

# Associations Between Cognitive Function and Naturally Occurring Daily Cortisol During Middle Adulthood: Timing Is Everything

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**Objectives.** We examined associations between cognitive function (CF) and the naturally occurring daily cortisol levels using data from the Midlife in the United States survey and the National Study of Daily Experiences.

**Methods.** A national sample of 1,500 (mean age = 57 years; range = 33–84, 56% female) completed a phone-based battery of cognitive tasks and 3–6 months later provided saliva samples upon waking, 30 min after waking, at lunch time, and at bedtime on 4 consecutive days.

**Results.** Higher CF, particularly executive function, was associated with healthier daily cortisol profiles, including a steeper diurnal cortisol slope, higher morning cortisol levels, and lower afternoon and evening cortisol levels.

**Discussion.** The results indicate that better CF is associated with healthier profiles of naturally occurring cortisol and underscore the importance of the timing of cortisol sampling.

**Key Words:** Cognitive function—Diurnal cortisol rhythm—Salivary cortisol.

SINCE the discovery of cortisol receptors in the brain (McEwen, Weiss, & Schwartz, 1968), researchers have been interested in understanding how cortisol is associated with cognitive function (CF). Although much of the research examining links between cortisol and CF has relied on the experimental manipulation of cortisol levels (Lupien & McEwen, 1997; Lupien et al., 2005), considerable efforts have been devoted to examining links between naturally occurring cortisol levels and CF (e.g., Seeman, McEwen, Singer, Albert, & Rowe, 1997). The diurnal rhythm of cortisol is garnering considerable empirical attention for its utility as an indicator of not only stress but also general neuroendocrine function and its potential links to physical, emotional, and cognitive health (Adam & Kumari, 2009). The current study was conducted to examine associations between CF and the dynamics of daily cortisol across the adult life span in a national sample of adults.

Cortisol is a hormone secreted by the hypothalamic–pituitary–adrenal (HPA) axis. It is released in response to stress (Dickerson & Kemeny, 2004) but is more than just a product of the stress response and is a widely used indicator of general neuroendocrine/HPA axis health (Hellhammer et al., 2007; Miller, Chen, & Zhou, 2007). Cortisol exhibits a diurnal pattern, reaching its peak within an hour after waking and declining thereafter, until reaching a nadir at approximately midnight (Kirschbaum & Hellhammer, 1989; Pruessner et al., 1997). The initial rise referred to as

the morning rise (MR) and the decline thereafter as the diurnal cortisol slope (DCS; Adam & Kumari, 2009; Cohen et al., 2006). Robust MR and DCS slopes are thought to reflect a healthy HPA axis function and flattened profiles being unhealthy (Adam & Kumari, 2009; Stone et al., 2001).

Additional evidence for patterns of healthy HPA axis function comes from a recent meta-analysis by Miller and colleagues (2007) considering associations between chronic stress and HPA axis dysregulation. The authors found that chronic stress-related HPA dysregulation manifests as a flatter MR and DCS and higher overall total cortisol output. Such dysregulation is also evidenced in lower morning cortisol levels and higher afternoon/evening levels. These convergent patterns suggest that there are certain characteristics of diurnal cortisol indicative of healthy HPA axis function (i.e., steeper MR and DCS, higher morning levels, and lower afternoon/evening levels), which can inform hypotheses associations between cortisol and other constructs of theoretical interest.

CF is one construct that has been linked to cortisol and received considerable empirical attention. Cortisol is thought to have proximal effects on CF by interfering with neural transmission and subsequent behavioral performance (Lupien & Lapage, 2001; Wolf, 2003; however, see Roozendaal, 2002) and more durable and distal effects via neuronal death from prolonged exposure to cortisol (Sapolsky, 1992). Preferential densities of cortisol receptors in the hippocampus

and frontal lobes have led researchers examining cognition–cortisol links to focus on tasks measuring episodic memory (EM), which is governed by the hippocampus (Squire, 1992), and executive function (EF), which is governed by the frontal lobes (Stuss & Knight, 2002). Although the majority of research linking cortisol to CF has used experimentation to examine how acute changes in cortisol are associated with CF (see Lupien & Lapage, 2001; Lupien & McEwen, 1997 for reviews), there is a growing body of work examining how naturally occurring cortisol levels and rhythms are associated with CF.

Flatter DCS slopes have been associated with poorer EM among older adults experiencing memory deficits and depressive symptoms (Fiocco, Wan, Weekes, Pim, & Lupien, 2006), older adults positive for the APOE- $\epsilon$ 4 allele, a known risk factor for dementia (Gerritsen, Comijs, Deeg, Penninx, & Geerlings, *in press*), and poorer EF among community-dwelling older adults (Beluche, Carrière, Ritchie, & Ancelin, 2009). For morning cortisol levels, Lupien and colleagues have shown that annual increases in 24-hr average basal cortisol levels are associated with poorer EM (Lupien et al., 1994) and smaller hippocampal volume (Lupien et al., 1998) among older adults. Similarly, Kuningas and colleagues (2007) found that higher morning cortisol levels were associated with poorer global CF, attention, and processing speed in older adults aged 85 years and older, whereas Beluche and colleagues (2009) found that higher morning cortisol levels were associated with poorer EF and EM in a community-dwelling sample of older adults. In contrast, Gerritsen and colleagues (*in press*) found that higher waking cortisol levels were associated with poorer EM performance but only among older adults carrying the APOE- $\epsilon$ 4, whereas Kalmijn and colleagues (1998) found no reliable association between morning cortisol levels and an index of global CF. Finally, regarding afternoon/evening cortisol levels, Carlson and Sherwin (1999) observed that older adults with higher afternoon levels of cortisol exhibited poorer EM performance, whereas 12-hr overnight basal cortisol levels of Seeman and colleagues (1997) were associated with poorer EM at baseline and greater declines in EM over a 2.5-year period among women. Similarly, Gerritsen and colleagues (*in press*) found that higher cortisol levels in the evening, just before bed, were associated with poorer EM performance among older adults possessing the APOE- $\epsilon$ 4 allele.

Research examining associations between the DCS, afternoon/evening cortisol levels, and CF seems to be rather consistent showing that a flatter DCS and higher levels of afternoon evening cortisol are associated with poorer CF. Findings regarding morning cortisol are mixed, possibly due to the timing of the cortisol assessments. Basal levels reported by Lupien were the average of samples taken over a 24-hr period reflecting average cortisol output over a given time period that includes morning levels. Second, Kuningas and Beluche observed that higher levels of cortisol

were associated with poorer CF, but Kuningas' morning sample was taken before 11 a.m. and Beluche's was taken at least 1 hr after waking. Thus, in both studies, the samples were possibly taken after the cortisol levels were likely already starting to decline. Positive associations between CF and morning cortisol levels might be expected proximal to waking when cortisol levels are expected to be higher and increasing, whereas negative associations might be expected once levels have started to decline.

Previous research on cortisol and CF has also largely focused on levels and dynamics of cortisol being important for predicting decrements in CF, implying a particular direction of effect. More recently, researchers have considered that cortisol and CF may have a more dynamic relationship. Existing models of HPA axis function support this notion. Although cortisol is released from the adrenals and binds to receptors in the hippocampus and frontal lobes, both these brain regions also provide feedback to the hypothalamus as part of HPA axis downregulation (Lupien & Lapage, 2001). Empirical support for such bidirectional associations also exists. Lupien and colleagues (2005) showed that evidence of children's CF, with respect to making emotional attributions, significantly predicted morning basal cortisol levels. Using prospective longitudinal data, Power, Li, and Hertzman (2008) showed that lower childhood CF was predictive of a flatter DCS forty-five years later during adulthood. Furthermore, Applehans and Luecken (2006) found that EF was associated with diminished cortisol reactivity to threat cues.

Recent theoretical development regarding CF as an important predictor of health complements these empirical findings. Williams, Suchy, and Rau (2009) have reviewed evidence linking individual differences in CF, particularly EF, to better self-regulation, suggesting that EF is a potentially important characteristic for understanding differential exposure, reactivity, and recovery from stress. Similarly, Gottfredson and Deary (2004) have suggested that CF, particularly intellectual abilities related to EF, may be associated with better health and longevity because of increased skills useful in adaptation and preventing chronic disease. Here, CF may be beneficial for adapting to stressful situations and tempering immediate and prolonged reactions, and this may be reflected in healthier naturally occurring cortisol profiles. Together, this evidence supports potential bidirectional links between CF and cortisol, however, evidence for such associations during adulthood and old age, and considering both EF and EM remains scant.

### *The current study*

The current study was conducted to examine associations between CF and naturally occurring cortisol levels obtained 3–6 months later using a national sample of adults ranging from 33 to 84 years of age. First, we examined associations between CF and both the MR and the DCS as well as cortisol levels at each of four specific sampling occasions (upon

waking, 30-min postwaking, before lunch, and before bed). Second, given the links between cortisol and the frontal lobes and hippocampus, we examined whether EF and EM function were each uniquely related to naturally occurring daily cortisol. Consistent with previous literature, we hypothesized that higher CF would be associated with MR and DCSs. Similarly, higher CF would be associated with higher cortisol levels upon waking and 30-min postwaking but lower levels before lunch and bed. Finally, given links between cortisol receptors in both the frontal lobes and the hippocampus, we expected EF and EM function to both exhibit unique associations with cortisol.

## METHODS

### Participants

The Midlife in the United States (MIDUS) II survey is comprised of 4,975 respondents (age range = 33–84 years). Of those participants, 4,445 completed the telephone cognition assessment and 2,022 completed the 8-day National Study of Daily Experiences (NSDE; 1,736 participants in the NSDE provided cortisol assessments). A total of 1,500 participants in MIDUS completed both the telephone cognition assessment and the NSDE cortisol sampling protocol and serve as the sample for the current study. The mean age of the sample was 57 years ( $SD = 12$ , range = 33–84), and 56% of the respondents were female. The participants were fairly well educated, with 30% having received a high school diploma or less, 51% having completed some college coursework or obtaining a bachelor's degree, and 19% having pursued education beyond a bachelor's degree. The current sample is slightly older, more educated, in better health, and had higher CF scores ( $ps < .05$ ) than the full parent sample; however, these differences were of extremely small effect size ( $R^2s < 1\%$ ).

### Procedure

Participants first completed the telephone cognitive assessment, and approximately three to six months later, they were enrolled in the NSDE. Once enrolled in the NSDE, they completed short telephone interviews about their daily experiences and emotions. The interviews lasted approximately 20 min and were conducted on eight consecutive evenings. Participants also provided four salivary cortisol samples on Days 2–5 of the study. Data collection for the 8-day interview protocol consisted of separate “flights” of 30 participants, with the start day of the interviews being staggered across the day of the week to control for the possible confounding between day of study and day of week. Participants received \$45 for completing the study protocol.

### Assessment of Salivary Cortisol

Respondents received a Home Saliva Collection Kit one week prior to their initial phone call. Saliva was obtained

Table 1. Descriptive Statistics of Cortisol Samples and Sampling Times

Sample	Cortisol (nmol/L)		Time	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Waking	15.03	7.08	6:42 a.m.	81 min
30 min postwaking	20.64	9.25	7:23 a.m.	84 min
Before lunch	7.52	4.71	12:42 p.m.	76 min
Before bed	3.67	4.34	10:30 p.m.	82 min

using salivette collection devices (Sarstedt, Nümbrecht, Germany). Sixteen numbered and color-coded salivettes and instructions were included in the collection kit. In addition to written instructions, telephone interviewers reviewed the procedures and answered any of the participant's questions. On Days 2 through 5, respondents provided four saliva samples per day that were later assayed for cortisol. Saliva was collected immediately upon waking, 30 min after waking, before lunch, and at before bed (Table 1). Data on the exact time respondents provided each saliva sample were obtained from the nightly telephone interviews as well as on a paper–pencil log sent with the collection kit. In addition, approximately 25% of the respondents ( $N = 430$ ) received a “smart box” containing a computer chip that recorded the time respondents opened and closed the box. Correlations between self-reported times across collection occasions were all above .9. Correlations between self-reported times and times obtained from the “smart box” ranged from .75 for the evening occasion to .95 for the morning occasion.

Upon completion of the saliva sampling procedure, the salivettes were shipped to the MIDUS Biological Core at the University of Wisconsin, where they were stored at  $-60\text{ }^{\circ}\text{C}$ . For analysis, salivettes were thawed and centrifuged at 3,000 rpm for 5 min, yielding a clear fluid with low viscosity. Cortisol concentrations were quantified with a commercially available luminescence immunoassay (IBL, Hamburg, Germany), with intra-assay and interassay coefficient of variations below 5% (Dressendorfer, Kirschbaum, Rohde, Stahl, & Strasburger, 1992). Almeida, McGonagle, and King (2009) and Almeida, Piazza, and Stawski (2009) provide additional information regarding the assessment of cortisol in this study.

### Cognitive Function

CF was assessed in a telephone interview using the Brief Test of Adult Cognition by Telephone (BTACT; Lachman & Tun, 2008; Tun & Lachman, 2006). The BTACT assesses key fluid cognitive domains, including episodic verbal memory (immediate and delayed recall; Rey, 1964), working memory span (backward digit span; Wechsler, 1997), EF (verbal fluency; Lezak, 1995), reasoning (letter series; Salthouse, & Prill, 1987; Schaie, 1996), and speed of processing (backward counting). A total CF score was obtained by summing the scores on the immediate and delayed recall

tasks and converting this to a  $z$  score. This standardized memory score was then averaged with  $z$  scores for the remaining four tests to compute an overall composite score. Factor analytic work also supports a two-factor model, broadly representing EF and EM factors (Lachman, Agrigoroaei, Murphy, & Tun, in press). EF was a  $z$ -score composite of the digit span backward, category fluency, number series, and backward counting tasks, and EM was a  $z$ -score composite of the immediate and delayed recall tasks.

### Covariates

**Smoking Status.**—Smoking status was determined by respondents identifying themselves as routine smokers as well as the number of cigarettes an individual reported consuming on a daily basis during the study period. Individuals who did not identify themselves as smokers or who did not report smoking any cigarettes during the study protocol were classified as nonsmokers. A dichotomous variable was used to index smoking status.

**Medication Use.**—Participants reported their current use of medications known to influence cortisol, including steroid inhalers, steroid medications, medications containing cortisone, birth control pills, other hormonal medications, and/or antidepressant/antianxiety medications (Granger, Hibbel, Fortunato, & Kapelewski, 2009). A dichotomous variable was created to indicate whether a participant reported taking any of the aforementioned medications currently.

**Self-rated Health.**—Participants rated their physical health on a 5-point scale (1 = poor, 2 = fair, 3 = good, 4 = very good, 5 = excellent).

**Data Reduction.**—Cortisol data from 27 participants (1.8% of the sample) identified as shift workers were excluded. Furthermore, cortisol samples greater than 60 nmol/L ( $n = 331$ , 1.4%) and for which corresponding collection times were missing ( $n = 220$ , <1%) were also excluded. Thus, the final analytic sample comprised 1,473 participants providing 23,017 useable saliva samples.

### Analytic Strategy

We modeled the diurnal rhythm of salivary cortisol using a three-level, piecewise multilevel model, which allowed us to explicitly model variability in cortisol levels across the day, across days, as well as across people (Equation 1). Time since the second cortisol sample is used as the time metric for this model, so the inflection point for the piecewise model is set at the highest level of cortisol typically observed in these data.

#### Level 1

$$\text{Cortisol}_{odi} = \beta_{0di} + \beta_{1di}\text{MR}_{1odi} + \beta_{2di}\text{DCS}_{2odi} + \beta_{3di}\text{DCS} \times \text{DCS}_{3odi} + e_{odi} \quad (1)$$

#### Level 2

$$\beta_{0di} = \delta_{00i} + \delta_{01i}\text{Wake-Up Time}_{di} - \text{MeanWake-Up Time}_{di} + u_{0di}$$

$$\beta_{1di} = \delta_{10i} + \delta_{11i}\text{Wake-Up Time}_{di} - \text{MeanWake-Up Time}_{di} + u_{1di}$$

$$\beta_{2di} = \delta_{20i} + \delta_{21i}\text{Wake-Up Time}_{di} - \text{MeanWake-Up Time}_{di} + u_{2di}$$

$$\beta_{3di} = \delta_{30i} + \delta_{31i}\text{Wake-Up Time}_{di} - \text{MeanWake-Up Time}_{di}$$

#### Level 3

$$\delta_{00i} = \gamma_{000} + \gamma_{001}\text{MeanWake-Up Time}_{di} + \gamma_{002}\text{Age}_{di} + \gamma_{003}\text{Sex}_{di} + \gamma_{004}\text{Education}_{di} + \gamma_{005}\text{Cognitive Function}_{di} + \gamma_{006}\text{Smoker}_{di} + \gamma_{007}\text{MedUser}_{di} + \gamma_{008}\text{Health}_{di} + v_{00i}$$

$$\delta_{10i} = \gamma_{100} + \gamma_{101}\text{MeanWake-Up Time}_{di} + \gamma_{102}\text{Age}_{di} + \gamma_{103}\text{Sex}_{di} + \gamma_{104}\text{Education}_{di} + \gamma_{105}\text{Cognitive Function}_{di} + \gamma_{106}\text{Smoker}_{di} + \gamma_{107}\text{MedUser}_{di} + \gamma_{108}\text{Health}_{di} + v_{10i}$$

$$\delta_{20i} = \gamma_{200} + \gamma_{201}\text{MeanWake-Up Time}_{di} + \gamma_{202}\text{Age}_{di} + \gamma_{203}\text{Sex}_{di} + \gamma_{204}\text{Education}_{di} + \gamma_{205}\text{Cognitive Function}_{di} + \gamma_{206}\text{Smoker}_{di} + \gamma_{207}\text{MedUser}_{di} + \gamma_{208}\text{Health}_{di} + v_{20i}$$

$$\delta_{30i} = \gamma_{300} + \gamma_{301}\text{MeanWake-Up Time}_{di} + \gamma_{302}\text{Age}_{di} + \gamma_{303}\text{Sex}_{di} + \gamma_{304}\text{Education}_{di} + \gamma_{305}\text{Cognitive Function}_{di} + \gamma_{306}\text{Smoker}_{di} + \gamma_{307}\text{MedUser}_{di} + \gamma_{308}\text{Health}_{di}$$

According to Equation (1), at Level 1, the cortisol level at occasion  $o$ , on day  $d$ , for person  $i$ , is a function of an intercept, which correspond to their cortisol level at the time they provided their second sample ( $\beta_{0di}$ ), and three slope parameters. The first slope parameter ( $\beta_{1di}$ ) reflects the MR and captures the rate of change between the first and second sampling occasions as a function of the amount of time that elapsed between them. The last two slope parameters ( $\beta_{2di}$  and  $\beta_{3di}$ ) represent the DCS. Linear and quadratic terms were included to capture both the rate of decline and the deceleration in the rate of decline in cortisol throughout the day as a function of the amount of time that has elapsed since the time of the second sample. Thus, all slope parameters can be interpreted as the rate of change in cortisol per hour from the time the second sample was taken.

At Level 2, the Level 1 intercept and slope parameters become outcomes, and each person's intercept, MR, and afternoon decline parameters on a given day are now predicted as a function of each person's average intercept ( $\delta_{00i}$ ) and slope ( $\delta_{10i}$ ,  $\delta_{20i}$ , and  $\delta_{30i}$ ) across the 4 days as well as a person-centered time-varying covariate, wake-up time, which allows for systematic day-to-day coupling between when one wakes up and the magnitude of the slope parameters characterizing their daily cortisol rhythm.

At Level 3, the Level 2 parameters become outcomes, and each person's average intercept, MR, and DCS slopes across the days are given as a function of the sample average intercept ( $\gamma_{000}$ ) and slope ( $\gamma_{100}$ ,  $\gamma_{200}$ , and  $\gamma_{300}$ ) parameters.

Table 2. Multilevel Model Predicting Morning Rise and Diurnal Cortisol Slope

	Intercept			Morning rise		
	Estimate	SE	<i>p</i>	Estimate	SE	<i>p</i>
Sample average	17.33	1.10	<.01	-6.55	1.41	<.01
Wake-up time (WP)	-1.20	0.18	<.01	1.11	0.34	<.01
Wake-up time (BP)	-0.72	0.20	<.01	0.73	0.29	<.01
Age	0.11	0.02	<.01	-0.07	0.03	<.01
Sex	-0.48	0.46	0.30	-2.17	0.64	<.01
Education (reference = high)						
Low	0.15	0.72	0.84	-1.45	0.95	0.31
Middle	0.39	0.56	0.48	-1.35	0.98	0.22
Cognitive function	0.47	0.25	0.09	-0.16	0.07	0.04
Smoking status	0.52	0.86	0.54	-2.03	1.17	0.08
Medication user	-0.31	0.51	0.55	-0.05	0.70	0.94
Self-rated health	0.94	0.25	<.01	-0.84	0.33	0.01
	Diurnal cortisol slope (linear)			Diurnal cortisol slope (quadratic)		
	Estimate	SE	<i>p</i>	Estimate	SE	<i>p</i>
Sample average	-2.00	0.25	<.01	0.08	0.01	<.01
Wake-up time (WP)	-0.07	0.05	0.16	0.01	0.00	0.02
Wake-up time (BP)	-0.05	0.05	0.33	0.01	0.00	<.01
Age	-0.01	0.00	0.02	0.0004	0.0001	0.02
Sex	-0.13	0.11	0.20	0.01	0.01	0.15
Education (reference = high)						
Low	-0.18	0.16	0.28	0.01	0.01	0.19
Middle	-0.11	0.13	0.40	0.01	0.01	0.40
Cognitive function	-0.15	0.06	0.01	0.01	0.00	0.03
Smoking status	0.28	0.20	0.19	-0.01	0.01	0.09
Medication user	0.14	0.12	0.25	-0.01	0.01	0.36
Self-rated health	-0.28	0.06	<.01	0.01	0.00	<.01

Note: WP = within person, BP = between person, sex (1 = female), smoking status (1 = smoker), medication user (1 = used medications). Model was centered at the time of the second cortisol sample.

Person-level predictors are also included at this level of analysis and are included to model differences in the intercept, MR, and DCS slopes as a function of individual differences in wake-up time ( $\gamma_{001}$ ,  $\gamma_{101}$ ,  $\gamma_{201}$ , and  $\gamma_{301}$ ), age ( $\gamma_{002}$ ,  $\gamma_{102}$ ,  $\gamma_{202}$ , and  $\gamma_{302}$ ), sex ( $\gamma_{003}$ ,  $\gamma_{103}$ ,  $\gamma_{203}$ , and  $\gamma_{303}$ ), education ( $\gamma_{004}$ ,  $\gamma_{104}$ ,  $\gamma_{204}$ , and  $\gamma_{304}$ ), CF ( $\gamma_{005}$ ,  $\gamma_{105}$ ,  $\gamma_{205}$ , and  $\gamma_{305}$ ), whether one is a smoker ( $\gamma_{006}$ ,  $\gamma_{106}$ ,  $\gamma_{206}$ , and  $\gamma_{306}$ ), took medications that would confound cortisol assessments ( $\gamma_{007}$ ,  $\gamma_{107}$ ,  $\gamma_{207}$ , and  $\gamma_{307}$ ), and their self-rated health ( $\gamma_{008}$ ,  $\gamma_{108}$ ,  $\gamma_{208}$ , and  $\gamma_{308}$ ). All predictors were entered simultaneously, so the resulting estimates are partialled for the other predictors in the model.

This model also contains a number of variance components.  $v_{00i}$ ,  $v_{10i}$ , and  $v_{10i}$  are Level 3 variance components and reflect individual differences in the intercept, MR, and linear DCS parameters, respectively.  $u_{0di}$ ,  $u_{1di}$ , and  $u_{2d}$  are Level 2 variance components and reflect within-person, day-to-day variability in the intercept, MR, and DCS slopes. Finally,  $e_{odi}$  is the Level 1, or residual variance, and reflects variability in cortisol levels within-persons across the day (within-day).

## RESULTS

Table 2 presents the results of the model (Equation (1)) estimating associations between CF and cortisol slopes covarying for wake-up time, age, sex, education, smoking status, medication use, and self-rated health. The intercept

of the model reflects the levels of cortisol at the time of the second sampling occasion (17.33 nmol/L). Since the model was centered at the time of the second cortisol sample, the MR estimate is negative and indicates that cortisol levels increased 6.55 nmol/L per hour elapsed between the first two samples. The DCS reflects the rate of change in cortisol levels for each hour since the time of the second sample. Here, the linear DCS slope parameter indicates that cortisol levels initially decreased at a rate of 2.00 nmol/L per hour initially, and the quadratic DCS effect indicates that the rate of decline was decelerating at a rate of .08 nmol/L per hour thereafter.

We observed a number of significant associations between our covariates and the parameters of the cortisol slopes. The within-person effect of wake-up time was significant indicating that on days people woke up later than usual, their cortisol levels at the second sampling occasion were significantly higher than usual, their MR was flatter than usual, and they exhibited a slightly greater rate of deceleration of the DCS ( $ps < .05$ ). Similarly, individual differences in wake-up time were associated with these parameters as well indicating that people who, on average, woke up later possessed lower cortisol levels at the second sampling occasion, a flatter MR, and a greater rate of deceleration in their DCS ( $ps < .01$ ). We also observed age differences in these parameters such that older adults had higher

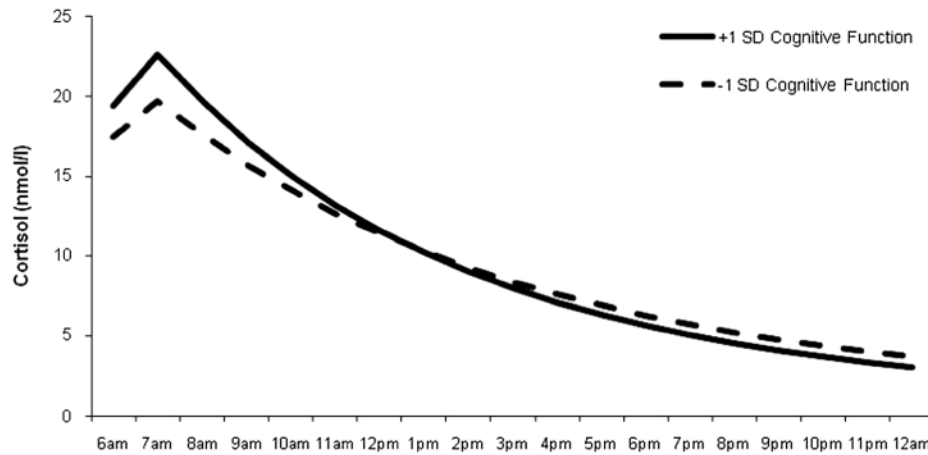


Figure 1. Diurnal cortisol rhythm as a function of cognitive function.

levels of cortisol at the second sampling occasion, a steeper MR, and steeper a DCS with a greater degree of deceleration ( $p < .01$ ). Women exhibited significantly steeper MR and DCS than did men ( $p < .05$ ). Smokers exhibited a steeper MR and a flatter DCS than did nonsmokers ( $p < .05$ ). Participants who reported better health had a steeper MR and DCS. Neither medication use nor education was significantly associated with any of the slope parameters. Importantly, higher CF was associated with slightly higher levels of cortisol at the time of the second sampling occasion ( $p = .09$ ) and a steeper DCS ( $p < .05$ ). Alternatively, lower functioning individuals exhibited lower cortisol levels at the time of the second sampling occasion and a flatter slope profile throughout the afternoon and into the evening (see Table 2 and Figure 1).

Next, we considered how CF was associated with cortisol levels at each sampling occasion. This was done by simply restricting the statistical model shown in Equation (1) to focus on each cortisol sampling occasions iteratively (i.e., four 2-level models), incorporating the same predictors and covariates. This allowed us to consider the specificity of

the association between CF and cortisol levels at the four occasions across the day (Figure 2). CF was associated with significantly higher levels of cortisol upon waking (estimate = .38,  $SE = .19$ ,  $p = .05$ ) and marginally at 30 min postwaking (estimate = .47,  $SE = .25$ ,  $p = .09$ ) but lower levels of before lunch (estimate = -.25,  $SE = .13$ ,  $p = .04$ ) and bed (estimate = -.26,  $SE = .11$ ,  $p = .01$ ).

Next, we considered whether individual differences in EF and EM were each uniquely associated with the parameters of the diurnal rhythm of cortisol as well as cortisol levels at each of the sampling occasions. To do this, we reestimated the models used for the previous set of analyses but entered EF and EM as simultaneous independent predictors. Higher EF was associated with a steeper DCS (estimate = -.17,  $SE = .07$ ,  $p = .01$ ) and a larger quadratic slope, reflecting a greater rate of deceleration in the DCS (estimate = .008,  $SE = .003$ ,  $p = .02$ ). No significant associations emerged between EM and the MR or DCS.

A similar pattern emerged when considering EF and EM as predictors of cortisol levels at each sampling occasion

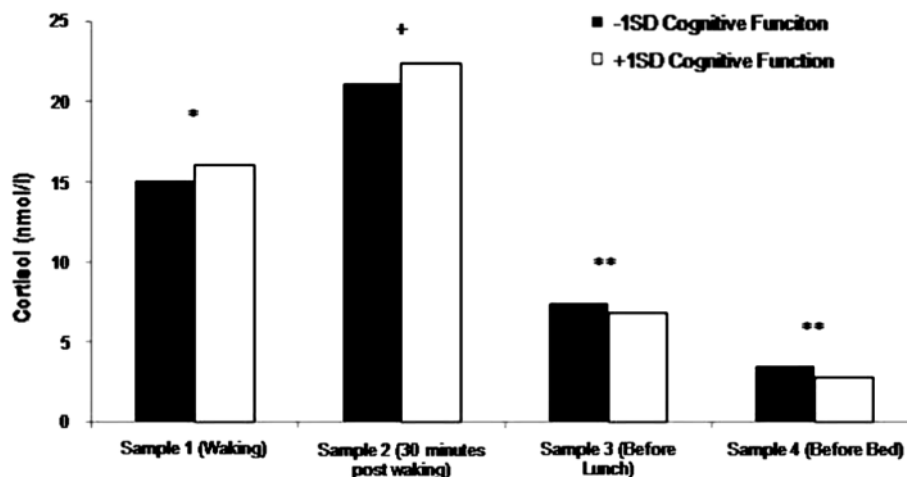


Figure 2. Cortisol levels as a function of cognitive function ( $+p < .10$ ,  $*p < .05$ ,  $**p < .01$ ).

Table 3. Multilevel Models Predicting Cortisol Levels at Each Sampling Occasion

	Sample 1 (wake up)			Sample 2 (30 min postwaking)		
	Estimate	SE	<i>p</i>	Estimate	SE	<i>p</i>
Intercept	14.15	0.89	<.01	17.72	1.15	<.01
Wake-up time (WP)	-0.11	0.14	0.47	-1.38	0.21	<.01
Wake-up time (BP)	-0.21	0.15	0.15	-0.48	0.20	0.02
Age	0.58	0.19	<.01	1.45	0.25	<.01
Sex	1.63	0.37	<.01	0.32	0.50	0.51
Education (reference = high)						
Low	-1.33	0.54	0.02	-0.08	0.73	0.92
Middle	-0.44	0.44	0.32	0.24	0.57	0.68
Executive function	0.24	0.23	0.29	0.34	0.32	0.28
Episodic memory	0.03	0.20	0.87	0.02	0.25	0.92
Smoking status	-0.41	0.67	0.54	0.56	0.87	0.52
Medication user	-0.47	0.38	0.22	-0.53	0.52	0.30
Self-rated health	0.41	0.19	0.03	1.03	0.25	<.01
	Sample 3 (before lunch)			Sample 4 (before bed)		
	Estimate	SE	<i>p</i>	Estimate	SE	<i>p</i>
Intercept	7.81	0.60	<.01	4.70	0.61	<.01
Wake-up time (WP)	-0.03	0.09	0.74	-0.02	0.07	0.77
Wake-up time (BP)	0.18	0.11	0.10	-0.11	0.10	0.26
Age	0.89	0.13	<.01	0.40	0.11	<.01
Sex	0.93	0.24	<.01	0.23	0.23	0.31
Education (reference = high)						
Low	-0.43	0.36	0.23	-0.11	0.34	0.74
Middle	0.15	0.29	0.61	-0.03	0.26	0.90
Executive function	-0.26	0.13	0.05	-0.25	0.12	0.04
Episodic memory	0.00	0.13	0.99	-0.16	0.12	0.17
Smoking status	1.59	0.45	<.01	0.49	0.34	0.15
Medication user	0.09	0.26	0.72	0.32	0.24	0.20
Self-rated health	-0.20	0.12	0.11	-0.36	0.12	<.01

Note: WP = within person, BP = between person, sex (1 = *female*), smoking status (1 = *smoker*), medication user (1 = *used medications*).

(Table 3). Higher EF was associated with significantly lower cortisol levels before lunch (estimate =  $-.26$ ,  $SE = .13$ ,  $p = .05$ ) and before bed (estimate =  $-.25$ ,  $SE = .12$ ,  $p = .05$ ). Once again, none of the effects with EM were statistically significant.

#### Age Differences in Cognition–Cortisol Associations

We also explored age differences in the associations between our indices of cognition and cortisol by adding the age by cognition interaction as a Level 3 predictor to Equation (1). None of the interactions were significant for either the CF composite or the EF and EM composites ( $ps > .16$ ). We also explored whether age differences might be most evident in the oldest segment of the sample by testing non linear age effects and similarly found no evidence to support age effects ( $ps > .33$ ).

#### DISCUSSION

The current study produced a number of findings. First, higher levels of CF were associated with healthier daily cortisol profiles, including a steeper DCS, higher cortisol levels upon waking and 30 min postwaking, and lower cortisol levels before lunch and bedtime, three to six months later. Second, the observed effects of CF on cortisol were largely specific to individual differences in EF as EM showed no

significant unique associations with any index of cortisol. Third, no significant age differences in the associations between CF and cortisol were observed. Furthermore, our confidence in these findings is bolstered by the emergence of these significant effects after covarying for relevant confounding factors, including sex, education, smoking status, medication use, and self-reported health. Finally, the current results underscore the importance of the timing of cortisol assessments and how cortisol levels across the day might be associated with other variables of theoretical interest.

As expected, higher levels of CF were associated with a steeper DCS. This result is consistent with previous studies showing a similar association between steeper DCS and higher CF among older adults (Beluche et al., 2009; Fiocco et al., 2006; Gerritsen et al., *in press*). The studies by Fiocco and Gerritsen, however, showed a flatter DCS being associated with poorer EM, whereas Beluche and our study observed associations specific to indices of EF. The sample employed by Fiocco self-identified as having memory deficits and suffered from a number of depressive symptoms, whereas Gerritsen only observed the association among older adults possessing a risk factor for memory impairment and dementia, APOE- $\epsilon 4$ . Thus, clinical or disease-related processes could be a confounding factor. Our results echo

those of Beluche who observed higher EF being associated with a steeper DCS among a community-dwelling sample of older adults and extend them to show similar associations in a large national sample of midlife and older adults.

Contrary to expectations, CF was not significantly related to the magnitude of the MR. One reason for the lack of association could be that only two samples were used to capture the MR. Other research examining the MR has employed more intensive sampling of cortisol levels proximal to waking (e.g., Fries, Dettenborn, & Kirschbaum, 2009) and observed a more complex pattern than we could. One study that has examined the relationship between the MR and CF did so among younger adults and failed to observe an association (Pruessner et al., 2007). Thus, although the existing body of research is small, there is little evidence to suggest that individual differences in CF are reliably associated with the MR. The differential pattern of associations between CF, the MR, and DS is consistent with recent reviews, suggesting that the MR and DCS may be distinct phenomena reflecting different underlying biological/neuroendocrine processes (e.g., Clow, Thorn, Evans, & Hucklebridge, 2004) and merits further empirical consideration to better understand factors associated with each.

Associations among CF and cortisol levels at each of sampling occasion revealed a complex, yet clear, set of findings. Higher levels of CF were associated with higher cortisol levels upon waking and 30 min postwaking but lower levels of cortisol before lunch and bed. These results are consistent with previous research showing higher morning cortisol levels and lower afternoon and evening cortisol levels being associated with higher CF (Beluche et al., 2009; Carlson & Sherwin, 1999; Gerritsen et al., in press). There is, however, research showing that higher morning cortisol levels are associated with lower CF (Kalmijn et al., 1998; Kuningas et al., 2007). These studies sampled cortisol in the morning but after the MR had occurred, and cortisol levels would have likely started declining. Thus, in terms of the timing of cortisol samples and their expected association with CF, a simple distinction between a.m. and p.m. seems a bit too gross. A positive association between cortisol levels and CF might be expected within the first hour of waking when cortisol levels are expected to be higher and increasing. Once cortisol levels start to decline after reaching the zenith, associations might become negative. Together, these results suggest that one important area of future research could be identifying how and when CF and cortisol levels should be associated depending on the timing of the cortisol sampling.

When considering how individual differences in EF and EM were associated with the MR, DCS, and cortisol levels at each sampling occasion, we found that the associations were specific to EF. Higher levels of EF were associated with a steeper DCS and lower cortisol levels before lunch and bed. These results differ from the findings using the CF composite in that EF was not significantly associated with

cortisol levels for either of the morning samples. The associations between the CF composite and morning cortisol levels were not particularly robust, and splitting this composite into the EF and EM composites may have come at the expense of reliability. The significant findings are, however, consistent with previous research showing higher EF among older adults with a steeper DCS and lower evening cortisol levels (Li et al., 2006) and extends this research to show an association that is observable in a national sample of midlife and older adults.

Our failure to observe associations between EM and cortisol is inconsistent with previous findings among aging samples (Carlson & Sherwin, 1999; Gerritsen et al., in press; Li et al., 2006) but could be due to differences in the tasks used to assess EM or differences in the sample composition. Individual differences in EM may be more discriminating during old age when age- and disease-related processes reflected in EM and hippocampal function are more prevalent as compared with midlife. Furthermore, more generally, MIDUS was designed as a study of midlife health and well-being. As such, the relative undersampling of older adults may have worked against us for detecting age differences in cognition–cortisol associations between middle age and very old adults. Nonetheless, these results suggest that DCS and cortisol levels across the day are reliably associated with EF but that the associations may depend on the time of day.

Our results are also consistent with recent theoretical accounts, suggesting that CF, and in particular EF, is an important predictor of neuroendocrine/HPA function (Power et al., 2008) and health more broadly (Gottfredson & Deary, 2004; Williams et al., 2009). Although individual differences in EF were predictive of healthier diurnal cortisol profiles, the mechanism(s) underlying this association is unclear. Williams and colleagues have argued that EF is implicated in self-regulation, including reactivity and recovery from stress. Thus, one explanation could be that individual possessing higher levels of EF may be better at tempering their reactions to stressful experiences which in turn leads them to have relatively healthier profiles of HPA axis function. Applehans and Leucken (2006) showed that higher EF was associated with dampened cortisol reactivity to threat. Similarly, using MIDUS/NSDE data, we have shown that higher CF was associated with dampened emotional reactivity to daily stressors (Stawski, Almeida, Lachman, Tun, & Rosnick, 2010). Future research aimed at understanding the mechanism(s) underlying such cognition–health linkages would be an important contribution.

### Limitations

Our estimate of the MR was defined by two cortisol samples and the DCS by three samples. More intensive sampling of cortisol throughout the day will provide better resolution of the slopes and trajectories of cortisol through



the day and allow for more precise test of how CF is associated with the MR and DCS. Recent work on the MR suggests that sampling every 15 min from waking through at least the first hour of the day may be needed to more accurately capture the complete dynamics of morning cortisol patterns (e.g., Hellhammer et al., 2007). Similarly, other large-scale studies have shown that the shape of the DCS may be more complex than the quadratic shape we presented here (e.g., Cohen et al., 2006), suggesting that more frequent sampling (hourly or bihourly) could provide a more comprehensive account of the dynamics of the DCS and reveal additional important associations. More intensive sampling regimens would also allow for a more precise triangulation when the association between cognition and cortisol changes direction.

Although we observed higher CF associated with higher morning cortisol, Hellhammer and colleagues (2004) showed hypocortisolism in the morning to be associated with better health. Hellhammer defined hypocortisolism based on 6-day work of low morning cortisol levels and a dexamethasone suppression test, which provide a much stronger basis for defining hypocortisolism. As such, we must view our results with appropriate circumspection in that although our results suggest a pattern of result reflecting relatively healthier versus relatively unhealthy patterns and profiles of cortisol, these results cannot be used as a concrete barometer of truly healthy or unhealthy and unhealthy people or hypocortisolism and hypercortisolism.

With respect to modeling the diurnal rhythm of cortisol, there is not field-wide agreement on the “correct” way to model the DCS as some research has modeled the DCS from waking (e.g., Adam, Hawkley, Kudielka, & Cacioppo, 2006), whereas others, like ourselves, have modeled the DCS from the peak or thereabouts (e.g., Kudielka, Broderick, & Kirschbaum, 2003). Some have even used both in the same study (Matthews, Schwartz, Cohen, & Seeman, 2006). A systematic examination contrasting these different methods and clear explication of the implications of each would be of tremendous benefit.

The measure of CF was designed to be used as a brief composite index for use in large-scale survey studies. It should also be noted that our index of EF comprised four indicators, whereas the index of EM comprised two indicators, which reflected different dimensions of performance on the same task. Thus, the reliability of these constructs may have affected our ability to detect associations. Future research would benefit from more thorough and systematic examinations of examining how EF, EM, and cortisol levels across the day are associated as well as consideration of additional domains of cognition would be of interest.

Finally, the current study is cross-sectional and cannot determine the direction of the association between cortisol and cognition. Although CF was assessed 3–6 months prior to cortisol, it is unlikely that the later affected the former. We, however, do not know that 3–6 months is the most

relevant window of time for durable downstream effects of cognition on cortisol. Longitudinal research tracking both over time and better understanding lead–lag relationships will be of great benefit for understanding the time course over which these dynamic relationships occur.

### Conclusions

The current study was successful in providing evidence for a complex relationship between CF and healthy profiles and levels of naturally occurring cortisol. Higher levels of CF were associated with a steeper DCS, higher levels of cortisol in the morning, proximal to waking, as well as lower cortisol levels in the afternoon and evening, and these effects were largely reflected in individual differences in EF but not EM. The results of the current study underscore the importance of the timing of cortisol sampling for understanding associations between naturally occurring daily cortisol and CF as well as other variables of theoretical interest as relatively higher levels of cortisol do not always appear to be bad.

### FUNDING

This research was supported by grants from the National Institute of Aging (P01-AG0210166 and R01-AG19239), the National Institute of Mental Health (T32-MH018904), and the Pennsylvania State University Center for Population Health and Aging.

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