relatively small snapshot of HPA functioning predicted concurrent and longitudinal health indices among adults, age 60 and older. Findings indicated that inflammatory risk burden and functional limitations in later adulthood are associated with two patterns of diurnal cortisol dysregulation: a flattened diurnal trajectory characterized by a weak CAR and a blunted diurnal slope, as well as an elevated trajectory characterized by consistently heightened cortisol levels across the day. These results are

consistent with SAVI, which posits that the physiological effects of stress on health is worse with advancing age (Charles, 2010). Results provide further evidence of the importance of the downstream effects of dysregulated diurnal cortisol and underscore the importance of interventions aimed at providing resources that could foster healthy HPA-axis functioning (e.g., Klein, Kim, Almeida, Femia, Rovine, & Zarit, 2014). Moreover, they indicate that a comprehensive approach to examining the dynamic fluctuation of cortisol across the day, which takes into account multiple aspects of the diurnal pattern simultaneously, may be more sensitive in predicting health outcomes than standard formulations of cortisol (e.g., CAR, DCSP, AUC_G).

Inflammation.

Among adults age 60 and over in our sample, dysregulated cortisol was associated with greater inflammatory risk burden. The bi-directional pathway between cortisol and inflammation is complex. Cortisol is recognized as an immunosuppressant, and inflammation and cortisol often share an inverse relationship; both, however, can also be elevated in certain situations. For example, the stress response elicits both cortisol release and immune system activation (Black & Barbutt, 2002). This concurrent association does not indicate the cause of elevations in both factors, nor does it inform the directional relationship between them. However, the finding that only dysregulated cortisol, and not higher inflammation risk burden, predicted longitudinal change in functional limitations suggests that they have differential influences on health indices. Although inflammation did not predict future functional limitations in the current study, chronic inflammation has been implicated in the pathogenesis of several chronic illnesses (Kotas & Medzhitov, 2015). Future research will need to examine the effects of both the neuroendocrine and immune system, as well as any potential synergistic effects, on functional outcomes.

Functional Limitations.

Among adults approximately 66 years and older, dysregulated cortisol predicted more functional limitations nearly 10 years later, beyond that predicted by age alone. The finding that dysregulated cortisol poses a greater threat for health outcomes of the oldest adults in our sample is consistent with SAVI and theories of biological aging such as the glucocorticoid case hypothesis. According to these theories, older age is related to greater physical vulnerabilities. For example, chronic stress aggregates over time to reduce physiological resiliency later in life, including the ability to recover from hormonal dysregulation (Porter & Landfield, 1998). Cortisol dysregulation may slowly erode physical functioning at all ages, but it could take years for these small assaults to accumulate to a point where decreases in functional abilities are evident. This reason could explain why the effect was only significant for the oldest adults in our sample.

Mechanistically, there could be a number of pathways through which the relationship between cortisol dysregulation and functional limitations emerges. One potential pathway is through weight gain. Cortisol inhibits insulin and releases glucose, which increases insulin resistance. Insulin resistance has also been related to increased appetite and decreased metabolic rate, which can contribute to obesity (e.g., Kahn & Flier, 2000). Another potential factor is the link between high levels of cortisol and inflammation (e.g., Kotas & Medzhitov,

2015), but in ways that may not have been captured by our inflammation measure. Greater inflammation has been linked to disease processes that decrease functionality – such as gout and osteoarthritis, as well as cardiovascular disease. As such, dysregulated cortisol profiles may be related to functional disability through obesity and diseases commonly related to functional limitations (e.g., cardiovascular diseases and musculoskeletal diseases where inflammation plays a strong role). More research is needed to determine which of these pathways may be most pernicious to health outcomes of older adults.

Variability versus dysregulation.

People with dysregulated profiles showed worse health outcomes than people with normative profiles, but people with variable profiles (a mix of normative and dysregulated days) did not, contrary to our hypothesis. At first glance, this finding supports research indicating that variability reflects an HPA axis that is responsive to the challenges of daily life (Adam et al., 2006). As Figures 2 and 3 illustrate, however, the health indices of people with variable profiles appear to fall between those with consistently normative profiles and those with consistently dysregulated profiles. Thus, our findings may also indicate that variable profiles reflect an HPA axis that is functioning adequately, but is beginning to show signs of wear (Yehuda et al., 1996). Additional longitudinal research is needed to test this possibility.

Flattened versus elevated profiles.

Analyses examining different patterns of dysregulation (i.e., flattened versus elevated) indicate that only elevated profiles interacted with age to predict health outcomes. This is consistent with studies showing that hyperactivity of the HPA axis is problematic (e.g., Entringer, Buss, Andersen, Chicz-DeMet, & Wadhwa, 2011), but is inconsistent with studies showing the negative correlates of flattened profiles (Sephton, Sapolsky, Kraemer, Spiegel, 2000). It is important to note, however, that the subgroup with elevated profiles was three times larger than the subgroup with flattened profiles. If the flattened subgroup had been larger, results may have been significant for that group, as well. More work is needed to disentangle the effects of flattened versus elevated profiles and how these might differ in their relation to disease processes and health outcomes across the lifespan.

Risk factor or early symptom?

For the longitudinal analyses, it is unclear if dysregulated cortisol is a causal factor in the development of functional limitations or is a harbinger of things to come. Cortisol has been implicated in disorders relevant for functional limitations, including osteoporosis (Canalis, 2003), frailty (Johar et al., 2014), and cardiovascular disease (for review, see Walker, 2007). Thus, it is possible that the biological wear-and-tear caused by ongoing, dysregulated diurnal cortisol eventually results in physical functioning impairments. However, dysregulated cortisol in advance of impaired physical functioning could also be a symptom of an underlying health issue. For example, increased thirst among people with diabetes is not the cause of diabetes, but rather a symptom (Clark, 2007). The same could be true of dysregulated cortisol. Even if secondary to the causal mechanism, however, nonnormative cortisol profiles have important long-term health implications.

Limitations.

It is important to recognize some of the limitations of this study. First, the sample was predominately White and well-educated, making it impossible to extrapolate our findings to people of other races and to individuals with lower educational attainment. It is possible that a highly educated sample has more resources when coping with daily life than a less educated sample. Similarly, the daily lives of ethnic minorities may differ from that experienced by white Americans and could potentially affect diurnal cortisol profiles. In addition, the subsamples differed from the full MIDUS II sample on some demographic and self-reported health variables. Thus, results should be interpreted cautiously when generalizing this information to all MIDUS II participants.

A second limitation is that functional limitations were derived through self-report. Although ratings obtained through self-report measures are consistent with objective health measures (Miilunpalo, Vuori, Oja, Pasanen, & Urponen, 1997), future research should replicate this study using objective physical performance measures. Finally, cortisol and inflammatory biomarkers were collected around the same time, which makes it impossible to determine causality.

Conclusions.

Despite the aforementioned limitations, this paper reveals an important link between daily life, aging, and physical health. Findings, which support SAVI, suggest that biomarkers may have different meanings for people of different ages, thereby underscoring the importance of examining health through a developmental lens.

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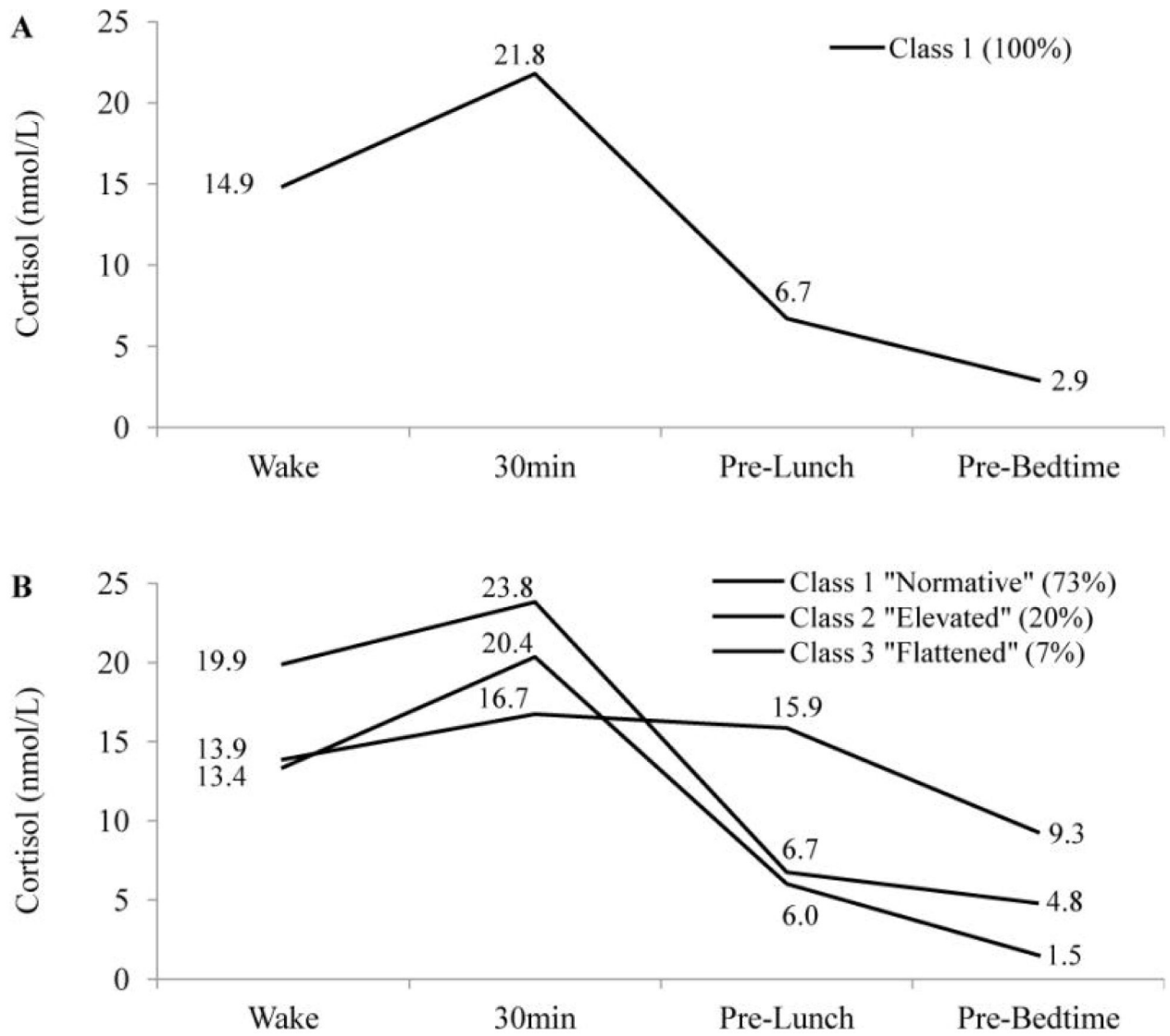


Figure 1. Cortisol profiles as calculated in Dmitrieva et al., 2013. Panel A represents average cortisol profiles across all days. Panel B represents the 3-class solution used in the current study.

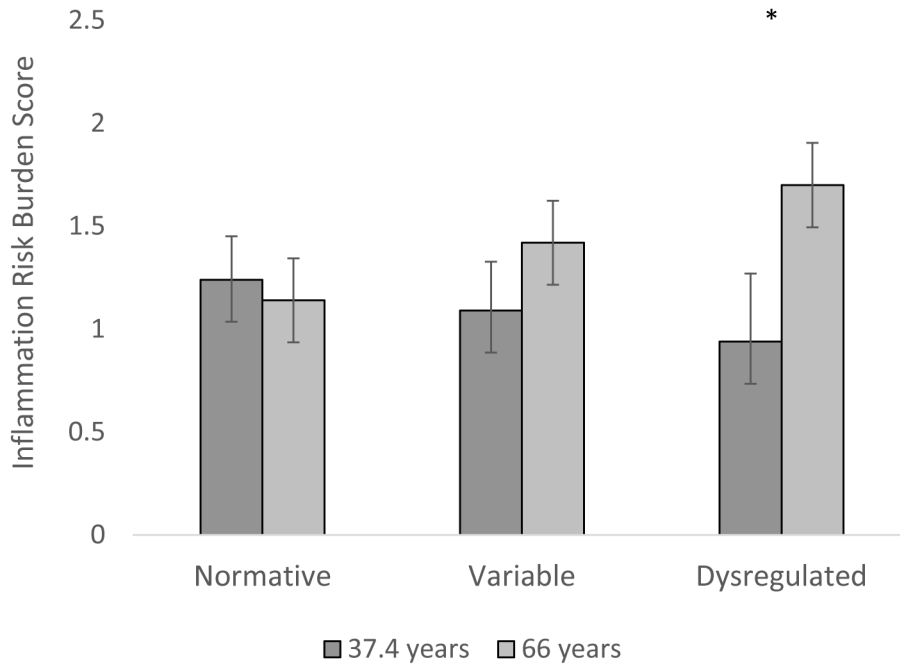


Figure 2.
Cortisol profiles and inflammation risk burden scores

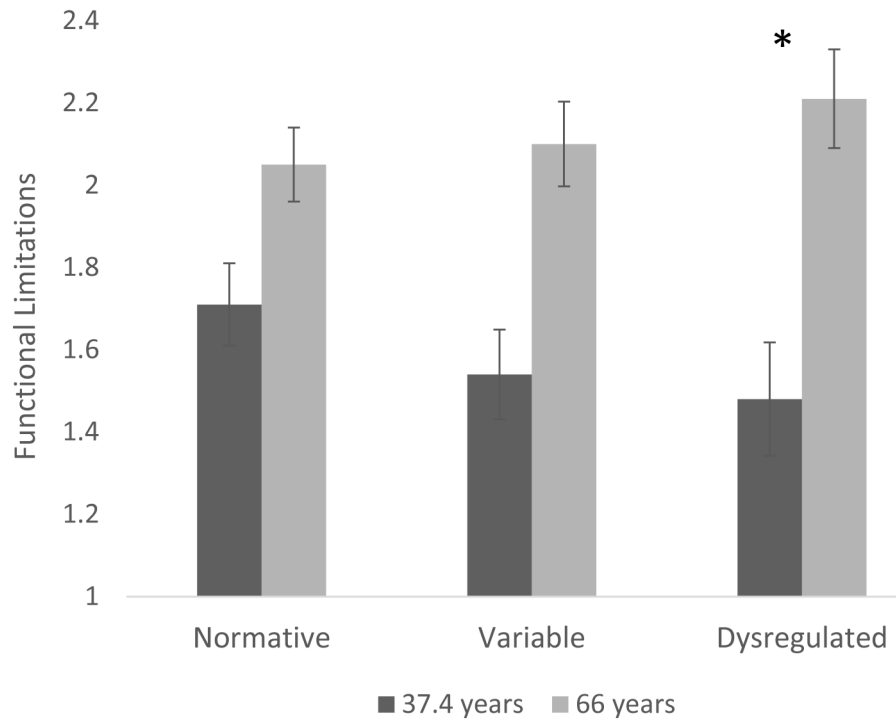


Figure 3.
Cortisol profiles and functional limitations

Demographic characteristics of the MIDUS II sample and each of the subsamples in the current study.

Table 1:

Demographic Characteristics	MIDUS II full sample (<i>N</i> = 4963)	NSDE II subsample (<i>n</i> = 799)	Biomarker subsample (<i>n</i> = 451)
Age (SD)	55.4(12.4)	55.6(11.5)	54.9(11.0)
Sex (% female)	53.3%	55.2%	53.4%
Race (%) ^{a, b}			
White	90.1%	93.7%	93.4%
Black/African-American	4.6%	2.1%	2.0%
Native American/Native Aleutian Islander/Eskimo	1.6%	1.6%	1.6%
Native Hawaiian or Pacific Islander	.1%	0.0%	.2%
Asian	.6%	.3%	0.0%
Other/Declined to State/Don't Know	3.0%	2.3%	2.8%
Education (% with Bachelor's degree or higher) ^{a, b}	37.1%	44.3%	46.3%
Marital Status (% Married)	70.6%	73.8%	73.8%
Current Work Status (% yes)	52.5%	52.5%	53.0%
Chronic Conditions (mean/SD) ^{a, b}	1.69 (1.73)	1.88 (1.64)	1.87(1.57)
0 conditions	33.0%	23.0%	21.7%
1 condition	23.0%	25.9%	25.7%
2 or more conditions	44.0%	51.1%	52.6%

^a: Difference between MIDUS II full sample and NSDE II subsample ($p < .05$)

^b: Difference between MIDUS II full sample and Biomarker subsample ($p < .05$)

^c: Difference between NSDE II subsample and Biomarker subsample ($p < .05$)

Table 2:

Cortisol profiles and age predicting inflammation risk burden score (n = 451)

	<i>Model 1</i>		<i>Model 2</i>	
	Unstandardized Coefficients <i>b</i> (<i>SE</i>)	Standardized Coefficients β (<i>SE</i>)	Unstandardized Coefficients <i>b</i> (<i>SE</i>)	Standardized Coefficients β (<i>SE</i>)
Intercept	.024(.071)	.024(.071)	.182(.199)	.098(.111)
Age	.000(.007)	.006(.075)	-.003(.006)	-.032(.074)
Dysregulated CP (ref = Normative)	.189(.170)	.189(.170)	.152(.146)	.153(.146)
Variable CP (ref = Normative)	.078(.118)	.079(.118)	.094(.110)	.094(.110)
Age *Dysregulated CP (ref = Age *Normative)	.014(.012)	.163(.140)	.024(.011)*	.272(.131)*
Age * Variable CP (ref = Age *Normative)	.013(.010)	.150(.119)	.012(.010)	.139(.115)
Sex (ref = Female)			-.151(.101)	-.151(.101)
Race (ref = White)			.306(.172)	.306(.172)
Education			-.016(.020)	-.039(.049)
W2 Chronic Conditions			.021(.034)	.035(.056)
W2 History of Smoking (ref = Yes)			-.219(.097)*	-.219(.097)*
W2 Body Mass Index			.062(.007)***	.328(.038)***
W2 Medication Use (ref = None)			.024(.102)	.024(.102)

* p < .05

** p < .01

*** p < .001

CP = cortisol profile

Table 3:

Cortisol profiles and age predicting change in functional limitations (n = 799)

	<i>Model 1</i>		<i>Model 2</i>	
	Unstandardized Coefficients <i>b</i> (SE)	Standardized Coefficients β (SE)	Unstandardized Coefficients <i>b</i> (SE)	Standardized Coefficients β (SE)
Intercept	1.815(.040)***	.020(.046)	2.084(.090)***	.193(.061)**
Age	.025(.003)***	.330(.045)***	.012(.003)***	.156(.036)***
Dysregulated CP (ref = Normative)	.015(.084)	.009(.097)	.015(.067)	.017(.078)
Variable CP (ref = Normative)	-.075(.062)	-.086(.073)	-.033(.046)	-.039(.054)
Age *Dysregulated CP (ref = Age * Normative)	.015(.006)*	.207(.084)*	.014(.005)**	.182(.069)**
Age * Variable CP (ref = Age * Normative)	.007(.006)	.098(.077)	.008(.005)	.102(.062)
Sex (ref = Female)			-.094(.043)*	-.111(.051)*
Race (ref = White)			-.019(.090)	-.023(.105)
Education			-.025(.010)**	-.071(.028)*
W2 Chronic Conditions			.038(.016)*	.069(.031)*
W2 Functional Limitations			.588(.042)***	.487(.035)***
W2 History of Smoking (ref = Yes)			-.163(.045)***	-.190(.053)***
W2 Body Mass Index			.021(.005)***	.128(.031)***
W2 Medication Use (ref = None)			-.042(.045)	-.045(.053)

* p<.05

** p<.01

*** p<.001

CP = cortisol profile

Table 4.

Comparison of cortisol profiles and commonly used operationalizations of diurnal cortisol

Outcome	Age*Cortisol Profiles	Age*AUC_G	Age*CAR	Age*DCSP
Inflammation risk burden score	<i>No covariates:</i> $p = .243$ <i>Covariates:</i> $p = .043$	<i>No covariates:</i> $p = .20$ <i>Covariates:</i> $p = .071$	<i>No covariates:</i> $p = .276$ <i>Covariates:</i> $p = .232$	<i>No covariates:</i> $p = .345$ <i>Covariates:</i> $p = .756$
W3 functional limitations	<i>No covariates:</i> $p = .017$ <i>Covariates:</i> $p = .009$	<i>No covariates:</i> $p = .148$ <i>Covariates:</i> $p = .158$	<i>No covariates:</i> $p = .191$ <i>Covariates:</i> $p = .105$	<i>No covariates:</i> $p = .016^*$ <i>Covariates:</i> $p = .113$

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