Social Science & Medicine 74 (2012) 607–615

Contents lists available at SciVerse ScienceDirect

Social Science & Medicine

journal homepage: www.elsevier.com/locate/socscimed

Social strain and cortisol regulation in midlife in the US

Esther M. Friedman [a,*], Arun S. Karlamangla [b], David M. Almeida [c], Teresa E. Seeman [b]

[a] Harvard Center for Population and Development Studies, Harvard University, 9 Bow Street Cambridge, MA 02138, USA
[b] University of California, Los Angeles, CA, USA
[c] Pennsylvania State University, PA, USA

ARTICLE INFO

Article history:
Available online 13 December 2011

Keywords:
U.S.A.
Biological markers
Cortisol
Diurnal rhythm
Social relationships
Social strain
Midlife in the U.S. (MIDUS)
Stress
Family

ABSTRACT

Chronic stress has been implicated in a variety of adverse health outcomes, from compromised immunity to cardiovascular disease to cognitive decline. The hypothalamic pituitary adrenal (HPA) axis has been postulated to play the primary biological role in translating chronic stress into ill health. Stressful stimuli activate the HPA-axis and cause an increase in circulating levels of cortisol. Frequent and long-lasting activation of the HPA-axis, as occurs in recurrently stressful environments, can in the long run compromise HPA-axis functioning and ultimately affect health. Negative social interactions with family and friends may be a significant source of stress in daily life, constituting the type of recurrently stressful environment that could lead to compromised HPA functioning and altered diurnal cortisol rhythms. We use data from two waves (1995 and 2004–2005) of the Midlife in the U.S. (MIDUS) study and from the National Study of Daily Experiences (NSDE) and piecewise growth curve models to investigate relationships between histories of social strain and patterns of diurnal cortisol rhythms. We find that reported levels of social strain were significantly associated with their diurnal cortisol rhythm. These effects were more pronounced for individuals with a history of greater reported strain across a ten-year period.

Introduction

The role of social support on a variety of health outcomes is well-documented in the sociological, psychological, and epidemiological literatures (see, for example, Anderson & Armstead, 1995; House et al., 1994; Seeman, Seeman, & Sayles, 1985; Uchino, Cacioppo, & Kiecolt-Glaser, 1996). Although attention has focused more heavily on the protective influences of social contact and support, a smaller literature has also documented the negative health consequences of adverse social interactions. Stressful relationships with family and friends, for example, are related to a variety of health outcomes, including functional limitations (Newsom, Mahan, Rook, & Krause, 2008), cardiovascular disease (Coyne et al., 2001; Ewart, Taylor, Kraemer, & Agras, 1991; Orth-Gomer et al., 2000), decreased immunity (Seeman, 1996), and even mortality (Patterson & Veenstra, 2010; Seeman, Kaplan, Knudsen, Cohen, & Guralnik, 1987).

The biological mechanisms through which these health effects of social relationships are thought to operate include influences on the brain and resulting changes in physiological activity in major biological regulatory systems (DeVries, Glasper, & Detillion, 2003; Hofer, 1987, 1995; McEwen, 2007). Functional magnetic imaging (fMRI) studies have begun to illuminate the ways in which social relationships are processed by the brain, showing effects on brain processes likely to influence biological systems, including HPA function (Eisenberger et al., 2007; Taylor et al., 2008). One study found that greater reported social support was associated with diminished neuroendocrine reactivity to social stressors (Eisenberger et al., 2007).

Indeed, a growing body of evidence indicates that both positive and negative social relationships influence biology (see Seeman & McEwen, 1996; Uchino, 2006 for reviews). Community-based studies, for example, have linked social support to lower heart rate, systolic blood pressure, serum cholesterol, smaller waist–hip ratios, lower risk of metabolic syndrome, lower urinary cortisol and catecholamines, and sharper, more pronounced diurnal cortisol rhythms (Ryff, Singer, & Love, 2004; Seeman & McEwen, 1996; Sjögren, Leanderson, & Kristenson, 2006; Vogelzangs et al., 2007). Greater reported social conflict, on the other hand, has been linked to higher blood pressure, cholesterol, inflammation, poorer metabolic profiles, and higher urinary catecholamines and cortisol (Seeman & McEwen, 1996). Experimental evidence similarly shows that positive social relationships decrease cardiovascular and neuroendocrine responses to challenging tasks (Floyd et al., 2007;

* Corresponding author. Tel.: +1 617 496 5797.
E-mail address: friedman@hsph.harvard.edu (E.M. Friedman).

0277-9536/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.socscimed.2011.11.003

Grewen, Anderson, Girdler, & Light, 2003) while interpersonal conflict or hostility leads to increased cardiovascular and neuroendocrine reactivity (Gerin, Pieper, Levy, & Pickering, 1992; Seeman & McEwen, 1996).

Why salivary cortisol?

Large-scale surveys have increasingly sought to include salivary cortisol assessments to index HPA-axis reactivity. This is because of the centrality of the HPA-axis in regulating multiple aspects of human physiology that are critical to health and well-being, and the hypothesized links between such HPA-axis activity and cognitive-emotional responses to the world around us, including importantly our social worlds. Stimuli that activate the HPA function cause an increase in cortisol which triggers downstream physiological responses that help provide the energy and physiological resources needed to adapt to that stimulus. Activation of cortisol also helps to contain other components of the physiological stress response such as increases in inflammatory processes which, if unchecked, can themselves have negative health consequences. Thus, short-term activation of the HPA-axis is necessary for optimal everyday physiological functioning. However, recurrent or chronic activation of this system has been linked to increased risks for a variety of adverse health outcomes, including cardiovascular disease, diabetes, cancer, cognitive decline, and reduced immune function (for a review, see McEwen & Seeman, 1999). In addition, the diurnal rhythm is sensitive to and altered by a variety of stressful situations (Adam & Gunnar, 2001; Steptoe et al., 2003; Vedhara, Hyde, Gilchrist, Tytherleigh, & Plummer, 2000).

Earlier work on the relationships between cortisol and health has focused on average cortisol measures with an interest in cortisol levels over the entire day. This is the approach used, for example, when collecting urinary cortisol, which involves one cortisol sample that is an aggregate measure of, typically, 12–24 h of cortisol (Seeman et al., 2002). With the advent of salivary cortisol protocols, research has examined patterns of cortisol activity at multiple times of the day for one or more days. Such data capture what is typically referred to as the "cortisol diurnal rhythm." The diurnal rhythm is characterized by a rapid increase in cortisol over the first 30–45 min after waking, followed by a rapid decline over approximately the next 2 h and then a slower decline through the late afternoon and evening. Younger, healthier individuals show a more pronounced diurnal rhythm with a higher morning peak and a lower night-time nadir and less healthy and older individuals have a flatter curve (Adam & Kumari, 2009). Examining salivary cortisol over the course of the day provides a more complete picture of cortisol regulation (or dysregulation). In fact, one of the primary advantages of salivary cortisol samples over urinary or blood samples is that they allow for repeated and unobtrusive measurement of cortisol over multiple times of the day (Almeida, McGonagle, & King, 2009).

Prior research on social relationships and cortisol

The influence of social relationships on cortisol response has been a topic of interest in both human and animal research. Animal research has long suggested that contact with others of the same species plays a critical role in successful development, and animals demonstrate the potential for both positive and negative health effects of the social environment (Cassel, 1976; Henry, Meehan, & Stephens, 1967; Levine, 1993). To date, research examining social support and cortisol in human populations has largely taken experimental approaches. Experimental manipulations provide strong evidence that social contact or support from a friend or partner during challenge tests (such as math or public speaking tasks) *decreases* neuroendocrine responses, including cortisol (Grewen et al., 2003; Seeman & McEwen, 1996; Uchino et al., 1996). In contrast, reported inadequate support has been linked to *greater* physiological reactivity, again including cortisol responses to laboratory-based challenge tests (Nausheen, Gidron, Gregg, Tissarchondou, & Peveler, 2007; Seeman & McEwen, 1996; Uchino et al., 1996).

Community-based and, more recently, population-level studies have also begun to focus on associations between aspects of the social environment and cortisol regulation. For instance, one community-based study of social strain and urinary cortisol found that increased frequency of demands and criticism was positively related to overnight urinary cortisol levels for men but not women (Seeman, Berkman, Blazer, & Rowe, 1994). Greater reports of hostility and cynicism are related to higher levels of cortisol in the daytime (Pope & Smith, 1991; Ranjit et al., 2009). In addition, social relationships with parents in childhood may have lasting effects on cortisol levels well into middle and later life (Repetti, Taylor, & Seeman, 2002; Taylor, Karlamangla, Friedman, & Seeman, 2011).

One of the difficulties in investigating the relationship between social stressors and salivary cortisol is that salivary cortisol must be measured at multiple time points over the day, and there are therefore many different measures of cortisol that may be used to capture a dysregulated rhythm. One might think about dysfunction as a blunted morning peak, a slower decline in cortisol levels in the evening, or as a measure of accumulated daily cortisol, such as the area under the curve. For the most part, the influence of social factors on cortisol appears to be strongest for measures capturing cortisol decline over the course of the day, particularly for the evening and resting cortisol levels (Adam & Kumari, 2009; Seltzer et al., 2009). Blunting of the diurnal rhythm over the day (lower peak and higher nadir) occurs systematically with age, and this same blunted rhythm is also evident for individuals exposed to frequent life stresses (Birditt, Cichy, & Almeida, 2011; Varadhan et al., 2008). We therefore hypothesize that individuals with greater levels of social strain will show a flatter cortisol rhythm overall, and show particularly pronounced dysregulation in the latter part of the day.

Conceptualization of social strain

Social strain may be conceived of in a variety of ways. It can be thought of as network stress, problematic social exchanges, or interactions with network members that induce psychological distress. In keeping with Goffman's analysis of "face work," we treat social strain as a characteristic of interactions that "is neither inherent nor a permanent aspect of the person" (Trevino, 2003, p. 37). The index of social strain that we use makes no assumption regarding the respondent's inherent qualities; it simply reflects the person's varied self-reported perceived experiences of critical, irritating, or other negative interactions with significant others in his or her social milieu. These experiences, we hypothesize, have adverse consequences that linger in the individual's biological repertoire.

Data and methods

The National Survey of Midlife Development in the United States (MIDUS) study was initiated in 1995 to determine how social, psychological, and behavioral factors interrelate to influence mental and physical health. The first wave (1995) collected sociodemographic and psychosocial data on 7108 Americans, ages 25–74 years, from a representative sample of English-speaking, non-institutionalized adults residing in the contiguous 48 states,

with oversampling of five metropolitan areas, twin pairs, and siblings.

Of the original 7108 MIDUS participants, 4963 were successfully re-contacted in 2004–2005 and completed the MIDUS II 30-min phone interview and two self-assessment questionnaires 9–10 years later using the original protocol (Love, Seeman, Weinstein, & Ryff, 2010). In this wave, a random subsample ($n = 1605$) also completed short telephone interviews about their daily experiences over eight consecutive days and collected saliva (for cortisol assessments) on four of the eight days. This National Study of Daily Experiences (NSDE) subsample and the MIDUS sample from which it was drawn had very similar distributions for key demographic factors (see Almeida, Wethington, & Kessler, 2002).

Salivary cortisol

Respondents received a Home Saliva Collection Kit one week prior to their initial phone call. In addition to written instructions, telephone interviewers reviewed the procedures and answered any of the participant's questions. On days two through five, respondents provided four saliva samples per day that were later assayed for cortisol. Respondents took these samples in their own home, by placing a roll of cotton in their mouths, chewing on it for approximately 30 s, and placing it in a tube called a salivette, which respondents stored at room temperature until they were returned to the clinic the next day. Saliva was collected immediately upon waking, 30 min after waking, before lunch, and before bed. Data on the exact time respondents provided each saliva sample was obtained from the nightly telephone interviews as well as on a paper–pencil log sent with the collection kit. In addition approximately a quarter of the respondents received a "Smart Box" containing a computer chip that recorded the time respondents opened and closed the box (See Almeida, McGonagle, et al., 2009; Almeida, Piazza, & Stawski, 2009). In our analyses, we use information on collection time from the home collection sheet times, unless they are missing, in which case the times reported in the interview are used instead. For all analyses, cortisol is recoded as the ln(cortisol + 1), in order to account for outlying cases and some small cortisol values.

We began with an initial NSDE sample of 1605 participants with 6383 days of cortisol data. We dropped days that appear to reflect time-recording error for one of the saliva samples or saliva sample, days when respondents woke unusually early, late, or remain awake for more than 20 h, values outside of the normal range (i.e.>60 nmol/L), which likely reflect either errors or the effects of medications, and individuals with missing predictor/covariate data. This left us with a final sample of 1502 people, 5629 days and 21,741 total saliva measurements. Respondents in the final sample had at least one valid salivary sample of cortisol, with some respondents providing as many as sixteen samples (four on each of four days).

Longitudinal reports of social strain

Adult social strain with family and friends were assessed from items in the self-administered mail questionnaires in the MIDUS data in 1995 (before collection of cortisol) and 2005 (concurrent with cortisol collection). Participants' perceptions as to the frequency of various types of social strain were queried with respect to relationships with spouse/partner (6 items), friends (4 items), and other family members (4 items). The items include the following: "How often do your *friends/spouse/family* make too many demands on you?"; "How often do they criticize you?"; "How often do they let you down when you are counting on them?"; "How often do they get on your nerves?" For the spouse/partner scale, two additional items are included: "How often does he or she argue with you?"; and "How often does he or she make you feel tense?".

All items are measured on a four point scale indicating whether this occurs 1 Often; 2 Sometimes; 3 Rarely; or 4 Never. The mean of all items was calculated for each relationship type (i.e. spouse, family, friends), with items recoded so that higher scores reflect higher strain. We then averaged the three scales into one global score measuring the respondent's average level of social strain from all sources (alpha = 0.86).

In addition to constructing separate strain scores for each wave, we also combined the scores for the two waves by dividing each wave's scores into quartiles and constructing a score across the two waves using the following coding:

(1) Not in the highest quartile of strain in either Wave 1 or 2
(2) Highest quartile strain in Wave 1 only
(3) Highest quartile strain in Wave 2 only
(4) Highest quartile strain in both waves

This construction allows us to distinguish subgroups on the basis of their joint patterns of reported frequency of social strain at both MIDUS I and MIDUS II. Though these designations do not account for variations in the frequency of social strain between the two waves, the information from these two time points nonetheless provides important longitudinal information, allowing us to distinguish those reporting more cumulative social strain (at least as indicated by reported high levels of social strain at both waves) – a group we hypothesized would be at highest risk for the biological consequences of social strain.

Control variables

Multivariable analyses also include controls for race, age, sex, and education. Both race and sex were coded as dichotomous indicator variables, with the first indicating whether a respondent was white or non-white and the latter, whether male or female. A three category age variable was included in the models with age coded as <50 years old, 50–64, and 65+. Education was included in all models as three dummy variables indicating whether the respondent completed (1) high school or less schooling; (2) some college; or (3) college degree or more (16+ years of education).

Analyses

Because previous studies indicate that cortisol rhythms are driven by time elapsed since awakening and less by clock time (van Cauter, 1990; Kumari et al., 2010), we examined cortisol trajectories as a function of time since waking. Based on visual examinations of average cortisol rhythms in the sample and in demographic strata defined by age, gender, race, and socioeconomic status and in line with other work (Hajat et al., 2010; Taylor et al., 2011), we modeled the diurnal cortisol trajectories as piecewise linear growth curves, using four linear splines with three knots, fixed at 0.5 h, 4.5 h, and 15 h after waking. The four spline pieces represent four phases of the day, with the first piece representing the morning rise (waking to half hour after waking); the second, a steep early decline (0.5–4.5 h after waking); the third, a more gradual late afternoon through evening decline (4.5–15 h after waking); and the final piece representing a later night plateau (15–20 h after waking).

The intercept (representing the waking value) and all four spline slopes were modeled as functions of the primary predictor (social strain) and covariates. In order to remove any bias that may arise from differences in sleep patterns, all models include controls for sleeping and waking habits based on information obtained from the log maintained by the participant. These variables include the

length of sleep the previous night, whether the respondent woke before the median wake up time of the sample, night bedtime, and whether or not it was a weekend day (for those who were employed). To capture the influence of too little and too much sleep, we categorized the previous night's sleep into three groups: <6 h, 6–8 h, and >8 h. Waking time and bedtime were used to compute the length of the waking day, which was averaged over all eight dairy days, to get average wake-day length for every participant. We control for these sleep-related variables in particular, because preliminary analyses indicated that the shape of the diurnal trajectories differed for these groups.

We used hierarchical, 4-level, linear mixed effects models to fit the cortisol growth curves and to account for within-individual, within-family (MIDUS included some siblings and twins), and within-day clustering. To account for the correlation between repeated measures of cortisol in the same individual (between 1 and 16 measurements per person), we included random effects for the intercept (wakening value of cortisol) and all four slopes. We also include a level for correlations between samples on the same day, along with random effects for the intercept and the second slope. Finally, to allow for correlation between members of the same family, we included an additional hierarchical level with random intercept. Model-predicted intercept and slopes were used to estimate mean values for other trajectory parameters, such as the magnitude of the daily peak, the nightly nadir, and the total cortisol exposure over 16 h since waking, which we refer to as the area under the curve (AUC). We do not include the late night plateau in our calculations of the area under the curve as this is only available for select respondents who stay up more than 15 h. The AUC was calculated using the trapezoidal rule (Yeh & Kwan, 1978), where the total AUC is the sum of the areas of several individual trapezoids. Estimates were calculated as follows:

$$\text{Peak} = \text{Intercept} + 0.5 \times \text{slope}_1$$

$$\text{Nadir} = \text{Peak} + 4 \times \text{slope}_2 + 10.5 \times \text{slope}_3$$

$$\begin{aligned}\text{AUC} = {} & 0.25 \times (\text{Intercept} + \text{Peak}) + 2 \times (2 \times \text{Peak} + 4 \\ & \times \text{slope}_2) + 5.25 \times (\text{Peak} + 4 \times \text{slope}_2 + \text{Nadir}) + 0.5 \\ & \times (2 \times \text{Nadir} + 1 \times \text{slope}_4)\end{aligned}$$

Slope_1, Slope_2, Slope_3, and Slope_4 refer to the model-estimated mean slopes (per hour) for the four piecewise linear segments of the trajectory.

Results

Table 1 provides descriptive information on the model variables for the analytic sample. Approximately 30 percent of participants were less than 50 years old at the time of the MIDUS II data collection, 40 percent were between 50 and 65 and nearly 30 percent were 65 and older. The sample was largely White and relatively well-educated, with over 40 percent having a college degree. There was substantial variance in reported social strain. For Wave 1, the average level of social strain across all relationship types was 2.05 (equivalent to responses of "rarely"). In Wave 2 the corresponding value was 1.98. The lowest levels of mean strain were for friends and the highest for spouse. The 10-year history of social strain in quartiles shows that although most people do not experience extreme levels of social strain, just over 13 percent of respondents are in the highest quartile of strain in both waves.

Fig. 1 shows the model-predicted diurnal cortisol rhythm as a function of time since waking in hours for the null model, with inflexions at 0.5 h, 4.5 h, and 15 h. These results are from a model controlling for early waking (waking before median), sleeping fewer than 6 h the night before, sleeping more than 8 h the night before, average hours awake, and weekend vs. weekday (if employed), but does not include demographic controls.

This figure shows the expected morning rise, or the cortisol awaking response, from waking until about half an hour after waking, followed by a rapid decline until 4.5 h after waking, followed by a more gradual late afternoon decline until 15 h after waking and finally, for respondents who are awake more than 15 h we find a flattening of their cortisol rhythm to a late night plateau. The first three slopes are statistically significantly different from zero at $p < 0.01$; slope 4 was not statistically different from zero. Model-predicted mean wakening value, peak and nadir, are 13.88 nmol/L, 19.09 nmol/L, and 2.00 nmol/L respectively. Estimated area under the log-cortisol curve (AUC) was 29.39 ln(nmol/L + 1)-hours.

Table 2 shows the results of our fully-adjusted models predicting Wave 2 salivary cortisol over the day as a function of Wave 2 social strain scores. This table displays the association between concurrent social strain on the waking value (intercept) and the four slopes, as well as the model-estimated peak (highest point), nadir (lowest point) and the full area under the curve for the day (AUC). We present results for mean strain (averaged across spouse, family, friends). Measures are treated as continuous in these models (range: 1–4). These results provide a cross-sectional snapshot of the relationship between the cortisol rhythm and social strain.

As Table 2 reveals, respondents reporting higher levels of social strain have a less rapid late day decline (less negative slope) and a higher nadir, suggesting that their cortisol levels do not come down as much in the evening hours as they do for their counterparts reporting lower levels of social strain. Higher levels of social strain are also associated with a somewhat (marginally significant) lower morning peak value. Taken in combination, these results suggest that respondents with higher levels of social strain exhibit a blunted cortisol rhythm over the day. That is, cortisol values do not go up as much in the early morning hours, do not come down as much later in the evening before bedtime, and do not reach as low a nadir as they do for individuals with lower levels of social strain. For instance, an individual with a mean strain score of four, who *often* experiences strain with family and friends, has a peak log-cortisol value that is 0.31 standard deviations ($2 \times 0.052/0.337$) lower than that of a matched counterpart with a mean strain score of two (who rarely experiences strain with family and friends). This difference in peak log cortisol translates to a 10 percent reduction in peak cortisol ($e^{-0.052 \times 2} = 0.90$). The log-cortisol nadir, on the other hand, is 0.33 standard deviations higher and the nadir is 15 percent higher for those with frequent strain (mean strain score of 4) compared to those with average levels of strain (mean of 2). To put this in perspective, differences in peak log-cortisol between those reporting high versus low social strain (for a two unit difference in strain, effect size = 0.31 standard deviations) is comparable to the differences between those with high school or less versus college or more education (effect size = 0.27 standard deviations), while the differences in log-cortisol nadirs between those with high vs. low social strain is 3 times larger than that seen for high school or less versus college or more-educated individuals (effect size 0.33 vs. 0.14 standard deviations).

These analyses indicate that the associations between social strain and cortisol are strongest for cortisol measures capturing the decline in cortisol over the latter part of the day. Over the day as a whole, cortisol rhythms are generally flatter for those with higher reported strain than for their counterparts with lower level of

Table 1
Descriptive statistics for analytic sample ($n = 1502$).

	Variable	Unit or category		
			Percent	
Demographics	Age	<50	30.83	
		50–65	40.68	
		65+	28.50	
	Sex	Male	44.07	
		Female	55.93	
	Race	White	93.01	
		Non-white or mixed race	6. 99	
	Education	High school degree or less	29.29	
		Some college	29.36	
		College degree+	41.35	
			Mean (SD)	
Wave 1 social strain	Spouse only ($n = 1178$)	Range, 1–4	2.22	(0.60)
	Friends only ($n = 1501$)	Range, 1–3.75	1.90	(0.48)
	Family only ($n = 1498$)	Range, 1–4	2.08	(0.58)
	Mean strain ($n = 1502$)	Range, 1–3.58	2.05	(0.43)
Wave 2 social strain	Spouse only ($n = 1151$)	Range, 1–4	2.15	(0.61)
	Friends only ($n = 1493$)	Range, 1–3.50	1.81	(0.49)
	Family only ($n = 1497$)	Range, 1–4	2.01	(0.58)
	Mean strain ($n = 1502$)	Range, 1–3.64	1.98	(0.44)
			Percent	
10-Year history of social strain	Spouse only ($n = 1117$)	Never highest quartile strain	66.61	
		Highest quartile strain Wave 1 only	9.67	
		Highest quartile strain Wave 2 only	14.06	
		Highest quartile strain both waves	9.67	
	Friends only ($n = 1492$)	Never highest quartile strain	71.92	
		Highest quartile strain Wave 1 only	6.23	
		Highest quartile strain Wave 2 only	14.61	
		Highest quartile strain both waves	7.24	
	Family only ($n = 1495$)	Never highest quartile strain	69.70	
		Highest quartile strain Wave 1 only	6.89	
		Highest quartile strain Wave 2 only	14.04	
		Highest quartile strain both waves	9.36	
	Mean strain ($n = 1502$)	Never highest quartile strain	64.65	
		Highest quartile strain Wave 1 only	11.12	
		Highest quartile strain Wave 2 only	10.79	
		Highest quartile strain both waves	13.45	

reported strain with family and friends. This pattern can also be seen in Fig. 2.

Fig. 2 shows the predicted cortisol trajectories over the course of the day for a predicted mean strain score of 1 ("never"), 2 ("rarely"), and 3 ("sometimes"). The average of the mean strain score for the analytic sample was 2 (see Table 1). Although all three groups show clear diurnals rhythms with a morning rise and a later day decline, the most pronounced trajectory is apparent for the lowest strain group, the flattest trajectory is for highest strain group, and those with mean levels of reported strain fall directly in between the other two groups.

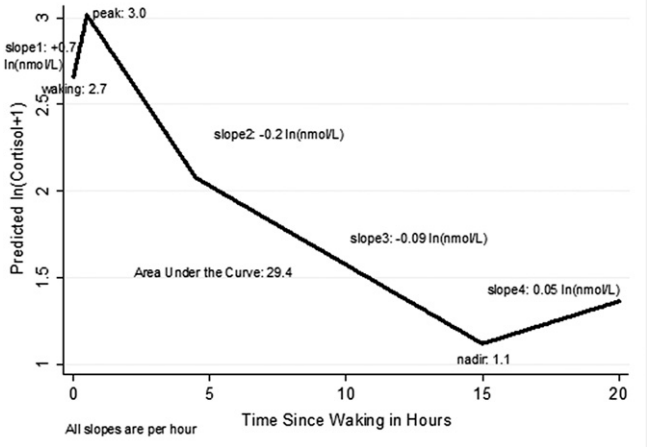

Fig. 1. Predicted cortisol diurnal rhythm for the null model ($n = 1502$).

In results not shown here, we also ran the model described above, with the addition of a difference score measuring the change in strain between Waves 1 and 2. The coefficients for the change score were not statistically significant. In addition, the significant values for the Wave 2 cortisol slopes remained strong and were sometimes even strengthened when the difference score was added. This suggests that it is Wave 2 levels of social strain that are most strongly related to Wave 2 cortisol, and that the change between the two waves does not explain the relationship between Wave 2 social strain and cortisol rhythm, though the relatively high stability in reports of strain makes it difficult to evaluate the impact of changes in strain.

Patterns of social strain over two waves

Another way to bring in information from both waves of social strain is by classifying respondents into categories based on whether they were in the highest quartile of social strain in Wave 1 only, Wave 2 only, both waves, or in neither wave. Looking at individuals in the highest quartile of strain allows us to assess how much experiencing extreme levels of social strain (as reported at two time points a decade apart) is related to cortisol dysregulation over the course of the day. By bringing together the two waves of information, the MIDUS data allow for a richer, longitudinal assessment of differences in reported frequencies of social strain based on data obtained approximately a decade apart. This allowed

Table 2
Coefficients and standard errors from spline models of log cortisol + 1 (nmol/L) as a function of Wave 2 social strain ($n = 1502$).

		Waking value	Slope 1: morning rise	Slope 2: first decline	Slope 3: late day decline	Slope 4: late night plateau	Peak	Nadir	AUC
	Mean	2.661	0.711	−0.236	−0.092	0.048	3.016	1.104	29.390
	SD	0.320	0.183	0.0461	0.030	0.048	0.337	0.433	5.414
Mean strain		−0.032 (0.025)	−0.041 (0.043)	−0.002 (0.007)	0.012** (0.004)	−0.008 (0.020)	−0.052^{+} (0.027)	0.072^{+} (0.043)	−0.109 (0.469)
Male		0.109** (0.022)	−0.169** (0.037)	0.031** (0.006)	−0.006^{+} (0.003)	−0.034^{+} (0.017)	0.025 (0.024)	0.089* (0.038)	1.707** (0.413)
Age (ref: <50)	50–64	0.007 (0.027)	0.127** (0.043)	−0.003 (0.007)	0.003 (0.004)	−0.032 (0.020)	0.071* (0.028)	0.090* (0.045)	1.149* (0.494)
	65+	0.069* (0.030)	0.165** (0.050)	0.017* (0.008)	0.010* (0.004)	−0.034 (0.024)	0.151** (0.0319)	0.328** (0.050)	3.978** (0.552)
White (ref: non-white)		0.146** (0.042)	−0.153* (0.072)	−0.029* (0.012)	−0.007 (0.007)	−0.032 (0.031)	0.069 (0.046)	−0.124^{+} (0.073)	−0.940 (0.791)
Education	≤HS	−0.142** (0.027)	0.103* (0.045)	0.012^{+} (0.007)	0.010* (0.004)	−0.023 (0.021)	−0.090** (0.029)	0.060 (0.046)	−0.187 (0.499)
(ref: college+)	Some college	−0.073** (0.026)	0.009 (0.044)	0.018* (0.007)	−0.001 (0.004)	0.022 (0.021)	−0.068* (0.028)	−0.007 (0.045)	−0.184 (0.491)

Notes: To assist with interpretation of effect sizes, the sample means and standard deviations for the parameters of the diurnal trajectory of log(cortisol) are listed under the column headings. These means and standard deviations came from a null model without demographic controls. Units for level values (waking, peak, nadir) are log (nmol/L). Units for slopes are log (nmol/L) per hour. Unit for AUC is log(nmol/L)-hour.
Standard errors in parentheses.
Models also control for wake before median wake time, number of hours awake (centered), whether weekend, slept fewer than 6 h or more than 8 h the night before. $^{+}p < 0.10$, $^{*}p < 0.05$, $^{**}p < 0.01$.

Fig. 2. Predicted ln(cortisol + 1) (nmol/L) over the day by Wave 2 mean social strain score ($n = 1502$).

us to differentiate those who reported the highest frequencies of social strain at both interviews from those with either "mixed profiles" (i.e., reporting higher frequency at one or the other but not both waves) or consistent profiles of low reported frequency of social strain, and to examine how the association between social strain and cortisol might vary as a function of these longitudinal profiles of reported social strain.

Table 3 shows the results of spline models predicting the cortisol diurnal rhythm as a function of 10-year history of social strain, assessing whether respondents were in the highest quartile of strain in Wave 1, Wave 2, both waves, or neither wave (reference category). This table shows the coefficients and standard errors for the waking values, the four slopes during the day, and the model-estimated peak, nadir, and AUC.

Compared to those reporting lower levels of social strain at both waves, those reporting the highest levels of strain at both waves exhibit significantly slower late day declines and marginally higher waking, peak and nadir values. They also have higher waking and nadir values than do those with higher strain only at Wave 2. Somewhat unexpectedly, we also saw a stronger association of "Wave 1 only" high levels of conflict on cortisol regulation than for "Wave 2 only" high conflict. Compared to those who were never in the highest quartile of reported strain, individuals with social strain only in Wave 1 exhibited slower rates of late afternoon decline (slope 3) but more negative later night slopes; they also had marginally higher night-time nadir values. Those who have high strain in Wave 2 only, on the other hand, do not differ significantly from individuals who are never in the highest quartile of strain.

Discussion

This paper examines hypothesized relationships between frequency of strain in salient social relationships and patterns of diurnal cortisol regulation. Findings suggest that individuals who perceive more frequent social strain in relationships with their spouse, family and close friends are at increased risk for poorer cortisol regulation. Their cortisol levels do not go up as much in the early morning hours, do not come down as much later in the evening before bedtime, and do not reach as low a point as they do for individuals with lower levels of strain. All in all, their rhythms are flatter than those of their counterparts.

We looked at strain at a point in time and as a ten-year cumulative history to get a complete picture of the role of strain in cortisol dysregulation. Lab-based data already support cortisol's immediate responsiveness to short-term strain (Gruenewald,

Table 3
Coefficients and standard errors from spline models of log cortisol + 1 (nmol/L) as a function of 10-yr history of social strain ($n = 1502$).

		Waking value	Slope 1: morning rise	Slope 2: first decline	Slope 3: late day decline	Slope 4: late night plateau	Peak	Nadir
	Mean	2.661	0.711	−0.236	−0.092	0.048	3.016	1.104
	SD	0.320	0.183	0.0461	0.030	0.048	0.337	0.433
Mean strain (reference: never highest quartile)								
Highest quartile Wave 1 only		−0.026 (0.035)	0.070 (0.059)	−0.001 (0.010)	0.010* (0.005)	−0.061* (0.027)	0.008 (0.034)	0.112+ (0.059)	0.700 (0.636)
Highest quartile Wave 2 only		0.056 (0.035)	−0.056 (0.060)	−0.008 (0.010)	0.005 (0.005)	0.018[a] (0.027)	0.028 (0.037)	0.047 (0.060)	0.341 (0.647)
Highest quartile both waves		−0.058+[b] (0.033)	−0.013 (0.056)	0.007 (0.009)	0.013* (0.005)	0.008[a] (0.026)	−0.057+[b] (0.035)	0.096+ (0.055)	0.174 (0.601)

Notes: To assist with interpretation of effect sizes, the sample means and standard deviations for the parameters of the diurnal trajectory of log(cortisol) are listed under the column headings. These means and standard deviations came from a null model without demographic controls. Units for level values (waking, peak, nadir) are log (nmol/L). Units for slopes are log (nmol/L) per hour. Unit for AUC is log(nmol/L)-hour.
Standard errors in parentheses. Models also control for wake before median wake time, number of hours awake (centered), whether weekend, slept fewer than 6 h or more than 8 h the night before, sex, age categories, white vs. non-white, education categories.
$^{+}p < 0.10$, $^{*}p < 0.05$, $^{**}p < 0.01$.
[a] Differs significantly from 'highest quartile Wave 1 only' group at $p < 0.05$.
[b] Differs significantly from 'highest quartile Wave 2 only' group at $p < 0.05$.

Kemeny, Ziz, & Fahey, 2004; Kirschblaum, Wust, & Hallhammer, 1992). Our study shows that there are long term implications of persistent exposure to social stressors. Cross-sectionally, someone with a mean strain score of four, who reports often experiencing strain with family and friends, exhibits a peak cortisol value that is nearly 10 percent lower and a nadir that is 15 percent higher than a counterpart with a mean strain score of two (equivalent to rarely). These effects, particularly for the latter part of the day, are more pronounced for those individuals who consistently report high levels of strain over time. Our findings also suggest that there may be a lag in the impact of social strain on dysregulations in neuroendocrine functioning – more persistent strain and earlier strain showing associations with later cortisol dysregulation whereas Wave 2 only strain (concurrent with cortisol measurements) has yet to show such effects.

These findings add to the growing literature showing that social influences are critical for healthy physiological functioning (Robles, Shaffer, Malarkey, & Kiecolt-Glaser, 2006; Seeman & McEwen, 1996). For instance, Robles et al. (2006) examine conflict between spouses in a laboratory setting and find that supportiveness during negative interactions between couples promotes adaptive physiological responses to interpersonal conflict. Seeman and McEwen (1996) show that social contact and support during high stress tasks (such as math or public speaking) decrease neuroendocrine responses, while inadequate support increases physiological reactivity. Our work looks at a larger, more representative sample of the population, and investigates cortisol regulation in daily life. We find that strained interpersonal relationships with family and friends have significant consequences for HPA regulation.

Consistent with the aspects of cortisol rhythm that we found to be most dysregulated for individuals who report greater social strain, flattened cortisol rhythms especially in the latter part of the day have been linked to a variety of physical health outcomes (Brunner et al., 2002; Matthews, Schwartz, Cohen, & Seeman, 2006; Smith et al., 2005), depression (Herbert et al., 2006; McEwen, 2007), cognitive decline (Seeman, McEwen, Singer, Albert, & Rowe, 1997), and even mortality (Kumari, Shipley, Stafford, & Kivimaki, 2011). Our findings are therefore consistent with the notion that strained social relationships have implications for health. This is in line with the broader idea that such effects on cortisol may reflect one of the pathways through which social relationships affect major morbidity and mortality.

Several limitations of this paper should be acknowledged. First, although we have information on social strain over two waves of data, we only have cortisol measures at one point in time. Without longitudinal data on cortisol, it is impossible to determine whether there is a causal relationship between social relationships and cortisol diurnal rhythm. Second, although we have two waves of data in which we can investigate social strain, we do not have a true history of strain over that time period, but only have two time points separated by ten years. Ideally, we would like to have more frequent measures of strain over that time period to get a richer picture of differences in chronic social strain. However, this lack of information should, if anything, result in greater measurement error as we have information for only two time points, and thus weaken our ability to detect a relationship to cortisol.

Despite these caveats, this work has important implications for the growing body of work showing a link between social relationships and health. This paper looks beyond social relationships at a point in time and shows that cumulative social strain over the long run is associated with poorer diurnal cortisol regulation – a potentially important contributor to downstream health. Our findings suggest that a longer-term perspective on social

relationships and health is necessary for understanding the lasting effects of negative social relationships and to get a more complete picture of how health inequalities develop within societies. This paper only considers social relationships at two points over a ten-year period. Future work should examine how social relationships over the life course – from childhood on – translate into accumulated impacts on health and well-being in midlife and beyond.

Acknowledgements

This research was supported, in part, by Grants P01-AG020166, R01-AG19239, and R01-AG019239 from the National Institute on Aging to conduct a longitudinal follow-up of the MIDUS (Midlife in the United States) investigation. The original study was supported by the John D. and Catherine T. MacArthur Foundation Research Network on Successful Midlife Development. The project described also received support from the UCLA Older Americans Independence Center, Grant P30-AG028748 from the National Institute on Aging. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute on Aging or the National Institutes of Health. The authors thank the Robert Wood Johnson Foundation Health & Society Scholars program and the UCLA Interdisciplinary Relationship Science Program sponsored by the National Science Foundation for their financial support. We are also grateful to Rob Mare, Judy Seltzer, and the members of the UCLA demography, family, and stratification research group for helpful advice as we developed the paper. A previous version of this paper was presented at the 2008 meeting of the Gerontological Society of America (GSA), National Harbor, MD.

References

Adam, E. K., & Gunnar, M. R. (2001). Relationship functioning and home and work demands predict individual differences in diurnal cortisol patterns in women. *Psychoneuroendocrinology, 26*, 189–208.

Adam, E. K., & Kumari, M. (2009). Assessing salivary cortisol in large-scale, epidemiological research. *Psychoneuroendocrinology, 34*, 1423–1436.

Almeida, D. M., McGonagle, K., & King, H. (2009). Assessing daily stress processes in social surveys by combining stressor exposure and salivary cortisol. *Biodemography and Social Biology, 55*, 220–238.

Almeida, D. M., Piazza, J. R., & Stawski, R. S. (2009). Inter-individual differences and intra-individual variability in the cortisol awakening response: an examination of age and gender. *Psychology and Aging, 24*, 819–827.

Almeida, D. M., Wethington, E., & Kessler, R. C. (2002). The daily inventory of stressful events: an interview-based approach for measuring daily stressors. *Assessment, 9*, 41–55.

Anderson, N., & Armstead, C. (1995). Toward understanding the association of socioeconomic status and health: a new challenge for the biopsychosocial approach. *Psychosomatic Medicine, 57*, 213–225.

Birditt, K. S., Cichy, K. E., & Almeida, D. (2011). Age differences in exposure and reactivity to interpersonal tensions among black and white individuals across adulthood. *Race and Social Problems, 3*, 225–239.

Brunner, E. J., Hemingway, H., Walker, B. R., Page, M., Clarke, P., Juneja, M., et al. (2002). Adrenocortical, autonomic, and inflammatory causes of the metabolic syndrome. *Circulation, 106*, 2659–2665.

Cassel, J. (1976). The contribution of the social environment to host resistance. *American Journal of Epidemiology, 104*, 107–123.

van Cauter, E. (1990). Diurnal and ultradian rhythms in human endocrine function: a mini review. *Hormone Research, 34*, 45–53.

Coyne, J. C., Rohrbaugh, M. J., Shoham, V., Sonnega, J. S., Nicklas, J. M., & Cranford, J. A. (2001). Prognostic importance of marital quality for survival of congestive heart failure. *The American Journal of Cardiology, 88*, 526–529.

DeVries, A. C., Glasper, E. R., & Detillion, C. E. (2003). Social modulation of stress responses. *Physiology & Behavior, 79*(3), 399–407.

Eisenberger, N. I., Taylor, S. E., Burklund, L. J., Eisenberger, N. I., Lehman, B. J., Hilmert, C. J., et al. (2007). Neural pathways link social support to attenuated neuroendocrine stress responses. *Neuroimage, 35*(4), 1601–1612.

Ewart, C. K., Taylor, C. B., Kraemer, H. C., & Agras, W. S. (1991). High blood pressure and marital discord: not being nasty matters more than being nice. *Health Psychology, 10*, 155–163.

Floyd, K., Mikkelson, A. C., Tafoya, M. A., Farinelli, L., La Valley, A. G., Judd, J., et al. (2007). Human affection exchange: XIII. Affectionate communication accelerates neuroendocrine stress recovery. *Health Communication, 22*(2), 123–132.

Gerin, W., Pieper, C., Levy, R., & Pickering, T. G. (1992). Social support in social interaction: a moderator of cardiovascular reactivity. *Psychosomatic Medicine, 54*(3), 324–336.

Grewen, K. M., Anderson, B. J., Girdler, S. S., & Light, K. C. (2003). Warm partner contact is related to lower cardiovascular reactivity. *Behavioral Medicine, 29*, 123–130.

Gruenewald, T. L., Kemeny, M. E., Aziz, N., & Fahey, J. L. (2004). Acute threat to the social self: shame, social self-esteem, and cortisol activity. *Psychosomatic Medicine, 66*(6), 915–924.

Hajat, A., Roux, A. D., Franklin, T. G., Seeman, T., Shrager, S., Ranjot, N., et al. (2010). Socioeconomic and race/ethnic differences in daily salivary cortisol profiles: the multi-ethnic study of atherosclerosis. *Psychoneuroendocrinology, 35*(6), 932–943.

Henry, J. P., Meehan, J. P., & Stephens, P. M. (1967). The use of psychosocial stimuli to induce prolonged systolic hypertension in mice. *Psychosomatic Medicine, 29*, 408–432.

Herbert, J., Goodyer, I. M., Grossman, A. B., Hastings, M. H., de Kloet, E. R., Lightman, S. L., et al. (2006). Do corticosteroids damage the brain? *Journal of Neuroendocrinology, 18*, 393–411.

Hofer, M. A. (1987). Early social relationships: a psychobiologist's view. *Child Development, 58*(3), 633–647.

Hofer, M. A. (1995). Hidden regulators: implications for a new understanding of attachment, separation, and loss. In S. Goldberg, R. Muir, & J. Kerr (Eds.), *Attachment theory: Social, developmental, and clinical perspectives* (pp. 203–230). Hillsdale, NJ: Analytic Press.

House, J. S., Lepkowski, J. M., Kinney, A. M., Mero, R. P., Kessler, R. C., & Herzog, A. R. (1994). The social stratification of aging and health. *Journal of Health and Social Behavior, 35*, 213–234.

Kirschblaum, C., Wust, S., & Hallhammer, D. H. (1992). Consistent sex differences in cortisol responses to psychological stress. *Psychosomatic Medicine*, 648–657.

Kumari, M., Badrick, E., Chandola, T., Adler, N. E., Epel, E., Seeman, T. E., et al. (2010). Measures of social position and cortisol secretion in an aging population: findings from the Whitehall II study. *Psychosomatic Medicine, 72*, 27–34.

Kumari, M., Shipley, M., Stafford, M., & Kivimaki, M. (2011). Association of diurnal patterns in salivary cortisol with all-cause and cardiovascular mortality: findings from the Whitehall II study. *Endocrine Research, 96*(5), 1478–1485.

Levine, S. (1993). The influence of social factors on the response to stress. *Psychosomatic Medicine, 60*, 33–38.

Love, G. D., Seeman, T. E., Weinstein, M., & Ryff, C. D. (2010). Bioindicators in the MIDUS national study: protocol, measures, sample, and comparative context. *Journal of Aging and Health, 22*, 1059–1080.

Matthews, K., Schwartz, J., Cohen, S., & Seeman, T. (2006). Diurnal cortisol decline is related to coronary calcification: CARDIA study. *Psychosomatic Medicine, 68*(5), 657–661.

McEwen, B. S. (2007). Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiological Reviews, 87*(3), 873–904.

McEwen, B. S., & Seeman, T. E. (1999). Protective and damaging effects of mediators of stress: elaborating and testing the concepts of allostasis and allostatic load. *Annals of the New York Academy of Sciences, 896*, 30–47.

Nausheen, B., Gidron, Y., Gregg, A., Tissarchondou, H. S., & Peveler, R. (2007). Loneliness, social support and cardiovascular reactivity to laboratory stress. *Stress: The International Journal on the Biology of Stress, 10*, 37–44.

Newsom, J. T., Mahan, T. L., Rook, K. S., & Krause, N. (2008). Stable negative social exchanges and health. *Health Psychology, 27*, 78–86.

Orth-Gomer, K., Wamala, S. P., Horsten, M., Schenck-Gustafsson, K., Schneiderman, N., & Mittleman, M. A. (2000). Marital stress worsens prognosis in women with coronary heart disease: the Stockholm female coronary risk study. *Journal of the American Medical Association, 284*, 3008–3014.

Patterson, A. C., & Veenstra, G. (2010). Loneliness and risk of mortality: a longitudinal investigation in Alameda County, California. *Social Science & Medicine, 71*(1), 181–186.

Pope, M., & Smith, T. (1991). Cortisol excretion in high and low cynically hostile men. *Psychosomatic Medicine, 53*, 386–392.

Ranjit, N., Diez-Roux, A., Sanchez, B., Seeman, T., Shea, S., Shrager, S., et al. (2009). Association of salivary cortisol circadian pattern with cynical hostility: multi-ethnic study of atherosclerosis. *Psychosomatic Medicine, 71*, 748–755.

Repetti, R. L., Taylor, S. E., & Seeman, T. E. (2002). Risky families: family social environments and the mental and physical health of offspring. *Psychological Bulletin, 128*, 330–336.

Robles, T. F., Shaffer, V. A., Malarkey, W. B., & Kiecolt-Glaser, J. K. (2006). Positive behaviors during marital conflict: influences on stress hormones. *Journal of Social and Personal Relationships, 23*(2), 305–325.

Ryff, C. D., Singer, B. H., & Love, G. D. (2004). Positive health: connecting well-being with biology. *Philosophical Transactions of the Royal Society London B Biological Sciences, 359*, 1383–1394.

Seeman, M., Seeman, T., & Sayles, M. (1985). Social networks and health status: a longitudinal analysis. *Social Psychology Quarterly, 48*, 237–248.

Seeman, T. E. (1996). Social ties and health: the benefits of social integration. *Annals of Epidemiology, 6*, 442–451.

Seeman, T. E., Berkman, L. F., Blazer, D., & Rowe, J. W. (1994). Social ties and support and neuroendocrine function: the MacArthur studies of successful aging. *Annals of Behavioral Medicine, 16*, 95–106.

Seeman, T. E., Kaplan, G. A., Knudsen, L., Cohen, R., & Guralnik, J. (1987). Social network ties and mortality among the elderly in the Alameda County Study. *American Journal of Epidemiology, 126*, 714–723.

Seeman, T. E., & McEwen, B. S. (1996). Impact of social environment characteristics on neuroendocrine regulation. *Psychosomatic Medicine, 58*, 459–471.
Seeman, T. E., McEwen, B. S., Singer, B. H., Albert, M. S., & Rowe, J. W. (1997). Increase in urinary cortisol excretion and memory declines: MacArthur studies of successful aging. *The Journal of Clinical Endocrinology & Metabolism, 82*, 2458–2465.
Seeman, T. E., Singer, B. H., Ryff, C. D., Dienberg, Love G., & Levy-Storms, L. (2002). Social relationships, gender, and allostatic load across two age cohorts. *Psychosomatic Medicine, 64*, 395–406.
Seltzer, M. M., et al. (2009). Psychosocial and biological markers of daily lives of midlife parents of children with disabilities. *Journal of Health and Social Behavior, 50*, 1–15.
Sjögren, E., Leanderson, P., & Kristenson, M. (2006). Diurnal saliva cortisol levels and relations to psychosocial factors in a population sample of middle-aged Swedish men and women. *International Journal of Behavioral Medicine, 13*, 193–200.
Smith, G. D., Ben-Shlomo, Y., Beswick, A., Yarnell, J., Lightman, S., & Elwood, P. (2005). Cortisol, testosterone, and coronary heart disease: prospective evidence from the Caerphilly study. *Circulation, 112*, 332–340.
Steptoe, A., Kunz-Ebrecht, S., Owen, N., Feldman, P. J., Willemsen, G., Kirschbaum, C., et al. (2003). Socioeconomic status and stress-related biological responses over the working day. *Psychosomatic Medicine, 65*, 461–470.
Taylor, S., EBurklund, L. J., Eisenberger, N. I., Lehman, B. J., Hilmert, C. J., & Lieberman, M. D. (2008). Neural bases of moderation of cortisol stress responses by psychosocial resources. *Journal of Personality and Social Psychology, 95*(1), 197–211.
Taylor, S. E., Karlamangla, A. S., Friedman, E. M., & Seeman, T. E. (2011). Early environment affects neuroendocrine regulation in adulthood. *Social Cognitive and Affective Neuroscience: Special Issue on Aging Research, 6*(2), 244–251.
Trevino, J. (2003). *Goffman's legacy*. Lanham, MD: Rowman and Littlefield.
Uchino, B. (2006). Social support and health: a review of physiological processes potentially underlying links to disease outcomes. *Journal of Behavioral Medicine, 29*, 377–387.
Uchino, B. N., Cacioppo, J. T., & Kiecolt-Glaser, J. K. (1996). The relationship between social support and physiological processes: a review with emphasis on underlying mechanisms and implications for health. *Psychological Bulletin, 119*, 488–531.
Varadhan, R., Walston, J., Cappola, A. R., Carlson, M. C., Wand, G. S., & Fried, L. P. (2008). Higher levels and blunted diurnal variation of cortisol in frail older women. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 63*, 190–195.
Vedhara, K., Hyde, J., Gilchrist, I. D., Tytherleigh, M., & Plummer, S. (2000). Acute stress, memory, attention and cortisol. *Psychoneuroendocrinology, 25*, 535–549.
Vogelzangs, N., Beekman, A. T. F., Kritchevsky, S. B., Newman, A. B., Pahor, M., Yaffe, K., et al. (2007). Psychosocial risk factors and the metabolic syndrome in elderly persons: findings from the Health, Aging and Body Composition study. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 62*(5), 563–569.
Yeh, K. C., & Kwan, K. C. (1978). A comparison of numerical integrating algorithms by trapezoidal, Lagrange, and spline approximation. *Journal of Pharmacokinetics and Pharmacodynamics, 6*, 79–98.