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STRESS, HEALTH, AND WELL-BEING ACROSS THE ADULT LIFE SPAN:

A MULTIPLE TIME-SCALE APPROACH

A Dissertation in

Human Development and Family Studies

by

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ABSTRACT

Daily stressors—minor hassles that disrupt daily life—and the biological and psychological responses to those stressors are associated with both proximal and distal health and well-being outcomes. Major stress process theories (e.g., stress and appraisal theory, allostatic load theory) suggest daily stressors may "pile up" over time (Lazarus & Folkman, 1984; McEwen, 1998). However, pathways that account for these associations across the adult life span are largely unknown and require a multi-timescale biopsychosocial approach to daily stress. At micro time-scales, new methods are needed to capture fluctuation in repeated measures (i.e., intraindividual variability, or IIV) and associated constructs. For example, how can we capture the fluctuation of stressor types an individual experiences across a typical week? How can we characterize robustness of diurnal cortisol regulation, a well-known biological marker of daily stress? At macro time-scales, empirical tests of theoretical biopsychosocial stress processes are needed to understand developmental change in stressor IIV and its long term outcomes. This dissertation consists of three studies that advance methods for analysis of daily stressor and cortisol IIV, examine developmental differences in stressor and cortisol IIV, and test stress process theory linking these IIV constructs to long-term biological and psychological outcomes.

Study 1 illustrates how an intraindividual variability (IIV) framework can be used to interpret categorical repeated measures data. Experience sampling studies often collect categorical repeated measures, including stressor types, activity types, and social partner types. Such variables are often analyzed as raw frequency counts, aggregate sums, or

collapsed binary indicators. Using 8-occasion categorical data on daily stressors from the National Study of Daily Experiences (N= 1,499, M_{Age} = 46.74, SD_{Age} = 12.91) I derive and compute six IIV metrics that invoke numeric and nominal measurement of the central tendency, dispersion, and asymmetry of individual's stressor experiences. I then examine how these metrics of IIV—*relative dominance, diversity, log-skew* and *mode, spread, order*—are related to age and interindividual differences in negative affect. Results demonstrate the utility of the numeric and nominal categorical IIV metrics; age gradients in the three numeric IIV stressor metrics reflect the changing roles and selective experiences that accompany socioemotional aging and five of six IIV metrics map differences in negative affect. Findings highlight how the unique constructs measured by these six metrics of categorical IIV may be used to examine dynamic process, study interindividual and age-related differences, and expand the variety of developmental research questions that may be answered using categorical repeated measures data.

Study 2 utilizes metrics from Study 1 to examine links between "chronic stressors," as indicated by high daily stressor exposure and low stressor diversity (i.e., many stressor experiences concentrated in one or few types), and chronic inflammation. A growing body of research has identified characteristics of stressor experiences (e.g., duration, controllability) that contribute to higher inflammation. The combination of high stressor exposure and low stressor diversity may lead to allostatic load due to failure to adapt to repeated stressors. Older adults may be at greater risk, given tendency to have lower stressor diversity than younger adults. Data for this study come from 1,011 adults aged 34-84 years who provided eight consecutive days of self-reported stressor experiences in the National Study of Daily Experiences and blood samples assayed for

six inflammatory markers in the Biomarker Project of the Midlife in the United States study. A structural equation model was used to examine the associations among systemic and endothelial inflammation, stressor exposure, stressor diversity, and age. As expected, results indicated higher stressor exposure combined with lower stressor diversity was related to higher endothelial inflammation. This combination is discussed as failure to adapt to consistently repeating stressor experiences.

Study 3 uses an IIV approach to examine the relation between Hypothalamic-Pituitary-Adrenal axis (i.e., HPA; anatomical structures that mediate physiological stress response) dysfunction and immune function. HPA axis function has a distinct diurnal pattern, peaking 30 minutes after waking, and declining thereafter until flattening in the evening. Links between cortisol trajectories and health have primarily examined individuals' typical cortisol levels and slopes. However, individuals differ in the extent that they deviate from their typical diurnal pattern. To describe each individual's typical diurnal trajectory, person-specific four-part linear spline models were fit to repeated measures of salivary cortisol (4 samples of salivary cortisol on 4 consecutive days, total of 26,191samples) obtained from N = 1705 participants (Age Range: 33-84 years) across 6,714 days. Summary measures of variability describe the extent that each individuals' repeated measures of cortisol fluctuated (i.e., cortisol variability) around his/her typical diurnal trajectory. A structural equation model was then used to test associations among diurnal cortisol trajectory slopes, cortisol variability, age, and two latent factors of inflammation (systemic and endothelial). Contrary to expectations, the combination of steeper slopes and low variability in diurnal trajectory related to higher endothelial inflammation. Implications of cortisol variability as an indicator of HPA dysregulation is

discussed, particularly as the present findings did not replicate those of the new cortisol variability literature.

Together, these papers aimed to elucidate associations among psychosocial stressor experiences, affect, and biological dysregulation at multiple time-scales in ways that support and inform major stress process theories. Each paper highlighted the usefulness of an IIV approach, and presented a novel method of examining the day-to-day dynamics of the stress process. Each paper additionally offered mathematical operationalization of stressor and stress response "pile-up" suggested in Lazarus and Folkman's (1984) psychological stress and appraisal and McEwen's (1998) allostatic load theories. Age differences in many of the forwarded metrics suggest developmental and aging-based changes across the stress process, further supporting the need for multiple time-scale designs.

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Chapter 1

Overall Introduction: Daily Stress Variability and Inflammation: Psychosocial and Biological Approaches

Day-to-day stressors, such as unexpected home chores or caring for a sick child, are associated long-term mental and physical health outcomes (Charles, Piazza, Mogle, Sliwinski, & Almeida, 2013; Cohen, Kessler, & Gordon, 1995; Lazarus & Folkman, 1984; Piazza, Charles, Sliwinski, Mogle, & Almeida, 2013). This "stress process" from daily stressor experience to disease risk occurs across multiple domains (e.g., environmental, psychological, biological, and behavioral) and at multiple timescales (e.g., millisecond to millisecond, minute to minute, hour to hour, and year to year). For example, stressor events elicit emotional and physiological reactions lasting minutes to hours after the stressor, and these responses "pile up" over years to increase risk of mental and physical illness (Cohen et al., 1995; Lazarus & Folkman, 1984; McEwen, 1998). At the same time, adult development and aging changes the stressors faced, as well as individuals' physiological and psychological responses to stressors. To quantify and identify components of the stress process and how they may differ across age, intraindividual variability approaches are particularly useful. Intraindividual variability is the relatively short-term fluctuations in a measure, theoretically driven by short-term processes (e.g. regulation, adaptation) or dynamic characteristics (e.g., lability, plasticity).

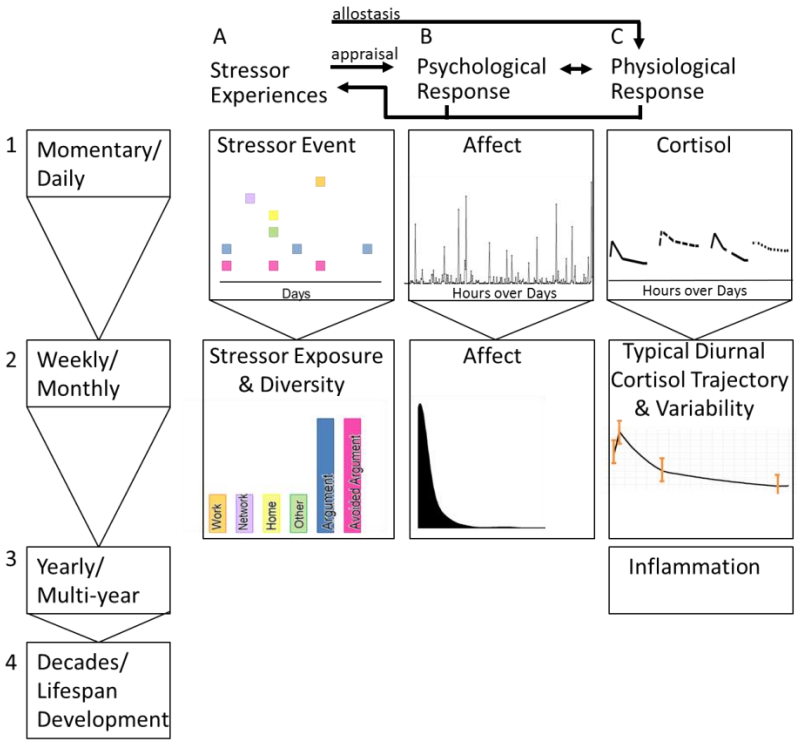
The studies that follow utilize an intraindividual variability framework to understand the psychological and biological pathways from daily stressor experiences to chronic inflammation, a biological risk factor for many age-related diseases (Ross, 1999; Straub, Miller, Schölmerich, & Zietz, 2000). The first study introduces an intraindividual variability approach to quantifying categorical variables, such as the stressor types (e.g. home overload, argument) that individuals experience. The second study uses those metrics to examine characteristics of stressors that may make individuals particularly prone to chronic inflammation. The third study applies a continuous intraindividual approach to diurnal cortisol, a hormone that responds to stress, by examining the association between cortisol variability and inflammation. All of these components of the stress process will be discussed in the context of adult development and aging.

The Stress Process

Illustrated in Figure **1-1**, is a conceptual diagram of the stress process similar to many other heuristic models of stress (e.g. see Lazarus & Folkman, 1989 p. 308, Cohen, Kessler, & Gordon, 1995 p. 11, Almeida, 2005), but specifically highlighting the timescale of the processes involved. I will first overview the theory behind the heuristic stress process indicated in the header row (A, B, and C), from stressor experience through psychological and physiological responses. Here, stressors are defined broadly as stimuli that demand psychosocial and/or physiological adaptation (Cohen et al., 1995). Following an environmental perspective, stressor exposure (A) can be measured in terms of frequency, threat or loss domain, and culturally agreed upon severity (Almeida, 2005).

Upon stressor exposure, an individual appraises the person-environment transaction as taxing or overwhelming his/her coping abilities and resources (arrow between stressor and psychological response) (Lazarus & Folkman, 1984). Included in the psychological response (B), the acute emotional response hinges on the appraisals that defined the stress (Lazarus & Folkman, 1984; McEwen, 1998). Perceived harm, loss, or threat elicits negative emotions (e.g., anger, fear, resentment, sadness). Emotions and appraisal change throughout the stressful transaction as coping behaviors (e.g., emotion regulation, direct problem solving, distracting activities) change the situation (Lazarus & Folkman, 1984).

Figure 1-1. Conceptual model for examining links among various components of the stress process at multiple time-scales.



Stressors may directly (arrow A to C) or indirectly—via emotional response (arrow B to C)— elicit physiological reactions (Cohen et al., 1995; McEwen, 1998). The longest established stress responding systems are the Sympathetic-Adrenal-Medullary (SAM), that secretes the hormones epinephrine and norepinephrine, and the Hypothalamic-Pituitary-Adrenal (HPA), that secretes adrenocorticotropic hormone that activates the adrenal gland to produce the hormone cortisol. These systems are interrelated (e.g., positive feedback loop between norepinephrine and cortisol) and subsequently regulate cardiovascular, metabolic, and immune responses to stress (Chahal & Drake, 2007; Straub et al., 2000). The process by which these physiological systems change to respond to challenges and return to baseline homeostasis is called allostasis.

Theoretically, the above acute stress processes are linked across time scales to long term outcomes via a variety of mechanisms. Adding timescale (leading column 1, 2, 3, 4) to the conceptual diagram of the stress process helps us organize the various pathways through which daily stress leads to health and well-being across timescales. Connecting daily stressor experiences to weekly/monthly stressor characteristics, such as stressor diversity and stressor exposure (column A, moving down in time-scale rows) are the person-environment transactions that create, for example, chronicity out of daily experiences (Lazarus & Folkman, 1984). Connecting appraisal and perceived outcomes of stress (e.g., high negative affect due to perceiving stressor as uncontrollable) at the momentary/daily level to weekly or monthly patterns of responses and even more stable patterns of behavior (column B, moving down in time-scale rows) is the “pile up” of (in)effective coping strategies and internalized expectations of stressor outcomes

(Lazarus & Folkman, 1984). Connecting daily physiological stress response to yearly and developmental time-scale dysregulation (and subsequently life span dysregulation predicts daily and momentary dysregulation patterns, in a bidirectional arrow along the column C) is allostatic load (McEwen, 1998). Allostatic load is the cumulative "wear and tear" on physiological systems due to repeated physiological activation (from novel stressors or lack of adaptation to repeated stressors), extended, or inadequate response to stressors (McEwen, 1998). Allostatic load also incorporates repeated experiences of negative emotions in response to stressors, and thus would also serve as an arrow from momentary stressors to momentary negative affect, and pile-up over time to reach longer time-scale biological dysregulation.

Socioemotional aging theories also bidirectionally connect lifespan development and biological vulnerabilities (bottom row) with daily stressor experiences, affect, and biological responses (Baltes & Baltes, 1990; Carstensen, Isaacowitz, & Charles, 1999; Charles, 2010). For example, as adults age, they accumulate experience emotion-regulating in response to stressors (i.e., moving down the time scale column of the arrow between stressor experiences and psychological response). This experience subsequently leads older adults to selectively avoid stressor experiences and employ emotion-related coping strategies, thus moving back up the time scale column to allow developmental processes to influence daily experiences. It is important to note that there are also bidirectional associations with sociocultural and personal resources and vulnerabilities not pictured here (Lazarus & Folkman, 1984; Pearlin, 1989). In this dissertation, I operationalize and test allostatic load theory's and stress and appraisal theory's links

between daily stressor experiences, emotions, and physiological wear and tear, and I examine the influence of developmental and aging processes on stress processes.

Time Scale and Intraindividual Variability

Stressor appraisals, emotional and physiological response, and coping behavior all display variation within-persons and across days (Montpetit, Bergeman, Deboeck, Tiberio, & Boker, 2010; Neupert et al., 2016; Ong, Bergeman, Bisconti, & Wallace, 2006; Sliwinski, Almeida, Smyth, & Stawski, 2009; Whitehead & Bergeman, 2013), suggesting that stress is indeed a dynamic within-person process that should be examined intra-individually. For example, on days when an individual faces a stressor, evidence suggests the individual's diurnal cortisol rhythm may change—a pattern that over time may lead to long-term health consequences (Stawski, Cichy, Piazza, & Almeida, 2013a). Defining the timescale of each examined variable helps reveal what mechanisms underlie these associations. The study of intraindividual variability (IIV) provides methods for assessing relatively shorter-term processes (e.g., row 1 and 2), in contrast to longer-term developmental change (e.g., row 3), and so is particularly useful in understanding daily stressor experiences. In the leading row of Figure 1-1, each shorter timescale is depicted as a zoomed in version of the successively more macro timescale.

Intraindividual variability metrics and models allow us to begin to define the *dynamic characteristics and processes* of emotion regulation from daily affect, allostatic load from daily physiology, and stressor exposure from daily stressor experiences (Ram & Gerstorf, 2009). For instance, we can take the time series represented in the first row of

each component of the stress process and summarize them with an intraindividual distribution (e.g., row 2, column A: intraindividual stressor type distribution; row 2, column B: intraindividual distribution of negative affect) or by modeling the intraindividual process and variability with traditional growth curve or time series approaches (e.g., row 2, column C: intraindividual diurnal cortisol growth curve, with residual variability) (Ram & Gerstorf, 2009). These approaches have been used to characterize IIV in a variety of domains, including cognition (e.g., low IIV in reaction time as an indicator of neurobiological robustness), social engagement (e.g., high IIV in activity diversity as an indicator of greater engagement), and emotion regulation (e.g., IIV in positive and negative affect and in emotion experience as indicators of emotion regulation) (Benson, Ram, Almeida, Zautra, & Ong, 2017; Eid & Diener, 1999; Lee et al., 2016; Stuart W.S. MacDonald, Li, & Bäckman, 2009; Christina Röcke & Brose, 2013). Age-related differences in IIV have subsequently been interpreted as increases in neurobiological frailty, lower social engagement, and improved emotion-regulation (Carstensen et al., 1999; Lee et al., 2016; Stuart W.S. MacDonald et al., 2009). Notably, these interpretations mostly center on IIV as a person characteristic, but theoretical interpretations of IIV as characterizing the context (e.g. stressor heterogeneity, Brose et al., 2013) or the person-context transaction (e.g., allostasis, Martin & Hofer, 2004) should also be considered. In this dissertation I use an IIV approach to operationalize stressor chronicity and HPA dysregulation.

Adult Development and Aging as Moderators of Links between Short-term Processes and Long-term Outcomes

In considering multi-timescale stress processes, it is particularly important to consider developmental and aging-related changes that may result in differences in IIV and/or how age may moderate links between IIV and biological and psychological well-being. In terms of stressor exposure, older adults select out of potentially stressful situations, and focus (optimize) emotion-regulation resources toward unavoidable stressors (Baltes, 1997). This results in lower stressor IIV: less stressor exposure, and less diverse stressor experiences with age (Brose, Scheibe, & Schmiedek, 2013; Koffer, Ram, Conroy, Pincus, & Almeida, 2016). Differences in day-to-day stressor exposure may then partially account for differences in affect variability and weekly/monthly affect among younger and older adults (Brose et al., 2013; Christina Röcke & Brose, 2013). Further, socioemotional aging theories and evidence suggests older adults are less affectively reactive to stress partly due to less threatening appraisals, more socioemotional-oriented goals, and avoidant coping techniques (Charles, 2010; Luong & Charles, 2014). In brief, associations among IIV in stressor exposure, affect, and long-term outcomes exist within the context of developmental changes in avoiding and regulating response to stressors.

Biologically, normative aging is associated with functional changes in many bodily systems that make older adults more vulnerable to adverse effects of stressor experiences. Though a thorough review of age-related biological changes is beyond the scope of this paper (see e.g., Epel & Lithgow, 2014; Gruenewald & Seeman, 2010a; Straub et al., 2000; Vitale, Salvioli, & Franceschi, 2013), there is a general trend of

accumulated “wear and tear.” Particularly relevant to the stress process, older adults tend to have poorer regulation over the neuroendocrine system (Chahal & Drake, 2007). Specifically, at the minute-to-minute timescale older adults experience prolonged cortisol secretion in response to stressors; and at the day-to-day timescale, while peak cortisol output during the diurnal rhythm is preserved with age, older adults display less decline throughout the day (Bergendahl, Iranmanesh, Mulligan, & Veldhuis, 2000; Chahal & Drake, 2007; Karlamangla, Friedman, Seeman, Stawski, & Almeida, 2013). As one of cortisol’s many functions is regulating inflammation, dysregulation in diurnal cortisol leads to higher inflammation with age (Straub et al., 2000). With the interdependence of biological systems, normative aging is still associated with spirals of dysregulation across systems that may exacerbate longer timescale effects of daily stress processes. In this dissertation I operationalize and test Baltes’ (1990) Selection, Optimization, and Compensation theory of aging, as well as related socioemotional aging theories (e.g., Socioemotional Selectivity Theory; Carstensen et al., 1999 ; Strengths and Vulnerability Integration Theory; Charles, 2010), and theoretical links between endocrine and immune system dysfunction with age (Straub et al., 2000).

Present Studies

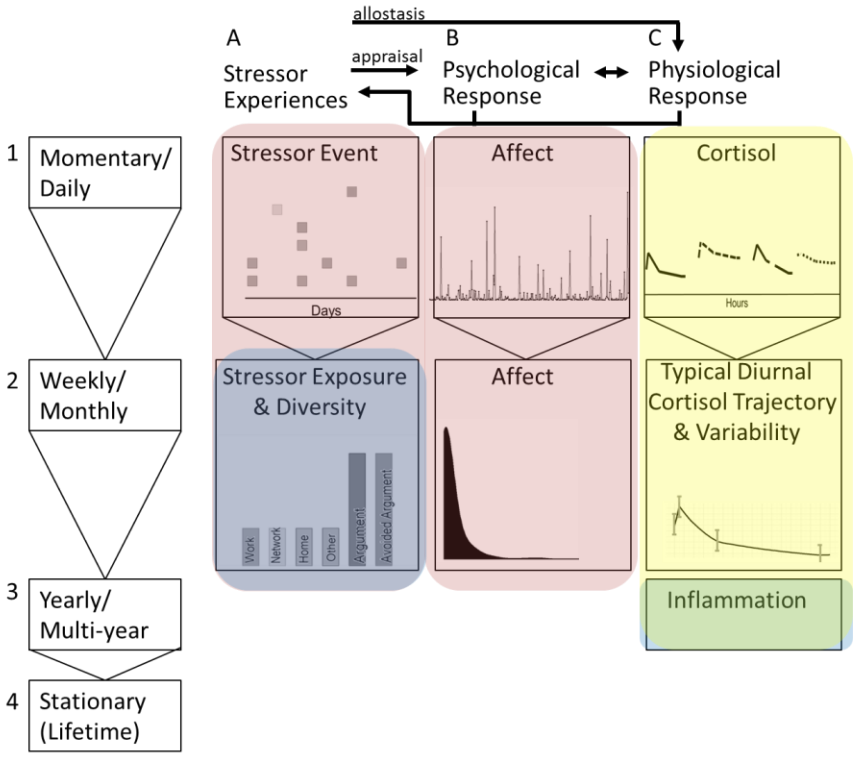
Together, the following dissertation studies use IIV methods to examine associations among stressor exposure, affect, and associated indicators of biological dysregulation at multiple time-scales. Study 1 (shaded red in

Figure 1-2) addresses a need for methods to examine IIV in categorical repeated measures, such as stressor types. The study first develops a framework of metrics to examine both quantitative and qualitative aspects of intraindividual variability in everyday stressor experiences. Then, it displays whether and how these indicators of psychosocial stressor variability are associated with mean day-to-day negative affect and age, as predicted by stress and appraisal and socioemotional aging theories. Study 2 (shaded blue in

Figure 1-2) uses one of the metrics introduced in study 1 to examine the association between day-to-day stressor diversity and a long-term physiological outcome, chronic inflammation. Chronic systemic inflammation is an important contributor and predictor of many physical health ailments, including cardiovascular disease, diabetes, and frailty (Goldberg, 2009). Founded in allostatic load theory, high exposure and low stressor diversity is hypothesized to be associated with higher systemic inflammation. Older age may exacerbate this link due to physiological vulnerability. Study 3 (shaded yellow in

Figure 1-2) provides a biological examination of the association between day-to-day regulation and allostatic load. Applying an IIV approach to daily cortisol trajectories, this study tests whether higher cortisol variability as an indicator of biological dysregulation is associated with higher inflammation, and again whether age exacerbates this link. Each study uses a subsample of the Midlife in the United States Study, a large adult lifespan sample allowing comparison of interindividual differences in intraindividual variation in psychosocial stressors, affect, and biological stress mediators.

Figure 1-2. Dissertation studies within the conceptual framework.


allostasis
A
Stressor Experiences
appraisal
B
Psychological Response
C
Physiological Response
1
Momentary/ Daily
2
Weekly/ Monthly
3
Yearly/ Multi-year
4
Stationary (Lifetime)
Stressor Event
Days
Affect
Cortisol
Hours
Stressor Exposure & Diversity
Work
Network
Home
Other
Argument
Avoided Argument
Affect
Typical Diurnal Cortisol Trajectory & Variability
Inflammation

Chapter 2

Study 1: More than Counting: an Intraindividual Variability Approach to Categorical Repeated Measures

Intraindividual variability (IIV) is fluctuation of an individual's repeated measures over micro time-scales. Within the lifespan developmental framework, studying IIV can illuminate individuals' dynamic characteristics and how they change over the life span (Nesselroade, 1991). Indeed, IIV methodology provides a window into important developmental processes (Ram & Gerstorf, 2009). For example, moment-to-moment or day-to-day affective variability can reflect personality traits (e.g., emotional stability; Eid & Diener, 1999; Fleeson, 2001), and age-related changes in emotion regulation (Liu, Bangerter, Rovine, Zarit, & Almeida, 2016; C. Röcke, Li, & Smith, 2009). Most IIV-based studies of aging have focused on continuous variables, but there is also a need to capture age-related changes in categorical IIV constructs (van Dijk & van Geert, 2015). In this paper we apply general IIV principles to study variability in *types* (i.e., categories) of events, activities, or social interactions over time (e.g., during a typical week). Based on principles underlying the statistical moments of continuous IIV distributions (iMean, iSD, iSkew), we develop and illustrate how six categorical IIV metrics may capture novel and important age-related processes. Specifically, we demonstrate how categorical IIV metrics and constructs can help articulate developmental and aging theories.

Stressor Experience as an Ecosystem

Our exploration into categorical IIV is motivated by daily stress research, where key variables are categorical – "Did a stressful event happen today? (yes/no); What type? (argument, home overload, work/education overload, etc.)". Repeated measurements from daily diary studies has enabled study of interindividual and age-related differences in *stressor exposure* (the total number of stressors an individual experiences) and *stressor reactivity* (intraindividual covariation between daily stressors and daily negative affect). Generally, both greater stressor exposure and reactivity are associated with poorer well-being, while stressor reactivity also relates to compromised health, and increased mortality risk (Almeida, 2005; Charles, Piazza, Mogle, Sliwinski, & Almeida, 2013; Mroczek et al., 2015). Developmentally, stressor exposure decreases across adulthood, while stressor reactivity has no clear, consistent age gradient (Bellingtier & Neupert, 2016). Invoking parallelism between biological and human ecology, Koffer and colleagues (Koffer et al., 2016) characterized individuals' daily stressor experiences as a stressor ecosystem that could be quantified using metrics from biology: abundance (number of organisms/stressor types) and diversity (relative abundance across species/stressor types). They found individuals with higher stressor exposure and lower *stressor diversity* had lower positive affect and higher negative affect (see also Brose, Scheibe, & Schmiedek, 2013). Stressor diversity decreased with age, with older adults being particularly vulnerable to chronic stressors. Theoretically, these findings provided a new operationalization of chronic stressors, demonstrated the usefulness of an ecosystem analogy for stressors and resource use, and examined how stressors influence individuals'

daily well-being across the life span. Methodologically, these findings demonstrated the utility of quantifying categorical IIV in the study of successful aging. We now reach further into the biological literature – a literature with established need and methods for examining categorical data – to identify metrics that systematically extract more information from categorical IIV data.

The Statistical Moments of IIV Distributions

IIV research often summarizes intensive repeated measures obtained on continuous scales. In the upper panel of Figure **2-1**, $T = 100$ simulated repeated measures from a hypothetical individual are summarized in the (IIV) distribution on the left. The *statistical moments* of the distribution – mean, variance, and skew – represent specific features that might differ across distributions: interindividual differences in IIV (e.g., Newell & Hancock, 1984). Our proposal is that, with categorical time-series, metrics for the first three statistical moments of categorical distributions – central tendency, dispersion, and asymmetry – will also hold value as interindividual difference measures. In the lower panel of Figure **2-1**, $T = 100$ repeated measures of a multi-category variable (e.g., for stressor or activity type, colored squares would represent when particular types of stressors or activities were reported) are summarized in the (categorical IIV) distribution on the left, the features of which (e.g., height of bars, color of bars, order of bars) might be indicators of IIV constructs. Borrowing from ecological literature, we explore the utility of three *numeric metrics* and three *nominal metrics* that describe both quantitative and qualitative aspects of the central tendency, dispersion, and asymmetry of

categorical IIV distributions. In the sections that follow, we walk through the Figure **2-2** flowchart, defining each distributional attribute of interest, describing associated research questions, articulating mathematical details of the categorical IIV metrics, and providing an empirical example using categorical IIV stressor distributions.

Figure **2-1.** *Continuous and Categorical IIV Data and Distributions*. A simulated *continuous* IIV data stream with *T*=100 occasions (top right) is collected into an intraindividual distribution (top left), and summarized by measures of central tendency (mean), dispersion (standard deviation), and asymmetry (skew). A simulated *categorical* IIV data stream with *T*=100 occasions (bottom right) is collected into an intraindividual distribution (bottom left). Each colored square represents when a particular category was reported. The categorical intraindividual distribution arranges the categories in height order by frequency. Like the continuous intraindividual distribution, categorical intraindividual distributions can be summarized by descriptions of central tendency, dispersion, and asymmetry.

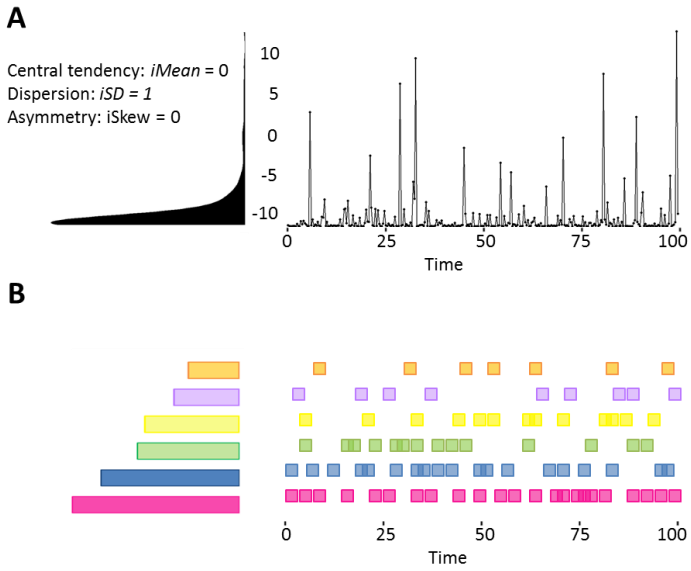
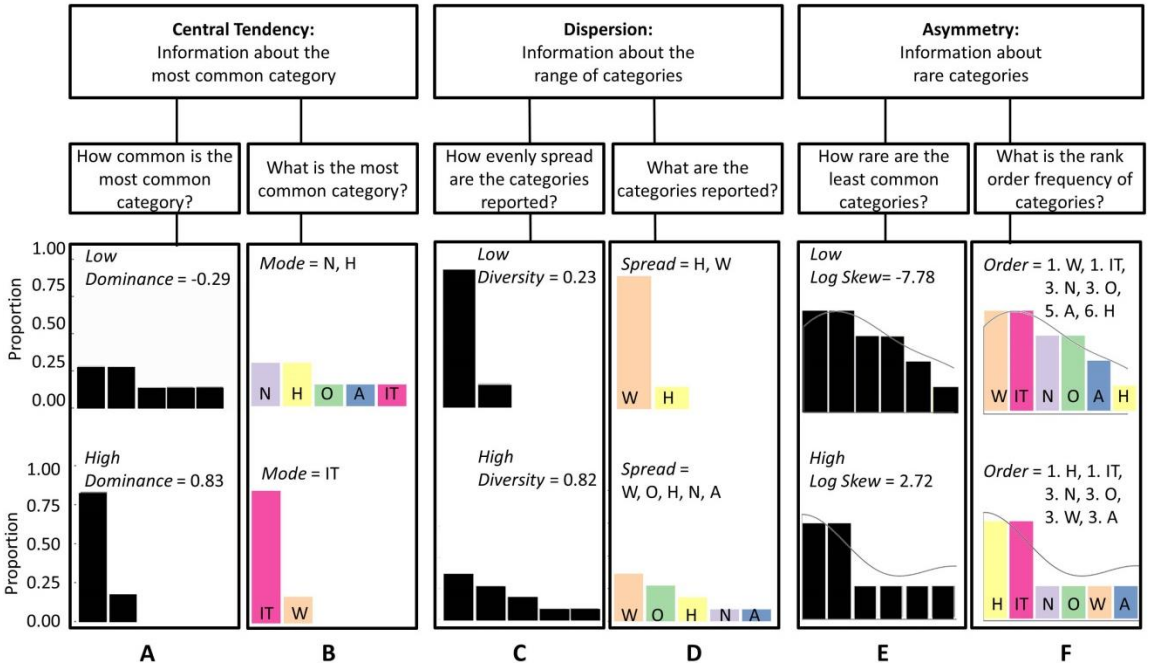


Figure **2-2.** *Flow chart guiding researchers from the distributional characteristic of interest (i.e., central tendency, dispersion, asymmetry) on the top row, to research questions on the middle row, to metrics that describe such characteristics on the bottom row.* Categorical IIV distributions that differ in central tendency (Panel A: with numeric relative dominance, Panel B: with nominal mode metrics), dispersion (Panel C: with numeric diversity, Panel D: with nominal spread metrics), and asymmetry (Panel E: with numeric log-skew, Panel F: with nominal order metrics). The distributions at the top and bottom of each Panel represent a different individual's stressor experiences; the six individuals' distributions are displayed either in in black and white (B, D, F), indicating a numeric approach, or in color (A, C, E), representing a nominal approach. Gray line is a smoothed density curve highlighting asymmetry of distribution. Note: IT= non-argument interpersonal tensions (*pink*), A=argument stressors (*blue*), W= work stressors (*orange*), H=home stressors (*yellow*), N=network stressors (*purple*), O=other stressors (*green*).



Numeric Metrics for Categorical IIV

We begin by examining utility of numeric metrics (depicted in Figure **2-2**, Panels A, C, and E) that describe the first three statistical moments of the categorical IIV distributions.

Central Tendency.

The central tendency of categorical distributions, the mode, is a nominal category, but a numerical counterpart, *relative dominance,* quantifies how dominant that mode is using the proportion of observations in the modal category. Figure **2-2**, Panel A depicts IIV stressor distributions from two persons, histogram bars ordered left to right by proportion of stressors in each category. Looking only at the *height* of the equally tallest bars, we see that the person at the top of the panel experiences the dominant stressor only slightly more frequently than other stressor types (low relative dominance; p_{i1} = .286). In contrast, the person at the bottom experiences the dominant stressor much more frequently than other stressor types (high relative dominance; p_{i1} = .833).

Stressor relative dominance indicates the extent to which the dominant stressor drives an individual's stressor experiences. A variety of aging-related hypotheses might be invoked using this metric. For example, life course role change theory (Pearlin, 1989) suggests stressor relative dominance will be lowest in midlife, when individuals simultaneously serve in multiple roles.

Dispersion.

The dispersion of a categorical distribution quantifies how evenly observations are distributed across categories. Ecologists describe an ecosystem's species *diversity* with a variety of metrics, the most popular being Shannon's (1948) entropy metric that quantifies relative abundance of different species in terms of evenness (Magurran & McGill, 2011). Looking at the relative height of the bars in Panel C of Figure **2-2**, we see that the person at the top of the panel has relatively low diversity ($diversity_i$ = .23), with most observations concentrated in one category. In contrast, the person below has high diversity ($diversity_i$ = .82), with observations relatively evenly distributed across five of the six possible categories.

In the stressor ecosystem, *stressor diversity* indicates heterogeneity of stressor experience. As previously mentioned, researchers have begun to test developmental hypotheses with stressor diversity metrics. For example, age-related selective pruning and regulation of experiences suggest stressor diversity decreases with age (Brose et al., 2013; Koffer et al., 2016).

Asymmetry.

Skew describes the asymmetry of probability distributions. For categorical distributions, skew is quantified in terms of "rarity" – how much the least common categories influence the distribution structure. In particular, *log-skew* indicates the proportion of observations in rare categories (the tail of the distribution) relative to the proportion of observations in common categories. Looking at the relative heights of the

tallest and shortest bars in Panel E of Figure **2-2**, we see that the person at the top of the panel has proportionally more observations in "rare" categories ($log\text{-}skew_i$ = -7.78) compared to the person at the bottom ($log\text{-}skew_i$ = 2.72). Generally, negative log-skew indicates that all types are fairly common while higher positive log-skew indicates that some types are very rare.

In the stressor ecosystem, *stressor log-skew* reflects whether an individual experiences stressors that are atypical for him/herself. Thus, stressor log-skew allows for testing of age-related changes in the rarity of stressor types. For example, socioemotional aging theories (Carstensen et al., 1999; Charles, 2010) suggest that older adults may, because of selective engagement with activities and social partners, have a few commonly experienced stressor types and very few rarely experienced stressor types (higher log-skew).

Nominal Metrics for Categorical IIV

Numeric metrics compress the complexity of the categorical distribution that, by definition, is already a concise multi-dimensional representation of taxonomic abundance (Li, Bihan, Yooseph, & Methé, 2012). When describing the visual depictions of low and high relative dominance, diversity, and log-skew, we only referred to the heights of the bars in Figure **2-2** (i.e., global quantifiable properties), without considering the *colors* of the bars (i.e., content differences). To capture the content information we outline three nominal metrics (depicted in Figure **2-2**, Panels B, D, and F) as qualitative counterparts to the quantitative metrics above.

Central Tendency.

The central tendency of categorical distributions is the mode – the most abundant category. Parallel to Panel A of Figure **2-2**, Panel B depicts categorical IIV stressor distributions obtained from two persons, histogram bars ordered left to right by proportion of stressors in each category. Looking now only at the *color* of the tallest bar, we see the person at the top of Panel B has a dual mode, *purple and yellow* (equivalent number of network and home stressors), while the person at the bottom has a *pink* mode (non-argument interpersonal tensions). In our 6-category example, the nominal mode has 6 possible values (or, when allowing for potential ties like the person at the top of Panel B, $2^6 = 64$ possible values).

In the stressor ecosystem, *modal stressor* is the expected stressor type an individual will encounter. Hypotheses regarding age-related differences in expected stressor type can then be tested with this nominal metric. For example, Socioemotional Selectivity Theory (Carstensen et al., 1999) suggests older adults are less likely than younger adults to report arguments as their modal stressor.

Dispersion.

From a qualitative perspective, the nominal *spread* or range of a categorical distribution is a list of the categories that have one or more observations. Looking again only at the *colors* of the bars in Panel D of Figure **2-2**, we see the person at the top has a spread of [*orange, yellow*] (i.e., [*work, home*]), while the person at the bottom has a

spread of [*orange, green, yellow, purple, and blue*] (i.e., [*work, other, home, network, and argument*]). In our 6-category example, nominal spread has $2^6 = 64$ possible values.

In the stressor ecosystem, *stressor spread* indicates the specific stressor types an individual experiences and across which coping resources must be deployed. Again, a variety of developmental hypotheses might be invoked using stressor spread. For example, life course role change theory (Pearlin, 1989) suggests stressor spreads experienced by older and younger adults differ, with younger adults' spreads including [work, home, argument], and older adults' spreads including [non-argument interpersonal tension, network].

Asymmetry.

Finally, the asymmetry of nominal categories—the nominal *order*— can be derived by rank-ordering the elements of the categories according to frequency of occurrence. Consider the bars in Panel F of Figure **2-2,** that have been ordered left to right based on height, tallest to shortest. The person at the top of the panel has nominal order of [*1. orange, 1. pink, 3. purple, 3. green, 5. blue, 6. yellow*] (i.e., [*1. work, 1. non-argument interpersonal tension, 3. network, 3. other, 5. argument, 6. home*], while the person at the bottom has nominal order of [*1. yellow, 1. pink, 3. purple, 3. green, 3. orange, 3. blue*] (i.e., [*1. home, 1. non-argument interpersonal tension, 3. network, 3. other, 3. work, 3. argument*]). In our 6-category example nominal order has $6! + 5! + 4! + 3! + 2! + 1! = 873$ possible values, and even more when adjusting rank numbers to reflect ties (i.e., equivalent frequencies) as above.

In the stressor ecosystem, *stressor order* indicates the relative frequency of stressor types, possibly reflecting the relative demands stressor types make on psychosocial resources. For example, for the person at the top of Panel F, work stressors occur more frequently than home stressors, whereas for the person at the bottom, home stressors occur more frequently than work stressors. Given such differences, stressor order might be used to articulate hypotheses derived from socioemotional theories of aging (Carstensen et al., 1999; Charles, 2010). In particular, such theories suggest arguments should appear later (i.e., relatively less frequently) in the stressor order for older adults than for younger adults.

The Present Study

Using a national study of individuals' daily stressor experiences, we demonstrate how an intraindividual variability framework can parse additional information from categorical repeated measures in three steps. First, we calculate six metrics that describe features of individuals' categorical IIV distributions following the examples in Figure **2-2**. Second, we examine age-gradients in the numeric metrics, expecting that older age is associated with more stressor dominance, less stressor diversity, and more stressor skew. Third, in the context of daily stress models, we assess the relation between interindividual differences in each categorical IIV metric and interindividual differences in negative affect. We expect higher stressor relative dominance, lower stressor diversity, and higher stressor skew to each be associated with higher negative affect, and we explore age-moderation of those associations. Similarly, but without directional specificity, we expect

negative affect differences across groups defined by modal stressor, stressor spread, and stressor order. Working from these initial demonstrations, we speculate how categorical IIV metrics may contribute to theory development or revision in multiple domains.

Method

Data are from Wave 1 of the National Survey of Daily Experiences (NSDE), the daily diary component of the Midlife in the United States Survey (MIDUS). Details relevant to the current analysis are given below (see also Almeida, Wethington, & Kessler, 2002).

Participants

As part of MIDUS 1 (1995–1996), 7,108 participants completed a telephone psychosocial battery (Brim, Ryff, & Kessler, 2004), with 1,843 of these individuals randomly selected to participate in the NSDE (Wave 1, 1996–1997), an 8-day daily diary study. Of these, 1,499 respondents (81% of those contacted) provided data on their daily experiences. Participants ranged from age 24 to 74 years (M = 46.74, SD = 12.91), and approximately half were female. The majority were white (91.45%), married or living with a romantic partner (77%), with an average of two children (M=2.30, SD = 3.01), median income of $55,000, and "very good" physical health (M = 3.60, SD = 0.96).

Procedure

Participants were compensated $20 in advance and asked to complete 8 consecutive days of semi-structured telephone interviews. They reported their experiences that day, including *stressor events* and *affect* (Almeida et al., 2002). Participants provided between 1 and 8 days of data (M = 7, SD = 1.41), with 87.19% providing 6 or more daily reports and 50.63% providing all 8 daily reports.

Measures

Daily Stressors. Individuals' stressor experiences were assessed using the Daily Inventory of Stressor Events (DISE; Almeida et al., 2002). Assessments of *arguments, non-argument interpersonal tensions*, and *network stressors* probed the experience of such occurrences as judged by the individual: "Did you have an argument or disagreement with anyone since (this time/we spoke) yesterday?"; "Since (this time/we spoke) yesterday, did anything happen that you could have argued about but you decided to let pass in order to avoid a disagreement?"; and "Since (this time/we spoke) yesterday, did anything happen to a close friend or relative (other than you've already mentioned) that turned out to be stressful for you?" Assessments of *work stressors, home stressors*, and *other stressors* were framed in terms of events that most people would consider stressful: "Since (this time/we spoke) yesterday, did anything happen at [question domain] (other than what you already have mentioned) that most people would consider stressful?" Assessment of *discrimination* was prefaced with: "Many people experience discrimination on the basis of such things as race, sex, or age. Did anything like this

happen to you since (this time/we spoke) yesterday?" Each day participants indicated whether they had (= 1) or had not (= 0) experienced each of the seven stressor types. On average, participants reported one or more stressors on 39.53% of study days, with *M*= 0.55 (*SD*= 0.47) stressors per day. The most common stressor type was non-argument interpersonal tensions (27.29% of stressor days), followed by arguments (18.13%), work (17.83%), home (14.94%), network (10.54%), other (9.39%), and discrimination (1.97%). For parsimony, categories with less than 5% of the total observations (discrimination) were removed, leaving $m = 6$ categories. *Stressor exposure* was calculated as the sum total number of stressors over the study period.

Negative Affect. Each day, participants indicated "How much of the time today did you feel _____?" on a 0-4 scale, where 0 = "none of the time," 1 = "a little of the time," 2 = "some of the time," 3 = "most of the time," and 4 = "all of the time." Daily *negative affect* (NA) was calculated as the average of responses to 12 items (Mroczek & Kolarz, 1998): depressed, restless or fidgety, so restless that you could not sit still, nervous, so nervous that you could not calm down, worthless, so sad that nothing could cheer you up, tired out for no good reason, that everything takes an effort, hopeless, angry or irritable. The eight daily NA scores were averaged to obtain a single *negative affect* interindividual differences variable (Cronbach's $\alpha = .89$).

Data Analysis

Our analytical goals were to (1) describe the first three statistical moments of categorical stressor type distributions by computing three *numeric* metrics (a) relative dominance of the modal stressor (b) stressor diversity, and (c) stressor log-skew, and

three *nominal* descriptives (d) modal stressor, (e) stressor range, and (f) stressor order, and (2) assess age-differences in numeric metrics, and examine how interindividual differences in the numeric and nominal metrics related to individuals' NA.

Preliminaries

To pre-process the data, we computed, for each individual *i*, the total number, n_{ij}, of stressors reported in each type, $j = 1$ to m (where $m = 6$), and the proportion of stressors in each type ($p_{ij} = \frac{n_{ij}}{\sum_{j=1}^{m} n_{ij}}$). We then ordered the proportions from largest to smallest (e.g., p_{i1} to p_{i6} with $p_{ij} \geq p_{ij+1}$) and retained the corresponding stressor type as a linked variable, *rank. type*$_{i1}$ to *rank. type*$_{i6}$, [e.g., 1. arguments, 2. non-argument interpersonal tensions, 3. home stressors, 4. network stressors, 5. work stressors, 6. other stressors]. In cases where proportions were equal, the linked ordering was adjusted to reflect equality in rankings [e.g., 1. arguments, 1. non-argument interpersonal tensions, 1. home stressors, 4. network stressors, 5. work stressors, 6. other stressors].

Numeric Metrics for Categorical IIV

Using the counts (n_{ij}) and ordered proportion scores (p_{i1} to p_{i6}) described above, we compute *relative dominance, diversity,* and *log-skew* indices for each individual's repeated measures of daily stressors.

Relative Dominance (central tendency). The *stressor relative dominance* score is the modal stressor's proportion of individual *i*'s total stressor experiences, $p_{i1} = p_{max}$ (Berger & Parker, 1970). Using the proportion instead of the number of modal stressor

events corrects for differences in total number of observations and allows for comparisons across individuals with differing total exposure to stressors (Magurran & McGill, 2011).

Diversity (dispersion). The diversity of each individual's stressor experiences across all study days is quantified using Shannon's (1948) entropy index. Specifically,

$$Diversity_i = -\left(\frac{1}{\ln(m)}\right)\sum_{j=1}^{m} p_{ij}\ln p_{ij} \quad (1)$$

where m is the number of available stressor categories (m = 6), and p_{ij} is the proportion of individual i's stressors that were in each category, j = 1 to m. Entropy scores can range from 0.0 (no diversity; all daily stressor experiences are of a single type), to 1.0 (maximum diversity; all six stressor types are evenly represented).

Log-skew (asymmetry). The rarity metric, log-skew indicates extent of the stressor distribution's asymmetry, with the assumption that non-modal stressor experiences are rare compared to the modal stressor and thus approximate a log-normal distribution. *Stressor log-skew* for each individual, *i*, is computed as

$$\log skew_i = \left[\frac{\frac{\sum(\log(n_{ij})^3}{m}}{\left(\frac{\sum(\log(n_{ij})-\mu_{\log(n_{ij})})^2}{m}\right)^{\frac{3}{2}}}\right] * \frac{m}{m-2} * \sqrt{\frac{m-1}{m}} \quad (2)$$

where $m = 6$ is the total number of stressor types, and n_{ij} is the number of stressors within each category.

Nominal Metrics for Categorical IIV

Using the ordered category labels, $type_{i1}$ to $type_{i6}$ from preliminary processing, we extract the nominal metrics, *mode, spread,* and *order*, for each individual's repeated measures of daily stressors.

Mode (central tendency). The stressor type, $type_{i1}$, with the largest p_{ij} is the individual's mode. Where there were ties (e.g., $p_{i1} = p_{i2} = p_{max}$), a new category was created to reflect the mixed-type mode.

Spread (dispersion). Each individual's unordered list of reported stressor types indicates the nominal spread of stressors. These lists are determined via each individual's *unordered* type indicators (e.g., derived from the binary lists indicating whether =1 or not = 0 an individual experienced each of the $j = 1$ to m stressor types during the study period). For example, in our $m = 6$ situation, one individual's spread may be $\boldsymbol{spread}_i$ = [$type_{i1}$, $type_{i2}$, $type_{i3}$, $type_{i4}$, $type_{i5}$, $type_{i6}$] * [0,0,0,1,0,1] = [$type_{i4}$, $type_{i6}$] while another individual may have $\boldsymbol{spread}_i$ = [$type_{i1}$, $type_{i2}$, $type_{i3}$, $type_{i4}$, $type_{i5}$, $type_{i6}$] * [1,1,1,1,1,1] = [$type_{i1}$, $type_{i2}$, $type_{i3}$, $type_{i4}$, $type_{i5}$, $type_{i6}$].

Order (asymmetry). The rank order of stressor types indicates the relative influence of each stressor type, from most abundant to least abundant. Each individual retains a concatenated string of the rank ordered $type_{ij}$ variables. Stressor types with $p_{ij} = 0$ remain in the string, as the lowest rank for the particular individual. Rank numbers are attached to the stressor type in order to reflect exact ranking and ties (e.g., [*1. home stressors, 1. non-argument interpersonal tensions, 3. network stressors, 3. Other stressors, 3. work stressors, 3. arguments*]). For programming purposes, we additionally maintained an

implicit ordering when stressor types were equal. Specifically, when frequencies were equivalent, ordering was given by sample-level frequency (an arbitrary choice for ordering within ties).

Interindividual Differences in Categorical IIV: Age Gradients and Associations with Negative Affect

With the six categorical IIV metrics calculated/derived, these new interindividual differences variables (and the constructs they measure) can be examined for relations with age and other interindividual differences. For the numeric metrics, age gradients were determined by regressing each metric on age and quadratic age:

$$Numeric\ IIV\ Metric_i = \beta_0 + \beta_1 Age_i + \beta_2 Age_i^2 + \varepsilon_i \quad (3)$$

Subsequent associations with negative affect were examined using three regressions (each numeric metric separately) of the form,

$$Negative\ Affect_i = \beta_0 + \beta_1 Numeric\ IIV\ Metric_i + \beta_2 StressorExposure_i + \beta_3 Age_i + \beta_4 Numeric\ IIV\ Metric_i * StressorExposure_i + \beta_5 Numeric\ IIV\ Metric_i * Age_i + \beta_6 StressorExposure_i * Age_i + \beta_7 Numeric\ IIV\ Metric_i * StressorExposure_i * Age_i + \varepsilon_i \quad (4)$$

where, with all grand-mean centered predictors, β_0 is the prototypical NSDE participant's expected negative affect, β_1 is the unique association between the numeric IIV metric (i.e., stressor relative dominance, stressor diversity, or stressor log-skew) and NA, β_2 is the unique association between stressor exposure and NA, β_3 is the unique association between age and NA, β_4 is the extent that the numeric IIV metric moderates the

association between stressor exposure and negative affect, $\beta_{5\text{-}7}$ are the extent that the age moderates the above associations, and ε_i is unexplained residual that is assumed independent and normally distributed. Stressor exposure, an established predictor of negative affect in the stress literature, is included as a covariate here in order to evaluate the contribution of the categorical IIV metrics above and beyond the simple "counting" of exposure to stressors.

For the nominal metrics, individual differences in negative affect were examined as group differences in an ANOVA framework (each nominal metric separately),

$$Negative\ Affect_i = \alpha_0 + \alpha_1 NominalMetric_i + \varepsilon_i \quad (5)$$

where α_0 is the mean level of negative affect in the reference category and the vector α_1 indicates how average negative affect at each level of the nominal metric differs from the reference category. All models were fit using R (e.g., lm function; R Core Team, 2016), with missing data treated as missing completely at random.

Results

Numeric Metrics of Categorical IIV

Descriptives. Descriptive statistics of the three numeric categorical IIV metrics are displayed in Table **2-1**. Stressor relative dominance ranged from 0.17 to 1 (*M* = .59, *SD* = .26), and was negatively associated with both stressor exposure (*r* = -.57), that ranged 0 to 4.14 (*M* = 0.55, *SD* = 0.48), and stressor diversity (*r* = -.95), that ranged from 0 to 1 (*M* = .44, *SD* = .30). Consistent with NSDE Wave 2 (see Koffer et al., 2016), stressor exposure and stressor diversity were positively correlated (*r* = .70). Stressor log-skew

ranged from -56.18 to 50.31 (*M* = 2.61, *SD* = 13.88), and was correlated with stressor relative dominance (*r* = .49), stressor diversity (*r* = -.51), and stressor exposure (*r* = -.33). The associations among the numeric metrics support their conceptual definitions: higher stressor relative dominance indicates a more recurrent modal stressor type, higher stressor diversity indicates more stressor type heterogeneity, and higher stressor log-skew indicates fewer rare stressors.

Table 2-1. *Descriptive Statistics of and Correlations among the Numeric Metrics of the Stressor Type Distribution in NSDE Wave 1.*

	N	*Mean*	(*SD*)	1.	2.	3.	4.	5.	6.
1. Stressor Relative Dominance	1,336	0.59	(0.26)	--					
2. Stressor Diversity	1,336	0.44	(0.30)	**-0.95**	--				
3. Stressor Log-Skew	1,335	2.61	(13.88)	**0.49**	**-0.51**	--			
4. Stressor Exposure	1,471	0.55	(0.48)	-0.57	0.70	-0.33	--		
5. Age	1,498	46.21	(23.87)	0.11	-0.13	0.06	-0.20	--	
6. Negative Affect	1,486	0.20	(0.28)	-0.17	0.20	-0.04	0.34	**-0.14**	--

Note: *SD* = Standard Deviation. Missing cases for stressor exposure variable are individuals who did not have stressor data across the entire reporting period. Missing cases for stressor diversity and relative dominance are individuals who reported no stressors (n = 132) or only discrimination stressors (n = 3) across the entire reporting period

Relations with Age and Negative Affect. From Table **2-1**, we see that older age is associated with higher stressor relative dominance (r = .11), lower stressor exposure (r = -.20) and lower stressor diversity (r = -.13). Individuals with higher overall negative affect (NA) tended to have lower stressor relative dominance (r = -.17), and higher stressor diversity (r = .20) and stressor exposure (r = .34). Stressor log-skew was very weakly associated with age (r = .06) and NA (r = -.04).

Age differences in stressor relative dominance were described by a decreasing linear gradient, β_1 = -0.01 (p = .04) with upward curvature, β_2 = 0.0001 (p = .01). Stressor diversity demonstrated an increasing linear age gradient, β_1 = 0.01 (p = .02) with downward curvature, β_2 = -0.0001 (p = .002). Stressor log-skew was described by a decreasing linear age gradient β_1 = -0.48 (p = .03) with upward curvature, β_2 = 0.006 (p = .01). Thus older adults experienced more stressor dominance, less stressor diversity, and more stressor skew than their younger counterparts.

Models regressing NA on each of the three numeric metrics are shown in Table **2-2**. In Model 1, where *stressor relative dominance* is the numeric IIV metric of interest, the prototypical NSDE participant's NA was estimated as β_0 = 0.21 (p < .001) on the 0 to 4 scale. Stressor relative dominance and stressor exposure were both associated with higher NA, β_1 = 0.09 (p = .03) and β_2 = 0.25 (p < .001) within the context of a significant stressor relative dominance x stressor exposure interaction β_4 = 0.21 (p = .01). That is, the relation between stressor relative dominance and NA was moderated by level of stressor exposure. Older age was associated with lower NA β_3 = -0.002 (p = .002), and damped associations between stressor relative dominance and NA, β_5 = -0.007 (p = .04), and stressor exposure and NA, β_6 = -0.004 (p = .03). The two-way interaction between

stressor relative dominance and stressor exposure was age invariant. In Model 2, *stressor diversity* was associated with lower NA, β_1 = -0.11 (p = .002), and stressor exposure was associated with higher NA, β_2 = 0.29 (p < .001), within the context of a significant stressor diversity x stressor exposure interaction, such that when stressor diversity was higher the link between stressor exposure and NA was weaker, β_3 = -0.20 (p = .002). Older age damped the association between stressor exposure and NA, β_6 = -0.005 (p = .03), and trended toward enhancing the association between stressor diversity and NA, β_5 = 0.005 (p = .08). The two-way interaction between stressor diversity and stressor exposure was age invariant.

In Model 3, *stressor log-skew* was associated with higher NA, β_1 = 0.002 (p = .002), along with stressor exposure, β_2 = 0.23 (p < .001), within the context of a significant stressor log-skew x stressor exposure interaction, β_3 = 0.003 (p = .02). These associations were age invariant, β_5 to β_7 all not significantly different than zero (ps > .30).

Recalling that both stressor relative dominance and stressor diversity capture the (lack of) heterogeneity of stressors we find that at average levels of stressor exposure, greater stressor heterogeneity is associated with lower negative affect. Heterogeneity is protective. However, the presence of "rare" stressors (e.g., high log-skew) contributes to higher negative affect. Overall, the evidence of both main effects and moderation suggest that the numeric categorical IIV metrics offer new information about how the stressor ecosystem contributes to individuals' well-being.

Table **2-2.** Negative Affect Regressed on Numeric Metrics of the Stressor Type IIV Distributions from NSDE Wave 1.

	Model 1: Numeric Metric = *Stressor Dominance*			Model 2: Numeric Metric = *Stressor Diversity*			Model 3: Numeric Metric = *Stressor Log-skew*		
	Est		(SE)	Est		(SE)	Est		(SE)
Intercept	0.21	*	(.01)	0.21	*	(0.01)	0.20	*	(0.01)
Numeric IIV Metric	0.09	*	(0.04)	-0.11	*	(0.04)	<0.01	*	(<0.01)
Stressor Exposure	0.25	*	(0.02)	0.28	*	(0.03)	0.22	*	(0.02)
Age	>-0.01	*	(<0.01)	>-0.01	*	(<0.01)	>-0.01	*	(<0.01)
Numeric IIV Metric x Stressor Exposure	0.21	*	(0.09)	-0.20	*	(0.07)	<0.01	*	(<0.01)
Numeric IIV Metric x Age	-0.01	*	(<0.01)	0.01	*	(<0.01)	>-0.01		(<0.01)
Stressor Exposure x Age	>-0.01	*	(<0.01)	>-0.01	*	(<0.01)	>-0.01		(<0.01)
Numeric IIV Metric x Stressor Exposure x Age	-0.01		(0.01)	0.01		(0.01)	>-0.01		(<0.01)
R^2	0.12			0.13			0.12		

Note: SE = Standard Error. Negative Affect is computed as a person-specific mean on a 0 to 4 scale for *T*= 8 days. Missing cases for stressor exposure variable are individuals who did not have stressor data across the entire reporting period. N_{Model1} = 1,312; N_{Model2} = 1,312; N_{Model3} = 1,311. Missing cases are individuals who did not have stressor and negative affect data (*n* = 28), or reported no stressors (*n* = 155) or only discrimination (*n* = 3) across the entire reporting period.

Nominal Metrics of Categorical IIV

Descriptives. While in principle there are 6 possible modes, the accommodation for ties provided for observation of 59 possible modal stressor combinations. Of the total *N* = 1336 sample, *n* = 325 (24.33%) individuals' modal stressor was non-argument interpersonal tensions, for *n* = 174 (13.02%) it was work stressors, for *n* = 148 (11.08%) arguments, for *n* = 101 (7.56%) home stressors, for *n* = 72 (5.39%) network stressors, and

for *n* = 49 (3.67%) other stressors. In addition to those who had one modal stressor, *n* = 55 (4.12%) had equally-proportioned arguments and non-argument interpersonal tensions modes, and *n* = 43 (3.22%) had equally-proportioned work stressor and non-argument interpersonal tension modes, with all other combinations being very rare. In sum, modal stressor types are extremely heterogeneous across the sample.

Of the 64 possible stressor spreads that might manifest in 6-category data, 63 were represented in the empirical data. The most frequent stressor spreads consist of only *other stressors* (*n* = 148, 11.08%); *network stressors* and *other stressors* (*n* = 81, 6.06%); *non-argument interpersonal tensions* and *other stressors* (*n* = 62, 4.64%); only *non-argument interpersonal tensions* (*n* = 53, 3.97%); only *network stressors* (*n* = 47, 3.52%); *network, work,* and *other stressors* (*n* = 38, 2.84%); *network, work, non-argument interpersonal tensions,* and *other stressors* (*n* = 35, 2.62%); *network, work, arguments,* and *other stressors* (*n* = 32, 2.40%); and *network, work, home, non-argument interpersonal tensions,* and *other stressors* (*n* = 30, 2.25%). Again there is lots of heterogeneity in how 8 days of stressor experiences are dispersed across categories.

Of the 873 possible orders that might manifest in 6-category data, only 395 different rank-ordered sequences were represented in the empirical data. The most prevalent sequences, though still quite rare were: *n* = 150 (11.23%) experienced the rank ordered sequence *1. non-argument interpersonal tensions,* with all other stressor types equally ranked at *2.*; *n* = 53 (3.97%) had order with *1. work stressors,* with the all other stressor types equally ranked at *2.*; *n* = 47 (3.53%) had order with *1. arguments,* with all other stressor types equally ranked at *2.*; and *n* = 41 (3.07%) had order with *1. non-argument interpersonal tensions, 2. arguments,* and all other stressor types equally ranked at *3.*

Again, there is substantial heterogeneity in how the stressors individuals experience are ordered with respect to relative frequency. In sum, all three nominal metrics reveal extremely abundant, unique IIV distributional attributes – even for a simple 6-category measurement scheme – highlighting both the value and *difficulty* inherent in categorical heterogeneity.

Relations with Negative Affect. Results from an ANOVA indicated that the 59 *mode groups* did not significantly differ on average NA, $F(58, 1268) = 0.96$, $p = .56$. Descriptive information for mean and standard deviation NA of most frequent mode types are displayed in Panel A of Figure **2-3**.

Results from an ANOVA testing whether the 63 *spread groups* differed on average NA revealed significant group differences, $F(62, 1264) = 2.07$, $p < .001$. Post-hoc (Tukey's HSD adjusted) tests depicted in Panel B of Figure **2-3** indicated that the [*network, other, work, home, argument, non-argument interpersonal tensions*] spread group ($M_{NA} = 0.36$, $SD_{NA} = 0.36$) had significantly higher average NA than the [*non-argument interpersonal tensions*] spread group ($M_{NA} = 0.09$, $SD = 0.15$; $p = 0.02$). The [*network, other, work, home, non-argument interpersonal tensions*] spread group ($M_{NA} = 0.38$, $SD_{NA} = 0.42$) also had significantly higher NA than the [*other*] spread group ($M_{NA} = 0.15$, $SD_{NA} = 0.21$; $p = 0.01$), the [*home*] spread group ($M_{NA} = 0.10$, $SD_{NA} = 0.20$; $p = 0.045$), and the [*non-argument interpersonal tensions*] spread ($M_{NA} = 0.09$, $SD_{NA} = 0.15$; $p = 0.001$).

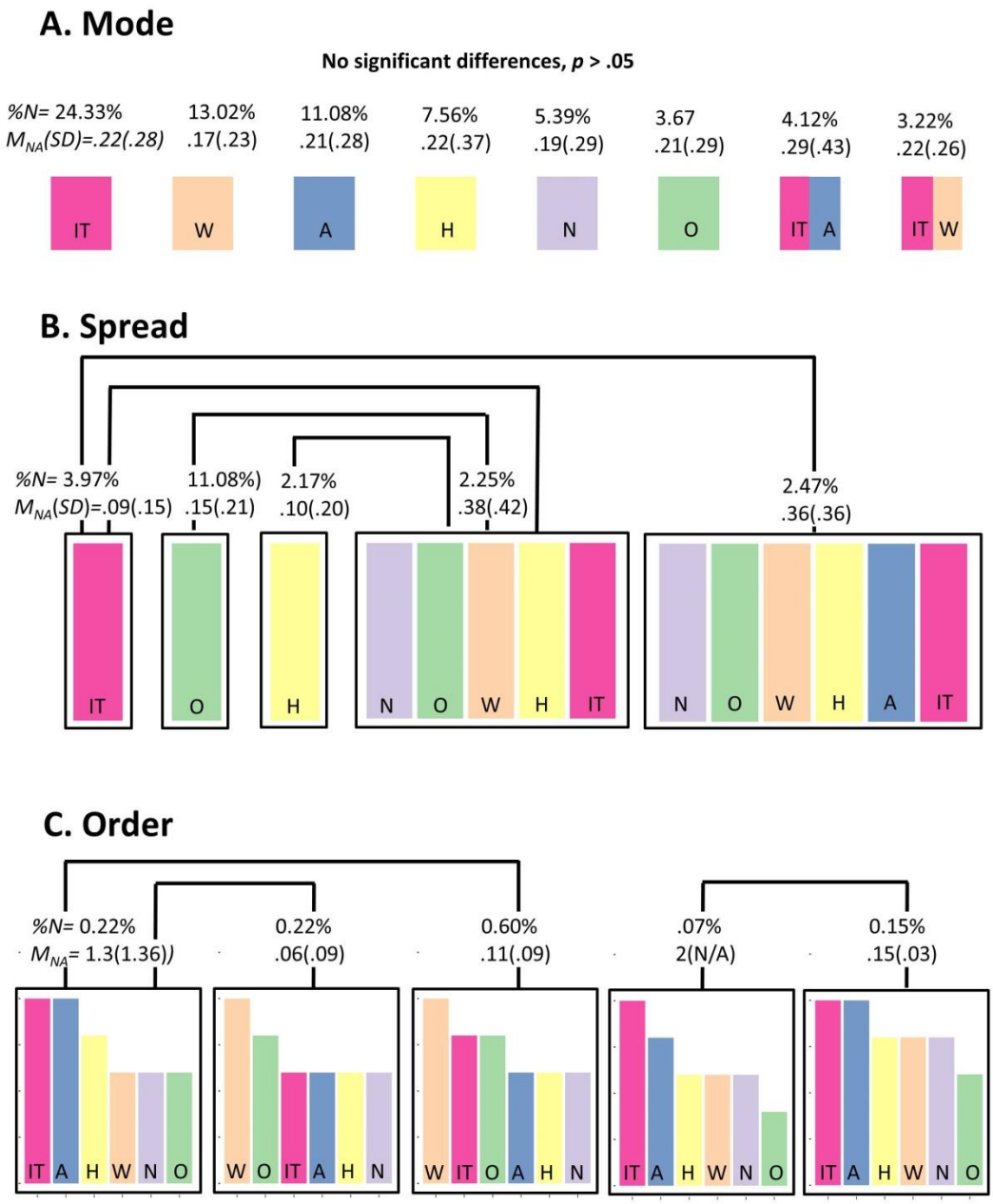
ANOVA and Tukey HSD adjusted post-hoc tests also revealed NA differences among the 395 *stressor order* groups, $F(393, 936) = 1.38$, $p < .001$ (one group removed for complete missingness on NA). From all possible order sequence comparisons, 518

(.007%) were significant (Tukey adjusted), of which we present a few sample cases. For instance, as shown in Panel C of Figure **2-3**, stressor order of [*1. non-argument interpersonal tensions, 1. arguments, 3. home, 4. work, 4. other, 4. network*] (M_{NA} = 1.30, SD_{NA} = 1.36) had higher average NA than stressor orders of [*1. work, 2. other, 3. non-argument interpersonal tensions, 3. arguments, 3. home, 3. network*] (M_{NA} = 0.06, SD_{NA} = 0.09; $p < .001$) and [*1. work, 2. non-argument interpersonal tensions, 2. other, 4. arguments, 4. home, 4. network*] (M_{NA} = 0.11, SD_{NA} = 0.09; $p < .001$). As well, stressor order of [*1. non-argument interpersonal tensions, 2. arguments, 3. home, 3. work, 3. network, 6. other*] (M_{NA} = 2.00, SD_{NA} = N/A; one individual) had higher NA than stressor order of [*1. home, 1. work, 3. non-argument interpersonal tensions, 3. arguments, 3. network, 6. other*] (M_{NA} = 0.15, SD_{NA} = 0.03; $p < .001$). Significant differences in average NA among stressor order groups suggest that nominal asymmetry in the relative frequency of stressor types impacts individuals' affective well-being.

In sum, for stressor types, we find that the *modal stressor* is not associated with negative affect, but that *stressor spread* and *stressor order* are indeed associated with negative affect. While difficult to parse, there appears to be value in trying to understand the differences measured by the nominal metrics.

Figure 2-3. *Nominal metrics associations with negative affect.* Panel A: Most frequent mode types in NSDE Wave 1 stressor data. Panel B: Stressor Spreads (individual spread represented as colors within each black box). Panel C: Sample of order sequences, represented as relative heights of the bar chart. 518 pairwise comparisons (.007% of total possible comparisons) were significant (Tukey adjusted $p < .05$). Note for all panels: For each group (mode type, spread group, and order sequence), the percentage of total

population (N = 1336), mean (M_{NA}) and standard deviation (SD) of negative affect are displayed. IT= non-argument interpersonal tensions (*pink*), A=argument stressors (*blue*), W= work stressors (*orange*), H=home stressors (*yellow*), N=network stressors (*purple*), O=other stressors (*green*).


A. Mode
No significant differences, p > .05
%N= 24.33%
M_NA(SD)=.22(.28)
13.02%
.17(.23)
11.08%
.21(.28)
7.56%
.22(.37)
5.39%
.19(.29)
3.67
.21(.29)
4.12%
.29(.43)
3.22%
.22(.26)
IT
W
A
H
N
O
IT A
IT W
B. Spread
%N= 3.97%
M_NA(SD)=.09(.15)
11.08%)
.15(.21)
2.17%
.10(.20)
2.25%
.38(.42)
2.47%
.36(.36)
IT
O
H
N O W H IT
N O W H A IT
C. Order
%N= 0.22%
M_NA= 1.3(1.36))
0.22%
.06(.09)
0.60%
.11(.09)
.07%
2(N/A)
0.15%
.15(.03)
IT A H W N O
W O IT A H N
W IT O A H N
IT A H W N O
IT A H W N O

Discussion

This study introduced six metrics that may be useful for examining interindividual differences in IIV when working with categorical repeated measures data. Specifically, we illustrated how three numeric metrics (relative dominance, diversity, log-skew) and three nominal metrics (mode, spread, order) can be used in analysis of large-scale daily diary data to measure dynamic characteristics of individuals' stressor experiences, and to examine how those characteristics are related to individual differences in overall negative affect. Results suggest that the six metrics capture meaningful aspects of individuals' stressor ecosystems and should be further incorporated into stressor theory. By systematically applying IIV principles to categorical variables, we hope that the six categorical IIV metrics provided here can expand the variety of research questions that may be answered using experience sampling data.

Individual Differences in Stressor-type IIV

Our exploration into categorical IIV metrics was situated in study of daily stress and analysis of the NSDE – a rich data set with many categorical repeated measures. In particular, we examined IIV in daily reports of the *types* of stressors individuals experienced each day. Analysis of such data has typically summed across types and/or days to quantify total *stressor exposure*, or placed the repeated measures within a multilevel modeling framework to examine *stressor reactivity* (Almeida, 2005). Although conceived as distinct, the different stressor types (arguments, work stressors, etc.) are often treated as fully interchangeable. Only a handful of studies have made use of the

stressor category information embedded within the NSDE and similar data sets. For example, Hay and Diehl (Hay & Diehl, 2010) and Neupert, Almeida, and Charles (Neupert, Almeida, & Charles, 2007) examined how protective factors, such as control beliefs and self-concept differentiation, interact uniquely with interpersonal, work, home, network, and health stressors, while Stawski, Cichy, Piazza, and Almeida (Stawski et al., 2013a) examined whether day-to-day differences in diurnal cortisol were related to experience of specific types of stressors. Taking a more holistic look at the stressor typology, two recent studies quantified and examined differences in *stressor diversity* (relative abundance of different stressor types; Brose et al., 2013; Koffer et al., 2016). The findings from these prior studies clearly indicate both the empirical value of the across-category information (e.g., increased prediction of well-being) and its theoretical importance for identifying the mechanisms through which stressor experience influence well-being (e.g., cross-domain resource depletion; Hobfoll, 1989). Here, we expand the ways the stressor category information can be summarized and used in analysis.

The value of the three numeric metrics, *relative dominance*, *diversity*, and *log-skew*, was demonstrated by their theoretically meaningful age gradients and the additional precision they contributed for prediction of individual differences in negative affect (above stressor exposure). In line with life course theory, stressor dominance is at its minimum in early midlife, when individuals are likely to be balancing multiple roles, and thus less likely to experience one stressor type far more than others (Pearlin, 1989). Similarly, stressor diversity reaches its maximum during midlife, indicating stressors are spread across several stressor types, as opposed to concentrated in a few stressor types. Finally, in line with socioemotional selectivity theory, older adults indeed have

proportionally more stressors in common rather than rare stressor type (Carstensen, Isaacowitz, & Charles, 1999). Replicating previous analysis of NSDE Wave 2 data (Koffer et al., 2016), we found that greater heterogeneity is associated with lower overall NA. Theoretically, higher stressor diversity may mean that experiencing a variety of stressors allows individuals to replenish the resources used up dealing with one type while they apply other resources to another type (Hobfoll, 1989). The link between higher log-skew (fewer rare stressors) and higher NA, corroborates the notion that spread across a variety of stressors, even those that are rare, may offer opportunity for resource replenishment.

It is important to note that in these data relative stressor relative dominance and stressor diversity were correlated r = -.95. The correspondence of the two measures demonstrates that when repeated measures data are characterized by relatively few occasions (T = 8 days) and relatively few categories (m = 6) these two measures do not have space to diverge (Magurran & McGill, 2011; also see our Cautionary Notes section). In longer time series, or with more categories, the measures may not be so highly correlated. Here, though, stressor relative dominance and diversity are both characterizing the same homogeneity/heterogeneity of individuals' stressor experience.

We also found value with the nominal metrics, *mode*, *spread,* and *order*. In these data, modal stressor was not associated with negative affect. However, this may be due to high number of p_{max} ties, which requires considering 59 stressor modal combinations. Again, this may be due to the study design. With only 8 days and 6 stressor types, the most preponderate category cannot yet assert itself. Longer time series will provide for more parsimonious representation of the modes (i.e., less ties). Significant group

differences emerged for both stressor spread and stressor order. In line with both Conservation of Resources Theory (Hobfoll, 1989) and Stress, Appraisal, and Coping Theory (Lazarus & Folkman, 1984), the differences among stressor spread and stressor order groups highlight the value of theorizing about and studying interindividual differences in both dispersion across the stressor space, and relative asymmetry in frequency of individuals' sources of stress.

Measuring Categorical IIV and Application to Developmental/Gerontological Research

We outlined six metrics that might be used to study interindividual differences in categorical IIV. Our proposal was based on the idea that categorical intensive repeated measures can be summarized using the same principles being applied to their continuous counterparts. That is, categorical time series also have central tendency, dispersion, and asymmetry. In considering what the statistical moments of categorical distributions are, we explored how metrics used in ecology to describe distributions of species might be adapted for use in developmental and psychological science to describe individuals' daily stressor experience. We found three numeric metrics: *relative dominance* as a measure of the centrality tendency of a categorical distribution, *diversity* as a measure of dispersion of a categorical distribution, and *log-skew* as a measure of asymmetry of a categorical distribution. As we explored the information potential of numeric metrics, we realized (as noted earlier) that the prioritization of numeric summaries only captured the height of each bar (numeric aspects) in the categorical IIV distribution. Thus, to capture the color

of each bar (nominal aspects), we identified three nominal metrics that also mapped to the statistical moments of a categorical distribution: *mode* as a measure of central tendency, *spread* as dispersion across categories, and *order* as asymmetry across categories. The numeric and nominal metrics can be applied individually or in combination. For example, the mode stressor type clarifies the qualitative differences among individuals with high stressor relative dominance.

In calculating these measures, we realized why so few researchers are working with categorical IIV. There are too many combinations. In our 6-category data, for example, there are 64 possible configurations of spread and 873 possible configurations of order. On the positive side, the study of IIV is meant to capture idiosyncratic experience throughout development (see Molenaar, 2004) and there is certainly potential for that with categorical IIV. On the negative side, finding a coherent story when working with 873 groups is a challenge for even the most creative psychologists (see Horn, 1967). Interpretation of NA differences is complicated due to the sheer number of groups (and thus sparse data to compare). The same issues arise when examining age differences, and even more-so when attempting to parse negative affect differences by nominal metric as moderated by age. There are, however, rich literatures in other fields (e.g., ecology, biology, sociology) where categorical IIV metrics are used to quantify and study biological and social phenomena (e.g., microbiome, K. Li et al., 2012; income inequality; Hirshman, 1964). In bioinformatics, chemistry, and big data enterprises more generally, there is a substantial body of research that makes use of combinatorial lists, for example in DNA sequencing and text analysis. In sum, there are good examples to follow as we attempt to make sense of the categorical data streams we and others have included in

experience sampling studies. Our hope in outlining these six metrics for categorical IIV is to prompt further consideration of how they might be used to articulate new research questions.

Many theories of aging highlight developmental changes that manifest in a "categorical" fashion. For example, Selective Optimization and Compensation (P B Baltes & Baltes, 1990) and Socioemotional Selectivity Theory (Carstensen et al., 1999) suggest that older adults selectively interact with specific types of social partners. The proposition implies data streams of the types of persons (e.g., family, friends, co-workers, health-professionals) an individual interacts with during normal daily life – a categorical IIV distribution. The metrics outlined here provide a method for characterizing and comparing younger adults' and older adults' social partner distributions – with specific hypotheses being that older adults have greater relative dominance (homogeneity/selectivity) compared to younger adults; and that there will be age differences in nominal spread groups (e.g., spreads that contain strangers versus spreads that contain family members) and nominal order groups (e.g., family before co-worker in the rank order).

Next steps include validating the value of the categorical IIV constructs measured by the six metrics proposed here through empirical studies that locate those constructs with respect to other constructs (e.g., well-being, personality) and developmental change. Recent examples in developmental research include studies of how activity diversity, stressor diversity, and emotional diversity are related to physical and mental well-being, and age (Benson et al., 2017; Brose et al., 2013; Koffer et al., 2016; Lee et al., 2016). Using typical methods (e.g., SEM, multilevel models) these papers begin establishing

theoretically informative findings regarding convergent validity, divergent validity, and stability/change of the diversity constructs. As this body of works extends to cover the other five metrics introduced here, the push into categorical IIV may help us to articulate, operationalize, and test some long-standing tenets of developmental theory.

Cautionary Notes

There are, of course, some caveats to keep in mind as we move into studying categorical IIV constructs. Our analysis of 8-day daily diary data underscored the need for study designs with more occasions. Our ability to locate individuals in between-person distributions was hampered by equivalence of proportions across categories and lack of separation between the dominance and diversity metrics (see above). Simulations and empirical studies both suggest that (continuous) IIV metrics require 25+ sampling occasions, depending on the construct of interest (Mejía, Hooker, Ram, Pham, & Metoyer, 2014). Categorical data streams may need to be longer. Biologists have highlighted the difficulty small samples pose for study of diversity and log-skew (Magurran & McGill, 2011), but in those discussions "small" is defined as < 100 observations. Our situation is more challenging.

Regarding the nominal metrics, several approaches may be helpful in our smaller, currently available data streams. While we used an analytical framework (ANOVA) where we kept all 59 modes/combinations of modes as separate factors, one could instead use a theory-based ranking system to deal with equal proportions, or a data-driven data reduction approach (e.g., with dissimilarity matrices and clustering) to obtain a more

manageable number of comparisons. Similarly, nominal spread lists capture some information also captured in numeric variance metrics; for example, the individual on the top of panel D may experience greater negative affect than the individual on the bottom due to the greater number of stressor types experienced along with the nominal differences in specific types experienced. Researchers could reduce the number of spread groups by examining the observed differences in the outcome variable(s) within individuals of similar numeric properties (e.g., controlling for the number of stressor types experienced, does stressor spread predict negative affect differences?).

Regarding the numeric metrics, ecologists (Magurran & McGill, (Magurran & McGill, 2011) suggest that with sample sizes of less than 100 cases, metrics should be chosen for their accuracy despite lack of independence (i.e., Shannon's diversity metric and relative dominance are notably accurate metrics for small sample sizes, despite substantial correlations with *m* = number of categories and *N = number of stressors*).

Consequently, it is important to note the non-linear relations among the numeric metrics, and caution against including the three metrics in one regression. Notice that the p_{ij} used in calculation of relative dominance (Equation 1) is exactly the same p_{ij} that is used in calculation of diversity (Equation 2). Mathematically, the measure of relative dominance is a component of the measure of stressor diversity. Thus, and particularly at extreme values of stressor dominance, the diversity metric are highly related. In fact, each of the three numeric metrics is derived in some way from, and correlates with, both the total number of categories (*m*) and the total number of observations in all categories ($N = \sum_{j=1}^{m} n_{ij}$). That is, the metrics are mathematically related to each other in known ways. As such, we encourage careful consideration of the time-series lengths, number of

categories, and inherent relations/properties of the score calculations before treating them as indicators of independent constructs and/or including more than one metric in a regression (inherent multicollinearity). Specifically, we recommend first using theory to choose an appropriate metric(s), followed by empirical examination of how the metrics are correlated, and if necessary, multivariate analytical approaches and/or computation of alternative dominance and diversity indices (see Magurran & McGill, 2011) that are of theoretical interest.

More broadly, we note that in contrast to models of underlying dynamic processes, net intraindividual variability metrics like those forwarded here provide descriptive statistics of time series data that are assumed independent and identically distributed (see discussion in Ram & Gerstorf, 2009). Net IIV metrics allow researchers to study interindividual differences, but do not explicitly describe dynamic processes (i.e., the metrics do not consider time dependencies). Careful consideration of the measurement methods along with theoretical and analytical consideration of the source of IIV (person, context, and/or person-context interaction; see Koffer & Ram, 2016) will be useful for understanding the meaning of categorical IIV with further work needed to extend these particular metrics for study of time-structured processes.

Outlook and Conclusion

The numeric and nominal metrics for categorical IIV allow for several theoretically important applications. With the metrics, we can test theories that specify expected outcomes of categorical distribution formation processes (Magurran & McGill, 2011).

For example, the theory of appraisal and coping suggests that stressor type distributions are influenced by baseline conditions, such as presence of a chronic condition (Lazarus & Folkman, 1984). We can now test this assumption by comparing stressor type IIV metrics before and after onset of illness. Furthermore, after unveiling the implications of the distributional features, we can potentially use categorical IIV metrics as indicators of successful aging. For example, there is some evidence suggesting it is adaptive to engage in greater diversity of activity types (Lee et al., 2016). When true, greater activity diversity might be indicative of successful aging. Relatedly, the categorical IIV metrics may offer specificity for intervention targets. For example, following from the present finding that high stressor relative dominance was associated with greater negative affect, we might look at how to support individuals with particular types of distributions – an approach already being used to identify intervention targets in ecology (Magurran & McGill, 2011).

Considerable research in cognitive aging (S. W. S. MacDonald, Li, & Bäckman, 2009) and affective regulation with age (Liu et al., 2016) have conceptualized and studied IIV using continuous variables of reaction time and positive and negative affect levels, respectively. As noted above, developmental research on stress, activity engagement, and emotion complexity (to name only a few) has also begun to demonstrate theoretically meaningful age differences using *categorical* IIV. The additional metrics introduced here provide an opportunity to expand the range of developmental questions that may be asked with categorical repeated measures. In the same way that metrics and models of continuous IIV have continued to advance our understanding of micro-time scale processes through the life span (Diehl, Hooker, & Sliwinski, 2015), we hope further

development of categorical IIV metrics will help uncover the information embedded in the plethora of categorical repeated measures being collected in psychological and aging research.

Chapter 3

Study 2: High Stressor Exposure and Low Stressor Diversity Linked to Inflammation

Laboratory studies have revealed acute inflammation occurs in response to psychosocial stressors, and large-scale epidemiological studies have tied chronic stress conditions to higher systemic inflammation (Glaser & Kiecolt-Glaser, 2005; Marsland, Walsh, Lockwood, & John-Henderson, 2017; Segerstrom & Miller, 2004). More recently, everyday stressor experiences outside of the lab (i.e., daily stressors) have also been linked to inflammation (Davis et al., 2008; Fuligni, Telzer, Bower, Cole, & Irwin, 2009; Gouin, Glaser, Malarkey, Beversdorf, & Kiecolt-Glaser, 2012). Higher daily stressor exposure was associated with higher systemic inflammation and even partially explained the higher levels of inflammation among those with chronic stress (Davis et al., 2008; Gouin et al., 2012). Further, people who experienced greater affective stressor reactivity (i.e., increased negative affect or decreased positive affect on days with reported stressors) exhibited higher inflammation (Sin, Graham-Engeland, Ong, & Almeida, 2015). A growing body of research has identified characteristics of stressor experiences (e.g., duration, controllability) that contribute to stronger immune response (Segerstrom & Miller, 2004).

A novel way to characterize individuals' daily psychosocial stressor experiences is by their stressor diversity – the extent to which stressor experiences are spread across multiple types (e.g., work, home overloads, arguments, etc.) (Brose et al., 2013; Koffer et al., 2016). The combination of high stressor exposure and low stressor diversity (i.e., many stressor experiences concentrated in one or few types) is related to particularly poor affective well-being (Koffer et al., 2016). Theoretically, this high exposure and low diversity of stressors may reflect persistent threat, extended duration of homogenous stressor events, or prolonged coping responses (Gottlieb, 1997).

The present study aimed to examine whether higher stressor exposure and lower stressor diversity are linked to particularly high inflammation across the adult life span. Older adults tend to report fewer and less diverse stressors than young adults, but they also experience elevated levels of systemic inflammation (Brose et al., 2013; Ershler & Keller, 2000; Koffer et al., 2016; Straub et al., 2000). Thus, it is important to understand how differences in psychosocial experiences might interact with age-related biological vulnerabilities.

Systemic Inflammation and Health

The natural (i.e., not pathogen-specific) immune response to injury, infection, or stress is inflammation. Blood vessels dilate to allow transport of cells, including neutrophils and macrophages that systemically and locally release toxins and produce pro-inflammatory cytokines that trigger continued inflammatory response. A negative feedback loop ends this acute inflammatory cascade as pro-inflammatory cytokines

stimulate the hypothalamic-pituitary-adrenal (HPA) axis to release more glucocorticoids that, in turn, inhibit inflammation. Current theories of acute stress-related immune response suggest systemic inflammation may be adaptive, as it prepares the body to fight unspecified threats and it self-ceases when the stressor experience is over (Dhabhar, 2014).

In contrast to acute stress, prolonged stress is associated with chronic systemic inflammation that is linked to a variety of disease outcomes (Franceschi & Campisi, 2014). The Glucocorticoid Receptor Sensitivity Hypothesis suggests chronic stress leads to continued high cortisol output from the HPA axis (Miller, Cohen, & Ritchey, 2002). In response, white blood cells down-regulate their glucocorticoid receptors, and become desensitized to cortisol's anti-inflammatory effects (Miller et al., 2002). Once de-sensitized, the negative feedback is no longer effective, and inflammation remains high. Chronic high systemic inflammation is strongly implicated in the progression of a variety of diseases (e.g., cardiovascular disease, certain cancers, autoimmune diseases, and Alzheimer's) and greater risk of mortality (Franceschi & Campisi, 2014).

Inflammatory Biomarkers

Systemic inflammation is indicated by a variety of biomarkers that can be analyzed as composite or unique indicators of inflammatory processes (Friedman, Christ, & Mroczek, 2015). Broadly, systemic inflammation is characterized by upstream dispatch of cytokines, upregulation of adhesion molecules, and high downstream acute phase protein levels. Each inflammatory marker thus has a specific biological function,

providing distinct pathways from stress to health (Goldberg, 2009; Malik et al., 2001). In the present study, I examined five inflammatory markers (interlukein-6, C-reactive protein, fibrinogen, soluble intercellular adhesion molecule-1, and E-selection) that have each been linked to psychosocial stress and health (Danesh, Collins, Appleby, & Peto, 1998; Friedman, Williams, Singer, & Ryff, 2009; Kiecolt-Glaser et al., 2003; Nyberg et al., 2014; Witkowska & Borawska, 2004). The following sections contain an overview of each inflammatory marker's biological function and association with health and chronic stress.

Interlukein-6 (IL-6). The proinflammatory cytokine IL-6 is an indicator of general systemic inflammation because it is expressed in many cells (e.g., macrophages, fat cells), it signals and coordinates further synthesis of immune cells and cytokines, and is known to mediate sickness behaviors typical of acute inflammation (Maggio, Guralnik, Longo, & Ferrucci, 2006). IL-6 is also key in promoting production of C-reactive protein (CRP) and fibrinogen (see below). Individuals facing conditions of chronic stress, such as caregiving and socioeconomic disadvantage, tend to have higher basal IL-6 (Gouin et al., 2012; Kiecolt-Glaser et al., 2003). High IL-6 has been associated with cardiovascular disease, hypertension, diabetes, cognitive decline, disability, sarcopenia, and mortality (Chrousos, 2009).

C-reactive protein (CRP). CRP is an acute phase protein produced in the liver that is used as an indicator of general systemic inflammation. Specifically, CRP reduces endothelial vascular dilation and increases platelet aggregation, but in excess, this clotting can lead to thrombosis (Danesh et al., 1998; Juster et al., 2011). Higher basal CRP is related to conditions of chronic stress, such as caregiving and socioeconomic

disadvantage (Alley et al., 2007; Kiecolt-Glaser, Bane, Glaser, & Malarkey, 2003). However, a recent meta-analysis determined that acute laboratory stress is not associated with increases in circulating CRP (Marsland et al., 2017). CRP is associated with disease outcomes, including cardiovascular disease, hypertension, diabetes, cognitive decline, disability, sarcopenia, and mortality (Danesh et al., 1998; Goldberg, 2009; McDade, Hawkley, & Cacioppo, 2006). A clinical cutoff of above 3 mg/L has also been established to indicate high relative risk for cardiovascular disorder, though above 10 mg/L indicates acute infection (Ridker, 2009).

Fibrinogen. Fibrinogen is an acute phase protein that facilitates clotting and is used to indicate systemic inflammation. Findings are mixed as to the association between stress and fibrinogen levels. Studies have found low socioeconomic status in childhood and adulthood, as well as chronic burnout due to workplace stress for women, are associated with higher fibrinogen (Pollitt et al., 2007; Toker, Shirom, Shapira, Berliner, & Melamed, 2005). However, there is also evidence that stress and fibrinogen are unrelated in some cases, such as work burnout in men (Toker et al., 2005). In excess, fibrinogen is associated with cardiovascular disease, hypertension, and diabetes (Danesh et al., 1998; Goldberg, 2009; Juster et al., 2011).

Soluble intercellular adhesion molecule-1 (sICAM-1). sICAM-1, expressed on endothelial cells and leukocytes, is an indicator of vascular wall inflammation. Specifically, sICAM-1 is stimulated by proinflammatory cytokines and promotes attachment and transendothelial migration of leukocytes. Researchers have recently begun linking psychosocial stressors, including socioeconomic adversity in childhood and adulthood and severe acute childhood stressors, to higher expression of adhesion

molecules, including sICAM-1 (Briassoulis, Papassotiriou, Mavrikiou, Lazaropoulou, & Margeli, 2007; Packard et al., 2011). Elevated sICAM-1 levels have been associated with hypertension, atherosclerosis, coronary heart disease, and diabetes (Hwang et al., 1997; Meigs, 2004; Witkowska & Borawska, 2004).

E-Selectin. E-Selectin is an adhesion molecule expressed only on the surface of endothelial cells. Its restricted location allows researchers to use E-Selectin as a specific marker of endothelial dysfunction (Cohen, Granger, & Fuller-Thomson, 2015; Meigs, 2004). Its role in inflammation is to recruit and bind leukocytes to endothelial cells when induced by inflammatory cytokines. Psychosocial stressors, such as bereavement and discrimination, have recently been linked to increased E-selectin (Cohen et al., 2015; Friedman et al., 2009). In turn, E-selectin is associated with increased risk of diabetes and vascular complications from diabetes, atherosclerosis and coronary heart disease (Goldberg, 2009; Meigs, 2004).

High Stressor Exposure, Low Stressor Diversity and Inflammation

We recently linked the combination of high stressor exposure and low stressor diversity with lower affective well-being (Koffer et al., 2016). Fundamentally, this combination may indicate stressor chronicity. In relation to chronicity as it is defined in psychosocial stress research, our operationalization focuses on the persistence of the threat posed by frequently occurring stressors of the same type, rather than the duration of the stressor event(s) (see Wheaton, 1994; McLean & Link, 1994; Gottlieb, 1997). While a stressor itself may not be continuous in nature, it is responded to as though it

were, due to its regularity (Wheaton, 1994). Stress and coping literature additionally suggests that the repeated occurrence of one type of stressor may indicate a failure to cope with that particular stressor type due to lack of resource fit or failure to replenish resources (Lazarus & Folkman, 1989). For instance, five home overload stressors over the course of a week might indicate lack of available resources appropriate for handling that particular stressor type (e.g., social support is depleted). The home overload may be perceived as uncontrollable due to its frequent repetition. Conversely, an argument, a network stressor, two work stressors, and a home overload stressor over the course of a week may require resources specific to each stressor (e.g., social support for home overloads versus time for work stressors). Resources from handling one stressor type may then be replenished while managing a stressor that requires different resources (Lazarus & Folkman, 1989; Hobfoll, 1991).

High stressor exposure and low stressor diversity might be particularly toxic in terms of inflammation for similar reasons as it functions in affective well-being: it reflects the transition from allostasis to allostatic load (McEwen & Stellar, 1993; Smyth, Zawadzki, & Gerin, 2013). In physiological stress literature, there are four stress response types that lead to allostatic load: “repeated hits” from novel stressors, lack of adaptation to stressors, prolonged response, or inadequate response to stressors (McEwen, 1998). Particular to inflammation, allostasis involves an increase in inflammation in response to psychosocial stress, that ceases with the end of the stressor (Dhabhar, 2014). With repeated activation via one of the above allostatic load response types, the immune system becomes dysregulated, resulting in higher systemic inflammation (Bauer et al., 2000; Miller, Cohen, & Ritchie, 2002).

Many studies have associated conditions of chronic stress with higher inflammation. However, relatively few have studied chronicity in everyday stressor experiences. In the few studies that have analyzed daily data, evidence is mixed on whether higher daily stressor exposure constitutes allostatic load. Some studies report higher inflammation with greater exposure (e.g., Fuligni et al., 2009; Gouin, Glaser, Malarkey, Beverson, & Kiecolt-Glaser, 2012), and others find no association (e.g., Sin, Graham-Engeland, Ong, & Almeida, 2015). Fuligni and colleagues (2009) found that higher frequency of daily interpersonal stressors across two weeks was associated with higher CRP. Gouin and colleagues (2012) found that dementia caregivers tended to report more stressors in the previous 24 hours and that these daily stressor experiences partly accounted for their higher inflammation compared to non-caregiving controls. However, Sin and colleagues (2015) found no association between daily stressor frequency (percentage of stressor days out of eight study days) and IL-6 or CRP, but rather greater affective response to stressors is associated with higher inflammation. Mixed results may reflect differences in stressor types measured, such that high exposure to homogenous stressors (e.g., interpersonal stressors, caregiving stressors) matters more than exposure alone.

When high stressor exposure is combined with low stressor diversity, the associated poor affective well-being indicates a lack of adequate psychosocial coping, potentially reflected in physiological response (Koffer et al., 2016). Thus we expect the allostatic load of high stressor exposure and low stressor diversity to manifest in the form of increased inflammation. While there is evidence of extended poor affective well-being associated with high stressor exposure and low stressor diversity (Koffer et al., 2016), it

must be tested whether physiological responses correspond with the psychological, as this is not always the case (McEwan & Seeman, 2009).

Age-related changes in inflammation, stressor exposure, and stressor diversity

With a life time of activation against pathogens and psychological stressors, older age is associated with higher inflammation (i.e. inflammaging) (Ferrucci et al., 2005; Straub et al., 2000; Wilson, Woody, & Kiecolt-Glaser, 2018). Specific theorized mechanisms of inflammaging are multifarious, including buildup of damaged and senescent cells, leaked toxins from dysfunctional microbiota and mitochondria, and increased coagulation (Franceschi & Campisi, 2014). Essentially, "vicious cycles" of dysregulation across interacting bodily systems (e.g., endocrine and immune systems) are theorized to be at the heart of chronic inflammation with age (Straub et al., 2000). As both the endocrine and immune system are involved in the body's response to stress, older adults are prone to dysregulated physiological response to stress.

Socioemotional developmental theories and empirical evidence suggest that though older adults have poorer physiological regulation in the face of stressors, they may have advantages in exposure and emotional response to stressors (Baltes, 1997; Charles, 2010). Older adults select themselves out of more stressor situations than younger adults, particularly using avoidant or secondary coping strategies (Baltes, 1990; Charles, 2010). Such strategies as well as other contextual changes with age mean older adults are exposed to fewer, more homogenous stressors than younger adults (Brose et al., 2013). When they are faced with stressors, older adults are more likely to use

reframing and secondary coping strategies to regulate their emotional response (Charles, Piazza, & Almeida, 2009). However, situations in which older adults must face a stressor, as in chronic or unavoidable stressors, these emotional advantages fade in the face of physiological vulnerability (Charles, 2010; Charles & Piazza, 2009).

With biological vulnerabilities from both age and chronic stress, older adults may be particularly vulnerable to high inflammation in the face of high stressor exposure and low stressor diversity. Theoretically, chronic stress and aging provide a "double jeopardy" risk of chronic inflammation (Gruenewald & Seeman, 2010). That is, age and chronic stress mirror each other in pro-inflammatory effects, and so their joint biological impact could prove even larger (Gruenewald & Seeman, 2010). Only one study to date has explicitly examined age differences in increased inflammation due to chronic stress. With a sample of adults ranging in age from 55 to 89, Kiecolt-Glaser and colleagues (2003) found that current and former caregivers had greater inflammation increases with age than did non-caregiving controls. However, a myriad of chronic stress studies using caregiving paradigms has supported the notion of increased inflammatory risk for older adults facing chronic stress (see Gouin, Hantsoo, & Kiecolt-Glaser, 2008). Due to the double jeopardy of aging and chronic stress, we expect older age to exacerbate the effects of high stressor exposure and low stressor diversity on inflammation.

The Present Study

The present study examined how between-person differences in stressor exposure and stressor diversity are linked to differences in inflammation. For specificity of

inflammatory process, I separated inflammatory markers into two latent inflammation categories—general systemic inflammation and endothelial inflammation— though associations with each factor were expected to be in the same direction. Individuals with higher stressor exposure were expected to have higher levels of inflammation, due to novel "repeated hits" to their allostatic systems. Individuals with lower stressor diversity were also expected to have higher inflammation, due to failure to adapt to repeated hits of the same stressor experiences. Of primary interest, however, is the interaction between stressor exposure and stressor diversity. The combination of high stressor exposure and low stressor diversity were expected to lead to particularly high inflammation. Additionally, older adults were expected to experience higher inflammation, in general. Age was examined as a moderator to test if older age exacerbates the effects of stressor exposure, stressor diversity, and their interaction on inflammation.

Method

Participants and Procedure

Data for the current analyses were drawn from the second wave of the Midlife in the United States (MIDUS) study and two of its subprojects, the National Study of Daily Experiences (NSDE; Almeida et al., 2009) and the Biomarker Project (Love, Seeman, Weinstein, & Ryff, 2010). All MIDUS participants first completed a mailed survey about physical and mental health as well as sociodemographic and lifestyle information (for further details see Brim, Ryff, & Kessler, 2004). Participants were then recruited from the

MIDUS sample to participate in the subprojects. This analysis makes use of data from the *N* = 1,011 adults who completed both the NSDE and the Biomarker Project (37% completed the NSDE before the Biomarker Project).

For each of eight consecutive evenings, NSDE participants answered an approximately 15-min telephone interview on stressor events, affect, and time use during the previous 24 hours, (Almeida et al., 2009). For completing the entire NSDE protocol participants were compensated $25 in advance. The separate biomarker protocol included a two day visit to a lab at one of 3 locations (UCLA, Georgetown, and University of Wisconsin, Madison). In the lab, participants reported their medical history and current medications, went through a physician-administered physical exam, and provided a fasting blood sample between 8 AM and 10 AM on the second day. From the blood samples, serum was isolated, aliquoted, frozen at −80°C, and stored in a −65°C freezer until assayed.

Participants (47% female) age ranged from 34 to 84 years (M_{Age} = 55.82, SD_{Age} = 11.69), were generally in good health (M = 2.70, SD = 0.12, on a 0-4 scale), were largely Caucasian (80.71%), and had generally obtained schooling beyond high school (65.68%). This sample did not differ significantly in age, sex, or income from the main MIDUS sample.

Measures

Inflammation. Blood samples were assayed for six inflammatory markers: IL-6, CRP, fibrinogen, soluble IL-6 receptor, soluble E-selectin, and soluble intercellular

adhesion molecule-1. Three 10 mL Serum Separating Tubes were centrifuged at 4°C for 20 minutes at 2000-3000 rpm. Then, 1 mL of sera was aliquoted into separate 2 mL vials and stored at -60 to -80 °C until shipped on dry ice to the assaying lab. Samples were stored in a -65°C freezer until they were assayed.

Serum IL-6 was assayed in the MIDUS Biocore Laboratory at the University of Wisconsin, Madison using Quantikine® high-sensitivity enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, MN). The inter-assay coefficient of variance (CV) was 12.31% and intra-assay CV was 3.25%. The assay range was 0.156 to 10 pg/mL. ELISA kits (R&D Systems, Minneapolis, MN) for sICAM and E-Selectin, and immunonephelometric assays (Dade Behring Inc., Deerfield, IL) for measuring fibrinogen and CRP were assayed in the Laboratory for Clinical Biochemistry Research at the University of Vermont, Burlington, VT. Correction factors for lot-to-lot changes in sICAM and sE-Selectin assays were also applied at the Laboratory for Clinical Biochemistry Research. Inter- and intra-assay CVs were as follows: sICAM (inter: 5%), sE-Selectin (inter: 8.8%, intra: 5.0%), Fibrinogen (inter: 2.6%, intra: 2.7%), and CRP (inter: 5.7%, intra: 4.4%), all within a standard acceptable range of <20% (DeSilva et al., 2003). Values below detectable ranges were replaced with one unit lower than the detectable range: for CRP, values below 0.15 ug/dL (N = 31) were adjusted to 0.14 ug/dL; for E-Selectin, values below 0.1 ng/mL (N = 1) were adjusted to 0.09 ng/mL; for sICAM, values below 45 ng/mL (N = 8) were adjusted to 44 ng/mL.

CRP values greater than the 10 mg/L clinical cutoff for acute infections (Pearson et al., 2003) were excluded (n=37). Total sample sizes for each marker were $N_{IL\text{-}6}$ = 1001, N_{CRP} =962, $N_{Fibrinogen}$ =999, N_{sICAM} =1001, and $N_{sE\text{-}Selectin}$ =1001. Missing cases were due

to blood draw refusal or inadequate sample volume for assaying. Data for all inflammatory markers were natural log-transformed to correct for positively skewed distributions, and fibrinogen values were scaled by 100 to maintain comparable estimates with the other inflammatory measures.

Stressor Exposure and Stressor Diversity. Participants' daily stressors were assessed each evening using the Daily Inventory of Stressor Events (DISE; Almeida, Wethington, & Kessler, 2002) semi-structured interview. Participants were asked whether they had experienced each of 7 stressor types: arguments, avoided arguments, discrimination, work/education stressors, home stressors, network stressors, and other stressors. Interview questions included: "Did you have an argument or disagreement with anyone since (this time/we spoke) yesterday?"; "Since (this time/we spoke) yesterday, did anything happen that you could have argued about but you decided to let pass in order to avoid a disagreement?"; and "Since (this time/we spoke) yesterday, did anything happen to a close friend or relative (other than what you've already mentioned) that turned out to be stressful for you?"; "Since (this time/we spoke) yesterday, did anything happen at [question domain] (other than what you already have mentioned) that most people would consider stressful?"; "Many people experience discrimination on the basis of such things as race, sex, or age. Did anything like this happen to you since (this time/we spoke) yesterday?" Each day participants indicated whether they had (= 1) or had not (= 0) experienced each of the seven types of events.

Computed from these 7 binary item responses, $stressorcount_{id}$ indicates the total number of stressors (across all 7 types) reported by individual *i* on day *d* (the daily sum of the 7 binary items; participants can only report one event per stressor type); and

stressortype$_{id}$ is a 7-category nominal variable indicating the type(s) of stressor reported by individual *i* on day *d*. Participants reported experiencing M= 0.58 (SD= 0.50) stressors per day. The most common stressor type was avoided arguments (31.22% of individuals' stressors), followed by arguments (16.95%), home (15.34%), work/education 14.49%), "other" (10.06%), network (9.54%), and discrimination stressors (<5%).

Stressor exposure is quantified as the average number of stressors an individual *i* reported across his or her total number of completed study days, $d = 1$ to T_i, where $T_i \leq 8$ (M = 7.37, SD = 1.29):

$$Stressor\ Exposure_i = \frac{1}{T_i}\sum_{d=1}^{T_i} stressorcount_{di} \quad (1)$$

Stressor diversity is quantified using Shannon's (1948) entropy index:

$$Stressor\ Diversity_i = -\left(\frac{1}{\ln(m)}\right)\sum_{j=1}^{m} p_{ij}\ln p_{ij} \quad (2)$$

where m is the number of available stressor categories ($m = 7$), and p_{ij} is the proportion of individual i's stressors on $d = 1$ to T_i that were in each category, $j = 1$ to m. Using this formulation, diversity values can range from 0 (no diversity), where all of an individual's daily stressor experiences are of a single type, to 1 (maximum diversity), where all stressor types are evenly represented.

Age. Age was computed as the difference between the date stressors were assessed and date of birth.

Covariates. Additional sociodemographic information, health information, and medical information were included in analyses to control for known confounds with stress and inflammation (Gouin et al., 2012; Miller et al., 2002). Participant sex, menopausal status, and years of education were measured in the MIDUS baseline survey,

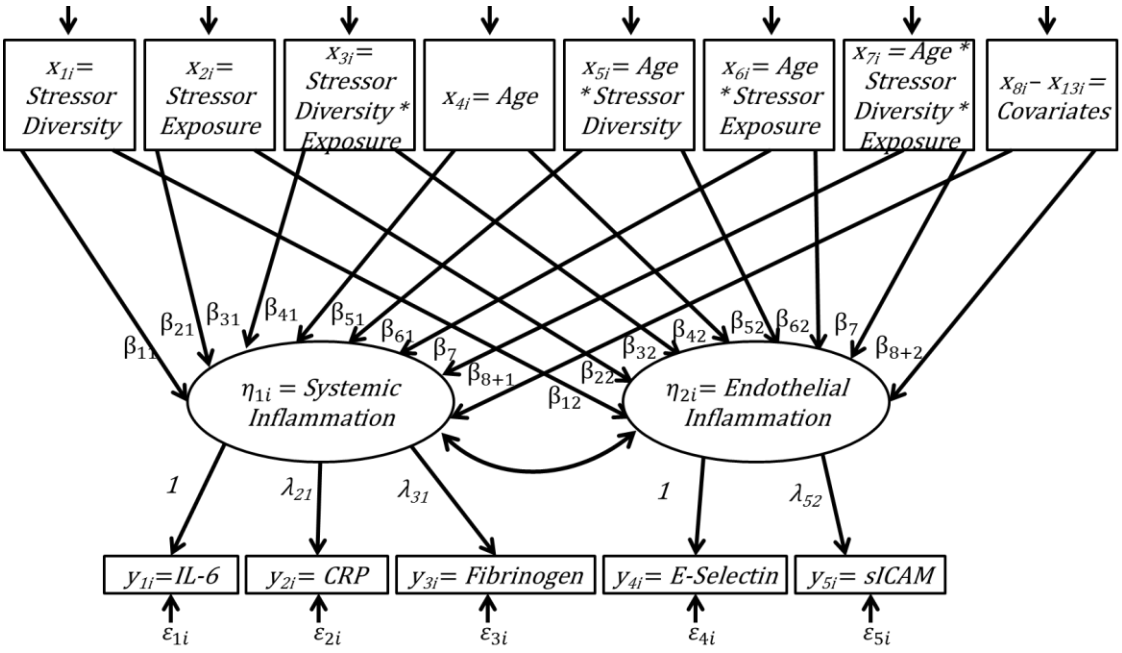
each of which have been linked to inflammation (Segerstrom & Miller, 2004). *BMI* was computed from measurements taken by biomarker project laboratory staff. *Comorbidities* was a sum score of twenty self-reported physician diagnosed conditions, including heart disease, high blood pressure, circulation problems, blood clots, heart murmur, transient ischemic attack or stroke, anemia or other blood disease, cholesterol problems, diabetes, asthma, emphysema or chronic obstructive pulmonary disease, tuberculosis, thyroid disease, peptic ulcer disease, cancer, colon polyps, arthritis, glaucoma, cirrhosis or liver disease, or depression. Medication use, including *corticosteroids*, *cholesterol medication*, *blood pressure medication*, (anti-hypertensives), *anti-depressant medication*, and *hormone-based medication* were dummy coded to indicate use (=1) or non-use (=0). These medications are all known to affect inflammation (Jain & Ridker, 2005; Kenis & Maes, 2002; Tatli & Kurum, 2005). *Time interval*, computed as the number of days between biomarker and stressor assessments was used as a sensitivity check for treating variables cross-sectionally (negative = participated in biomarker project first, positive = daily diary first).

Data Analysis

Relations among inflammation, stressor exposure, stressor diversity, and age, were examined using a structural equation model. The outcomes of interest were included as two latent factors that were theoretically defined and indicated by markers of systemic inflammation (IL-6, CRP, and Fibrinogen) and endothelial inflammation (E-selectin and sICAM-1), respectively. The separation of the markers into two factors provided for

specificity in measurement of individuals' inflammatory process. Particularly, the second factor separates the more endothelial-specific markers that have been less frequently studied in association with stress. The measurement and structural models are depicted in Figure **3-1**.

Figure **3-1**. Structural equation model with latent factors for systemic inflammation and endothelial inflammation regressed on stressor diversity, stressor exposure, age, their interactions, and covariates.



Where, in the measurement model at the bottom of the figure, y_{1i} through y_{5i} IL-6, CRP, Fibrinogen, E-Selectin, and sICAM-1, respectively, η_{1i} is systemic inflammation, η_{2i} is endothelial Inflammation, and the variance of ε_i=Θ is a diagonal matrix, with elements θ_{11}, θ_{22}, θ_{33}, θ_{44}, θ_{55}.

The structural model at the top of the figure regressed each factor on the variables of interest. Here β_2 is the difference in inflammation due to one more stressor experience an individual experiences on average per day. β_3 is the difference in inflammation uniquely due to the spread and evenness of stressors across stressor types. β_1 is the difference in inflammation uniquely due to a one year difference in age. Of particular interest, β_4 is how stressor diversity moderates the relation between stressor exposure and inflammation and, the extent that age moderates the above associations (β_{5-7}). e_m is residual error.

The model was fit to the data using the lavaan package (Rosseel, 2012) in R (R Development Core Team, 2016), with incomplete data treated as missing at random (Enders, 2010) and all predictors grand mean centered so parameter estimates depict effects for the average participant. Model parameters were evaluated for statistical significance at $\alpha = 0.05$.

Results

Descriptive statistics for the study variables are shown in Table 3-1. Consistent with expectations, the five inflammatory markers were all correlated (*r*s range from .07 to .50), with the strongest correlations among IL-6, CRP, and Fibrinogen. Inflammation was positively associated with age (IL-6, Fibrinogen, and sICAM-1), BMI (IL-6, CRP, Fibrinogen, and E-selectin), and comorbidities (IL-6, CRP, Fibrinogen, E-selectin, and sICAM-1). The pattern of correlations among the inflammatory markers suggested that

general systemic markers of general systemic inflammation (CRP, IL-6, and Fibrinogen) reflect a different kind of inflammation than the markers of endothelial inflammation (E-Selectin and sICAM-1).

The inflammatory markers were not related to either stressor exposure or stressor diversity. Stressor exposure and stressor diversity were highly positively correlated (r = .66). Stressor exposure was higher for women (r = .11), was negatively related to age (r = –.19), and not associated with education (r = .06), BMI (r = .02), or comorbidities (r = .02). Stressor diversity was not related to sex (r = .06), was negatively related to age (r = –.14), and not associated with education (r = .04), BMI (r = .04), or comorbidities (r = .07). While there were no linear associations among stressor exposure, stressor diversity, and inflammation, the present study is most interested in how stressor diversity moderates the association between stressor exposure and inflammation.

Table 3-1. *Sample-Level Descriptive Statistics and Correlations*

	M	*SD*	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)
(1) IL-6	0.77	0.73	--	.50	.40	.17	.15	–.09	–.08	.21	.05	–.05	.35	.23	–.07
(2) CRP	0.38	1.16		--	.50	.10	.17	–.03	–.04	.03	.18	–.06	.43	.16	.09
(3) Fibrinogen	5.81	0.27			--	.07	.15	–.01	–.05	.11	.16	–.04	.28	.15	–.01
(4) E-selectin	3.59	0.53				--	.10	.03	.02	–.05	–.11	–.00	.20	.06	–.05
(5) sICAM-1	5.61	0.38					--	–.04	.03	.13	–.01	–.08	.07	.11	.06
(6) Stressor Exposure	0.58	0.50						--	.66	–.19	.11	.06	.02	.06	.02
(7) Stressor Diversity	0.42	0.27							--	–.14	.06	.04	.04	.07	–.03
(8) Age (34-84)	55.34	11.65								--	–.06	–.07	–.03	.36	0.00
(9) Sex (0 = men)	0.57	0.5									--	–.03	.01	.11	–.01
(10) Years of Education	16.30	2.36										--	–.05	–.05	–.04
(11) BMI	29.68	6.46											--	.16	.05
(12) Comorbidities	4.13	2.95												--	.03
(13) Project Lag	-0.04	1.46													--

Note: *N* ranged from 819 (due to missing sociodemographic variables) to 1011. *M* = Mean; *SD* = Standard Deviation. All inflammatory markers were natural log transformed.

Results from the structural equation model examining how general systemic inflammation and endothelial inflammation were related to stressor diversity, stressor exposure and age is shown in Table **3-2**. Overall, the model fit the data reasonably well, χ^2 (58) =267.97, $p < .001$; CFI = .83; and TLI= .71, while SRMR = .03 and RMSEA = .06 are within acceptable ranges, and provided tests for the hypotheses of interest.

The measurement model for the two inflammation factors is shown in the bottom portion of the table. The general systemic inflammation factor was indicated by IL-6 (Standardized λ_{11}= 0.65), CRP (Standardized λ_{21} = 0.80), and Fibrinogen (Standardized λ_{31} = 0.61), reflecting the strong correlations seen in Table 1. The endothelial inflammation factor was indicated by E-Selectin (Standardized λ_{42} = 0.29) and sICAM-1 (Standardized λ_{52} = 0.34). Although this factor may not be well-defined, reflecting differences between E-selectin and sICAM-1, the positive correlation is captured and invokes the intended construct.

The structural model, wherein the two inflammation factors were regressed on the predictors of interest (stressor exposure, stressor diversity, age) and covariates is shown in the top portion of Table **3-2**. Stressor exposure (β_{21} = 0.01, p = .87) was not associated with general systemic inflammation. However, higher stressor diversity was associated with lower systemic inflammation (β_{11} = -0.18, p = .04). Stressor diversity did not significantly moderate the effect of stressor exposure on systemic inflammation (β_{31} = 0.03, p = .85), and as such, the slopes for stressor exposure on inflammation do not differ by stressor diversity value in Figure **3-2**. Older age was associated with slightly higher inflammation (β_{41} = 0.004, p = .01), but did not moderate the effects of stressor exposure (β_{61} = 0.001, p = .85), stressor diversity (β_{51} = 0.004, p = .56), or the interaction of

stressor exposure and stressor diversity (β_{71} = -0.002, p = .88) on inflammation. Female sex (β_{91} = 0.14, p < .01), comorbidities (β_{71} = 0.01, p = .04), BMI (β_{81} = 3.76, p < .01), blood pressure medication use ($\beta_{10,1}$ = 0.08, p = .03), and hormonal medication ($\beta_{13,1}$ = 0.12, p = .01) were all positively associated with systemic inflammation, while cholesterol medication use was negatively associated with systemic inflammation ($\beta_{11,1}$ = -0.08, p = .03). Education ($\beta_{16,1}$ = -0.01, p = .43), corticosteroid use ($\beta_{12,1}$ = -0.04, p = .59), antidepressant use ($\beta_{14,1}$ = 0.07, p = .12), and menopausal status ($\beta_{15,1}$ = -0.01, p = .59) were not associated with systemic inflammation. In support of treating the data as cross-sectional, the time interval between the daily diary and the lab visit was not associated with systemic inflammation ($\beta_{17,1}$ = 0.00, p = .98). Follow-up analyses with only those who completed the daily diary before inflammatory markers revealed the same pattern of findings. In summary, stressor exposure, and stressor diversity's moderation of stressor exposure did not show expected association with systemic inflammation across adulthood, though stressor diversity did show an expected negative association with inflammation.

Similarly, stressor exposure (β_{22} = 0.04, p = .44) was not uniquely associated with endothelial inflammation. Stressor diversity (β_{12} = 0.03, p = .72) was also not uniquely associated with endothelial inflammation. However, there is a significant interaction between stressor exposure and stressor diversity (β_{32} = -0.33, p = .02). Displayed in Figure **3-3**, we see how stressor diversity moderates the association between stressor exposure and inflammation. When stressor diversity is low (solid line), high stressor exposure is associated with higher endothelial inflammation.

Age was not associated with endothelial inflammation (β_{42} = 0.002, p = .26), and did not moderate the effects of stressor exposure (β_{62} = 0.002, p = .56) or diversity (β_{52} =

-0.003, p = .63). Of the covariates, male sex (β_{92} = -0.06, p = .07) and BMI (β_{82} = 0.79, p = .03) were positively associated with endothelial inflammation, while corticosteroid use ($\beta_{12,2}$ = -0.12, p = .03), and hormonal medications ($\beta_{13,2}$ = -0.09, p = .08)were negatively associated with endothelial inflammation. Again, the time interval between the daily diary and the lab visit was not associated with endothelial inflammation ($\beta_{17,2}$ =- 0.001, p = .95), and follow up analyses with only those who participated in the daily stress diary first did not change the findings. In summary, stressor diversity moderates the effect of stressor exposure as expected, such that high stressor exposure and low stressor diversity are associated with particularly high endothelial inflammation.

Table **3-2**. *Confirmatory Factors of General Systemic Inflammation and Endothelial Inflammation Regressed on Stressor Exposure, Stressor Diversity, and Age.*

	General Inflammation Factor				Endothelial Inflammation Factor			
Covariates	Stand β	Unstand β		SE	Stand β	Unstand β		SE
Stressor Exposure β_{2i}	0.01	0.01		(0.06)	0.13	0.04		(0.05)
Stressor Diversity β_{1i}	-0.11	-0.18	*	(0.09)	0.04	0.03		(0.07)
Stressor Exposure * Stressor Diversity β_{3i}	0.01	0.03		(0.16)	-0.31	-0.33	*	(0.14)
Age β_{4i}	0.11	0.00	*	(0.00)	0.12	0.00		(0.00)
Age * Stressor Exposure β_{6i}	0.01	0.00		(0.01)	0.09	0.00		(0.00)
Age * Stressor Diversity β_{5i}	0.03	0.00		(0.01)	-0.06	0.00		(0.01)
Age * Stressor Exposure * Stressor Diversity β_{7i}	-0.01	0.00		(0.01)	-0.20	-0.02		(0.01)
Comorbidities β_{8i}	0.08	0.01	*	(0.01)	0.17	0.01		(0.01)
BMI β_{9i}	0.52	3.76	*	(0.29)	0.33	0.79	*	(0.37)
Sex (Male = 0) β_{10i}	0.15	0.14	*	(0.04)	-0.19	-0.06		(0.03)
Blood Pressure Medication β_{11i}	0.08	0.08	*	(0.04)	0.09	0.03		(0.03)
Cholesterol Medication β_{11i}	-0.08	-0.08	*	(0.04)	0.02	0.01		(0.03)
Corticosteroids β_{12i}	-0.02	-0.04		(0.07)	-0.16	-0.12	*	(0.06)
Hormone Medication β_{13i}	0.08	0.12	*	(0.05)	-0.19	-0.09		(0.05)
Anti-depressant Medication β_{14i}	0.05	0.07		(0.04)	0.05	0.02		(0.03)
Menopause Status β_{15i}	-0.02	-0.01		(0.03)	-0.09	-0.02		(0.02)
Education (years) β_{16i}	-0.03	-0.01		(0.01)	-0.11	-0.01		(0.01)
Time Interval β_{17i}	0.00	0.00		(0.01)	-0.01	0.00		(0.01)
Factor Loadings	Stand. λ	Unstand. λ		SE	Stand. λ	Unstand λ		SE
IL-6	0.65	1.00			--	--		--
CRP	0.80	1.97	*	(0.13)	--	--		--
Fibrinogen	0.61	0.35	*	(0.02)	--	--		--
E-Selectin	--	--		--	0.29	1.00		--
sICAM-1	--	--		--	0.34	0.84	*	(0.36)

Note: χ^2 (58) =267.97, $p < .001$; CFI = .83; TLI= .71, SRMR = .03; RMSEA = .06. *N* ranged from 819 (due to missing sociodemographic variables) to 1011. Time Interval indicates number of days between biomarker and stressor assessments (negative = participated in biomarker project first). Stand.= Standardized. Unstand. = Unstandardized. SE = Standard Error.

Figure **3-2.** *Stressor Diversity does not Moderate Association between Stressor Exposure and Systemic Inflammation.*

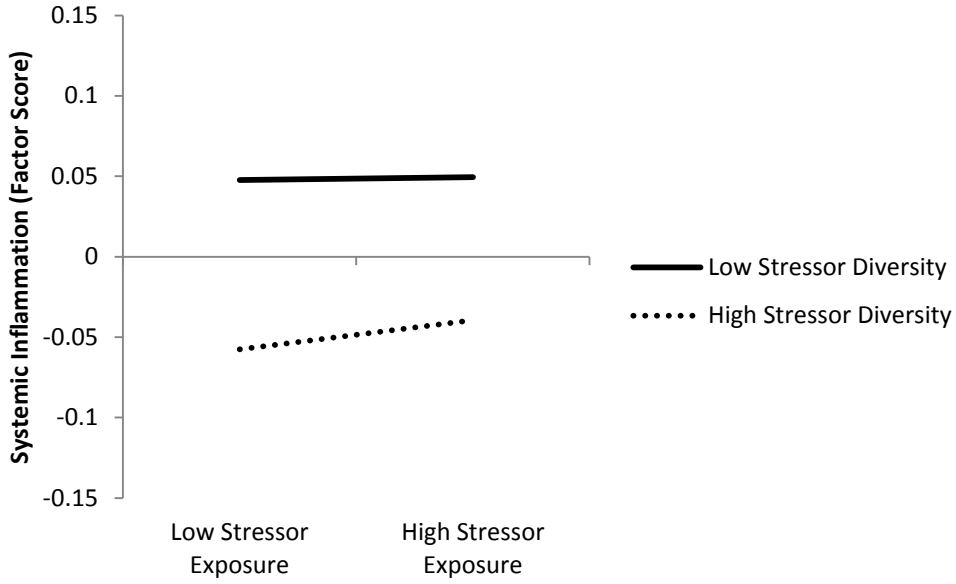
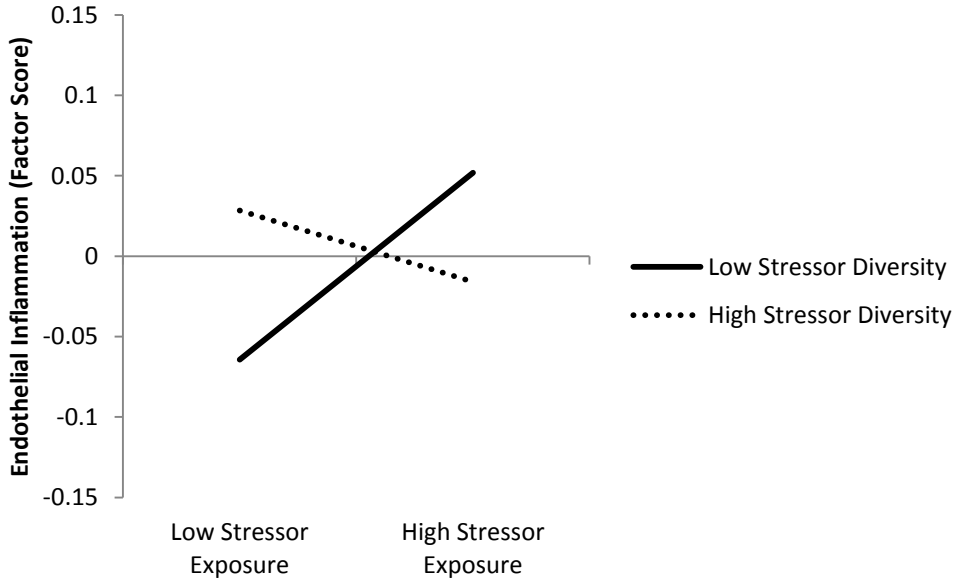


Figure **3-3.** *Stressor Diversity Moderates Association between Stressor Exposure and Endothelial Inflammation.*



Discussion

This study examined how variability in daily stressor experiences related to systemic and endothelial inflammation across adulthood using data from 1011 individuals aged 34-84 years old who provided blood samples and 8 days of daily diary stressor reports. As hypothesized, the combination of high stressor exposure and low stressor diversity was associated with high endothelial inflammation. Contrary to the hypotheses, these effects were age invariant, and did not replicate with general systemic indicators of inflammation. The study provides insight into how the diversity of daily stressor types relates to inflammation through the adult lifespan.

High Stressor Exposure, Low Stressor Diversity and Inflammation

The present study suggests that high stressor exposure and low stressor diversity are associated with endothelial inflammation (i.e., e-selectin and sICAM), but not with general systemic inflammation (i.e., IL-6, CRP, and fibrinogen). These results add to a new and growing literature associating stress with endothelial dysregulation and inflammation (Friedman et al., 2009; Non, Rimm, Kawachi, Rewak, & Kubzansky, 2014; Slopen et al., 2010; Wellen, 2005). Discrepant associations between stress and various inflammatory markers also contributes to our understanding of stress and inflammation across multiple time scales (e.g., minutes-long stressors versus constant role-based stressors), modes of stress research (e.g., experimental versus naturalistic), and inflammatory markers (Marsland et al., 2017). In this case, we use a daily diary approach

to assess chronicity of stressors in individuals' everyday lives and how that relates to chronic inflammation with both general systemic inflammatory markers and endothelial inflammatory markers. Both stressor chronicity and chronic inflammation constructs are hypothesized to change across years. The lack of association among stressor variables and chronic systemic inflammation were surprising, as IL-6 has been robustly associated with acute and chronic stress (Glaser & Kiecolt-Glaser, 2005; Gouin et al., 2008; Marsland et al., 2017). However, a recent meta-analysis found that CRP and fibrinogen are not reliably associated with acute lab stressors (Marsland et al., 2017), in line with the lack of associations in the present findings. Nevertheless, the trending result that higher stressor diversity related to lower general systemic inflammation lends some support to the association that is evidenced in endothelial inflammation.

Results from the model regressing endothelial inflammation on stressor exposure, stressor diversity, and age support the hypothesis that high stressor exposure and low stressor diversity is a particularly toxic form of stress. This suggests that frequent repetition of a dominant stressor type (relative to other stressor types) reflects a transition from allostasis in response to a daily stressor to allostatic load (McEwen, 1998; Smyth, Zawadzki, & Gerin, 2013). The persistent threat of dominant stressor types may prompt a prolonged stress response. Similarly, if high stressor exposure and low stressor diversity reflects failure to effectively cope with a particular stressor type (Lazarus & Folkman, 1984), the individual may experience a lack of physiological adaptation when that stressor type occurs. Notably, neither high stressor exposure nor low stressor diversity on its own was associated with higher inflammation. That higher inflammation does not exist for high exposure in the presence of high stressor diversity suggests repeated

exposure to novel daily stressor types does not constitute allostatic load. The present findings highlight the importance of considering the interaction between mean levels and variance in stressor experiences.

The pattern of findings (i.e., no main effects of stressor exposure, but an interaction between stressor exposure and stressor diversity) may help clarify mixed findings regarding associations between daily stressor exposure and inflammation in prior research. Previous studies of daily hassles use a sum total number of stressor events to assess the association between stressor exposure and inflammation, which has not reliably been associated with immune response (Segerstrom & Miller, 2004). This measurement is not nuanced enough to account for features of stressor exposure, such as diversity of stressor type, that may underlie associations with inflammation. It may be that inflammation is higher in populations who face the same chronic stressor (e.g., caregiving (Gouin et al., 2012; Gouin, Glaser, Malarkey, Beversdorf, & Kiecolt-Glaser, 2012) or report greater exposure to one type of stressor (e.g., interpersonal stress (Fuligni et al., 2009) due to an interaction among stressor exposure and stressor diversity.

Age is Associated with Inflammation but Does Not Moderate Stressor Exposure and Stressor Diversity

Supporting previous literature and inflammaging theories (e.g., (Franceschi & Campisi, 2014; Straub et al., 2000)), older age was related to higher systemic inflammation. However, contrary to expectation, age was not uniquely associated with endothelial inflammation. As older adults tend to experience lower stressor exposure and lower stressor diversity, the lack of age effects on endothelial inflammation may be partly

due to collinearity. Similarly, a strong main effect of age may have partly accounted for lack of interaction between stressor exposure and stressor diversity on general systemic inflammation mentioned above.

Contrary to expectation, the effects of stressor exposure and stressor diversity on inflammation were age-invariant. While there is strong theoretical support for older age and stress producing an interactive vulnerability to higher inflammation, empirical support remains slim due to small sample sizes and age-homogenous samples (Marsland et al., 2017; Segerstrom & Miller, 2004). The present study provided a unique opportunity to examine age moderation of the association between an operationalization of naturalistic daily stressor chronicity and inflammation. While there has been some evidence of age-related immune vulnerability to naturalistic stressors (though with notably few studies including pro-inflammatory cytokines) (Segerstrom, Boggero, Smith, & Sephton, 2014), evidence is mixed for chronic stress and stressor event checklists (Gouin et al., 2012; Segerstrom et al., 2014). While the present findings do not support age moderation of stress on inflammation, these findings must be considered within the particular context of the study design and construct development. For example, the timing of inflammation measurement in the present study was wide-ranging and the exact time-scale of the daily stressor chronicity construct needs further study. There remains a need to examine age change in inflammation, particularly testing under what conditions age may moderate of the association between stress and inflammation (Marsland et al., 2017).

Limitations and Future Directions

While the present study supports the utility of examining daily stressor exposure in the context of stressor diversity, conclusions regarding the associations among daily stressors, inflammation, and age must include consideration of the study's limitations. While the large, age-heterogeneous sample provided a unique opportunity to examine daily stressors and inflammation across the adult lifespan, participants in the sample were healthier and more educated than the general population (U.S. Census, 2014). Particularly, selection bias in older participants particularly lends caution to generalizability of the age-related findings, and indeed may contribute to age-invariant vulnerability to stressors.

The time sampling of stressors and inflammation also has implications for interpreting the present findings in the context of prior research. The present study summarizes intraindividual daily stressor experiences across a week, creating an indicator of a person's typical stressor experiences. Aforementioned naturalistic stressor studies (e.g., Gouin et al., 2012) examined circulating inflammation proximally to stressors—within 24 hours— thus measuring inflammatory response to stressors. In contrast, the present study's median lag between stressor measurement and biomarker assessment was six months, thus measuring longer-term allostatic load processes. Inflammation measured more proximally to the stressor measurement would aid understanding of how stressor exposure and diversity affect acute inflammatory response. As previously alluded to, the time scale of the constructs at play have yet to be fully determined, though we currently make the assumption that the processes take place over longer time spans than the months between measurements. This is supported by our previous findings replicating associations among stressor exposure, stressor diversity, and negative affect from both 8

days of daily data and 63 days of daily data (Koffer et al., 2016). Thus, the present analysis treats the data as cross-sectional. Future work should examine the development of stressor chronicity and allostatic load longitudinally.

In addition to understanding the time scale at which daily stressor chronicity and inflammation are associated, future work is needed to understand antecedents, mechanisms, and consequences of such associations. High stressor exposure and low stressor diversity are associated with particularly high negative affect and low positive affect, and affect is subsequently associated with inflammation (Cohen et al., 2015; Koffer et al., 2016; Sin et al., 2015). Thus, it would be useful to test whether affect mediates the association between stressor chronicity and endothelial inflammation. Similarly, measures of stressor appraisal, such as severity ratings or resource demand, may help us understand the driving forces of stressor chronicity's consequences. Physiological mediators, such as glucocorticoid sensitivity should also be tested to clarify the biological mechanism relating stressor chronicity and inflammation. Building on the present findings, it will be useful to test whether endothelial inflammation may mediate longitudinal associations between stressor chronicity and cardiovascular disease. Understanding what is underlying the present associations will allow further theoretical clarity in daily stress processes as well as long term allostatic load processes.

Synopsis

The present study provides evidence that high daily stressor exposure and low stressor diversity are linked to greater endothelial inflammation throughout adulthood.

Future work would benefit from including stressor diversity alongside stressor exposure when examining associations between daily stress and inflammation, as the combination operationalizes chronicity in daily stressors. Further examination of the link between daily stressor experiences and endothelial inflammation may be particularly useful as a potentially modifiable pathway from stress to disease. With specificity of inflammatory pathway (i.e., systemic and endothelial) and stressor time-scale (i.e., chronicity of daily stressor experiences), the present study provides

Chapter 4

Study 3: Cortisol Variability and Immune Function

Though acute inflammation is one of the body's allostatic responses to pathogens and psychosocial stress, chronic systemic inflammation is implicated in many age-related diseases (Freund, Orjalo, Desprez, & Campisi, 2010). Cortisol, a hormone released from the Hypothalamic Pituitary Adrenal (HPA) axis, plays an important role in moderating inflammation. However, dysregulation in the HPA or immune system can obstruct the negative feedback loop of these systems, and perpetuate chronic low grade inflammation (Miller, Chen, & Zhou, 2007; Miller et al., 2002). Age-related biological changes in neuroendocrine and immune function make older adults particularly vulnerable to "vicious cycles" of dysregulation in the two systems (Gruenewald & Seeman, 2010b; Straub et al., 2000). Thus it is important to understand how dysregulated HPA and inflammation are associated across the adult lifespan (Gruenewald & Seeman, 2010b).

Measurement of dysregulated HPA functioning is operationalized in the literature by flatter diurnal cortisol trajectories and particularly high or low daily cortisol output (i.e., area under the curve, AUC) (Miller et al., 2007; Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). However, cortisol trajectories are not stable across days (Chen et al., 2017; Dmitrieva, Almeida, Dmitrieva, Loken, & Pieper, 2013), and recent evidence suggests that within-person, day-to-day variability may denote HPA dysfunction above and beyond mean cortisol trajectory or AUC (Herriot, Wrosch, Gouin, & Miller, 2017; Sannes, Mikulich-Gilbertson, Natvig, & Laudenslager, 2016). Higher cortisol variability, operationalized as the standard deviation of residual AUC scores, has even been recently associated with higher CRP, an indicator of systemic inflammation

(Herriot et al., 2017). The present study replicates and builds off of this new literature by examining how cortisol variability, operationalized as the standard deviation of residual variance in the diurnal cortisol trajectory, relates to five inflammatory markers indicating systemic and endothelial inflammation across a large, relatively healthy adult lifespan sample.

Cortisol and Inflammation

Healthy HPA functioning involves a diurnal rhythm of the hormone cortisol. The diurnal cortisol trajectory consists of a morning rise (i.e., cortisol awakening response; CAR) peaking 30 minutes post waking, and a persistent decline throughout the rest of the day (i.e., diurnal cortisol slope; DCS). Theoretically, CAR energizes a person to start their day, while DCS allows for recovery from stress through the day (Chen et al., 2017; Dmitrieva et al., 2013). Note in this case, "stress" refers to any stimulant that increases cortisol (e.g., exercise, eating, pain, negative affect, stressor events). Integrating across the diurnal trajectory provides another metric of HPA functioning: the Area Under the Curve (AUC) of the cortisol trajectory that indicates the average cortisol level across the day. AUC increases with age and is higher for men than women (Karlamangla et al., 2013; O'Donnell, Badrick, Kumari, & Steptoe, 2008). Further, AUC has a quadratic association with health (i.e., both extremely high and low cortisol output are associated with pathogenesis) (Miller et al., 2007). Steeper CAR and DCS, as well as moderate AUC, are subsequently associated with more quickly habituated acute cortisol responses to stress throughout the day (Chen et al., 2017).

The endocrine and immune systems are linked via several mechanisms, one of which is cortisol's inhibitory effect on inflammation. This relation may be reflected in the diurnal rhythm of certain inflammatory markers. For instance, IL-6, a key biomarker of inflammation, follows a diurnal rhythm that mirrors the diurnal cortisol rhythm (i.e., reaches a trough between 9 and 10 AM and increases through the rest of the day). Although these two diurnal trajectories have not yet been established as directly associated (Nilsonne, et al., 2016), cortisol's inhibitory effect on inflammation has been well-established in the acute stress response. In response to acute physical or psychological stress, the immune system increases pro-inflammatory cytokines that signal and coordinate the inflammatory cascade. In turn, inflammation stimulates increased cortisol output, that inhibits pro-inflammatory cytokines and stimulates anti-inflammatory cytokines to mitigate further inflammatory response. Through this negative feedback loop, inflammation can be kept in check during acute stress or infection.

Following allostatic load theory, stress mediators, such as cortisol, may become dysregulated with repeated activation (McEwen, 1998). Specifically, there are four patterns of allostatic load, and each pattern elicits compensatory responses by stress mediators that, over the long-term, can result in their respective regulatory systems becoming overloaded and dysfunctional (McEwen, 1998). The first pattern, "repeated hits" of stress, can lead to either overactive or underactive stress response, depending on stressor severity and frequency. The second and third, failure to adapt to the same stressor and failure to turn off the stress response, respectively, both lead to overexposure to stress mediators. The fourth, inadequate response to stress, leads to dysregulation of systems

that rely on the typical stress response, such as the immune system (McEwen & Seeman, 2009).

Specific to the HPA and immune systems, allostatic load reflected in cortisol and chronic inflammation are linked. The glucocorticoid resistance model suggests that in response to chronically high exposure to cortisol (e.g., as from allostatic load pattern 1, 2, or 3), white blood cells downregulate their responsiveness to cortisol (Cohen et al., 2012; Miller et al., 2002). This counter-regulatory response prevents cortisol from inhibiting inflammation, leading to chronic low-grade inflammation. Operationalized as either flatter trajectories or extreme aggregate levels, dysregulated cortisol is associated with systemic inflammation (Hackett et al., 2013; Hammer & Steptoe, 2004; Sephton, Sapolsky, Kramer, & Spiegel, 2000).

Operationalizing HPA dysfunction as Cortisol Variability

Diurnal cortisol trajectories are not stable across days. At least half of the variance in cortisol trajectories is within-person, compared to between-persons (Almeida, Piazza, & Stawski, 2009; Chen et al., 2017; Dmitrieva et al., 2013). This may be because throughout the day, an individual's HPA axis responds to a myriad of behaviors (e.g., exercising, eating, and smoking cigarettes), experiences (e.g., stressors, positive events), and feelings (e.g., pain, negative affect) that differ from day to day. For example, Stawski and colleagues (2013a) found that on days with one or more reported stressor events, peak cortisol, lunchtime cortisol, and the total area under the curve (AUC) were higher than on stressor-free days. Thus, variation in cortisol may reflect allostatic responses to

such stressor events. This implies that while comparing between-person cortisol trajectories or AUC represents an individual's mean experience, these aggregations do not account for moment-to-moment or day-to-day fluctuation in cortisol patterns (i.e., intraindividual variability, IIV, in cortisol) that may reflect important regulatory information (Marceau et al., 2013).

Recently, cortisol IIV has been used as a marker of HPA dysregulation (Sannes et al., 2013; Sannes, Dolan, Albano, Ceballos, & McGregor, 2015). Theoretically, higher cortisol variability may indicate allostatic load, such that the HPA system is failing to adequately regulate functioning (Sannes et al., 2016). Alternatively, higher cortisol IIV could reflect repeated activation in response to stressors (Stawski et al., 2013a) that can lead to allostatic load. In other words, while it may be adaptive to have higher cortisol variability to deal with environmental circumstance (e.g., repeated novel stressors), this pattern may be associated with longer term health consequences (Marceau et al., 2013; Gatzke-Kopp, 2011).

Empirically, higher cortisol variability is associated with poor psychological outcomes. Greater variability in cortisol has been associated with more depressive symptoms, higher psychological distress, and incidence of bipolar disorder and major depression (Havermans et al., 2010; Sannes et al., 2013; Sannes et al., 2016). Recently, cortisol variability was first associated with another marker of biological dysregulation—chronic inflammation, indicated by CRP (Herriot et al., 2017). Above and beyond daily levels and slopes of cortisol, it may be the failure to maintain homeostasis, as indicated by increased cortisol variability that is linked to higher systemic inflammation.

The Role of Aging in Cortisol Output and the Cortisol-Inflammation Association

Aging is theorized to disrupt neuroendocrine mechanisms underlying the diurnal cortisol rhythms (Chahal & Drake, 2007). As part of an aging-related "anabolic-catabolic imbalance," older age is associated with higher catabolic (i.e. those that break down tissue and bone) hormone output, like cortisol, relative to anabolic (i.e., those that promote growth) hormones, like DHEAS (Epel, Burke, Wolkowitz, 2007). Theorized mechanisms behind age differences in cortisol include diminished negative feedback loops for cortisol production and prolonged cortisol response to stress (Chahal & Drake, 2007). This manifests in flatter cortisol slopes, higher evening cortisol, and thus higher AUC (Karlamangla et al., 2013; Larsson, Gullberg, Råstam, & Lindblad, 2009; Van Cauter, Leproult, & Kupfer, 1996). However, most work has addressed between-person differences in mean cortisol slopes and levels, as opposed to intraindividual-variability in cortisol on a day-to-day or moment-to-moment basis (Herriot et al., 2017; Stawski et al., 2013a).

Some endocrine aging theory and empirical evidence suggest that older adults would also have greater within-person and within-day cortisol variation (Almeida et al., 2009; Bergendahl et al., 2000; Chahal & Drake, 2007). As Bergendahl and colleagues (2000) suggested, healthy older adults have the same capacity to raise total daily cortisol as younger adults, but disrupted regulatory mechanisms that coordinate pulsatile and diurnal rhythms. Theoretically, the aforementioned disrupted cortisol negative feedback and prolonged cortisol response to environmental stimuli may underlie greater cortisol variation (Chahal & Drake, 2007). Changes in glucocorticoid receptors with age may also underlie greater variability in cortisol regulation throughout the day (Bergendahl et al.,

2000). Among the few studies that have examined intraindividual variability in cortisol, there is some empirical evidence that older adults experience greater cortisol intraindividual variability at multiple timescales (Almeida et al., 2009; Bergendahl et al., 2000; Herriot et al., 2017). Older men may experience greater day-to-day variability in CAR, though women have not shown such an effect (Almeida et al., 2009). I therefore expect that older age will be associated with higher cortisol variability.

Older adults also tend to have higher inflammation, a phenomena termed "inflammaging" (Straub et al., 2000). Specific theorized mechanisms of inflammaging are multifarious, including buildup of damaged and senescent cells, leaked toxins from dysfunctional microbiota and mitochondria, and increased coagulation (Franceschi & Campisi, 2014). Additionally, as the endocrine and immune systems interact, "vicious cycles" of dysregulation in both systems can occur due to dysregulation of either system (Straub et al., 2000). The joint effects of normative aging and allostatic load may exacerbate the association between HPA dysfunction and inflammation (Gruenewald & Seeman, 2010b; Heffner, 2011).

Present Study

The current study examined whether variability in cortisol beyond an individual's typical diurnal trajectory is linked to inflammation. Following recent work indicating intraindividual cortisol variability is a measure of HPA dysregulation, I expected individuals with higher cortisol variability to have higher inflammation after accounting for baseline cortisol trajectories or levels. Second, I tested whether this association is

moderated by age. I expected older age to be associated with higher inflammation and to exacerbate the link between cortisol variability and inflammation.

This study adds to the literature with the robustness of its sample, measurement, and analysis. The age heterogeneity of the sample (age 34-84 years) allowed us to capture age differences across midlife and older age. Inflammation was also assessed with five biomarkers of systemic and endothelial inflammation (interlukein-6, C-reactive protein, fibrinogen, soluable intercellular adhesion molecule-1, and E-selection) that have been individually linked to cardio-metabolic health outcomes (Danesh et al., 1998; Goldberg, 2009; Gruenewald, Seeman, Ryff, Karlamangla, & Singer, 2006; Hwang et al., 1997). This allowed for replication across markers, as well as deeper understanding of specific pathways by which cortisol variability may relate to inflammation. Cortisol variability was also conservatively modeled. First, I fit each individual's average diurnal trajectory with person-specific four-part spline models. Then, deviations from each individual's average trend reflected de-trended daily and momentary cortisol fluctuation. I also explore whether cortisol variability moderates associations between cortisol trajectory and level (i.e., specifically CAR and DCS) and inflammation.

Methods

Participants and Procedure

Cortisol, sociodemographic, and inflammation data for the current analyses are drawn from the second wave of the Midlife in the United States (MIDUS) study.

Participants complete a mailed survey about physical and mental health as well as sociodemographic and lifestyle information (for further details see Brim, Ryff, & Kessler, 2004). *N* = 2,022 adults were recruited from the national MIDUS sample to participate in the National Study of Daily Experiences (NSDE; Almeida et al., 2009). A subsample of the NSDE, *n* = 1,736 (85.86%) participants, also completed a cortisol sampling protocol on Days 2-5 of the interview.

Participants were sent an in-home saliva collection kit, including written and DVD collection instructions, salivettes (Sarstedt, Nümbrecht, Germany) that were labeled with color-codes indicating day and numbered indicating time of day for each collection, and shipping material for the collected samples. During the first of eight nightly interviews, the interviewers reviewed the procedures for saliva collection that began the following day. Participants were asked to provide saliva samples upon waking, 30 minutes post-waking, before lunch, and before bed for four consecutive days, and to record the exact time of sampling on a provided log sheet. During each corresponding nightly interview, participants were asked again to report on the exact time of saliva sampling (correlated with self-reported log sheet $r > 0.90$) (Almeida et al., 2009). A quarter of the participants received and stored their salivettes in a "smart box"—a container for salivette storage that was engineered specifically for the present study to record all times that the box was opened and closed. Sampling time compliance was fairly high, as correlations between self-reported times and "smart box" times ranged from .75 to .95 across the four sampling points. For completing the entire NSDE protocol, participants were compensated $25 in advance.

Of those who completed the cortisol procedure, 922 also completed a biomarker protocol, including a two day visit to a lab at one of 3 locations (UCLA, Georgetown, and University of Wisconsin, Madison). In the lab, participants reported their medical history and current medications, went through a physician-administered physical exam, and provided a fasting blood sample between 8 AM and 10 AM on the second day. From the blood samples, serum was isolated, aliquoted, frozen at −80°C, and stored in a −65°C freezer until assayed.

Participants (56% female) ranged in age from 34 to 84 years (M_{Age} = 55.43, SD_{Age} = 11.55), were generally in good health (M = 2.71, SD = 0.93, on a 0-4 scale), were largely Caucasian (82.73%), and most had obtained schooling beyond high school (66.12%). This sample did not differ significantly in age, sex, or income from the main MIDUS sample.

Measures

Cortisol and daily sleep and behavior data were drawn from the NSDE. Inflammatory markers, medication use, and physical health measures were drawn from the biomarker project, and sociodemographic data were drawn from the MIDUS survey.

Cortisol

A total of 1733 participants provided saliva samples, with mean of 3.9 days of samples provided per person, for a total of 6,883 days of data with 26,557 saliva samples.

Out of 6,714 days (from 1727 people) with reported wake sample times, 151 days were removed due to waking before 4 AM and 65 days were removed due to waking after 11 AM, and 44 days were removed for having waking length longer than 20 hours. A further 123 days were removed for obtaining pre-lunch cortisol values more than 10 nmol/L higher than the 30 minutes post waking sample, as this indicated either a salivette switch or compliance issues. The final sample for assessing diurnal cortisol was 1705 participants, with 6714 days, and 26,191 samples. Salivettes (Sarstedt, Numbrecht, Germany) were shipped to the MIDUS Biological Core at the University of Wisconsin and stored at –60 °C. Salivettes were thawed and centrifuged at 3000 rpm for five minutes. Free cortisol concentrations were measured with a commercially available immunoluminescence assay (IBL, Hamburg, Germany). The inter-assay coefficient of variation was 15%, while the intra-assay coefficient of variation was 3%, within the acceptable range of below 5% (Dressendorfer et al., 1992). Per usual, cortisol values were log transformed for analysis.

Inflammation

Blood samples were assayed for six inflammatory markers: IL-6, CRP, fibrinogen, soluble IL-6 receptor, soluble E-selectin, and soluble intercellular adhesion molecule-1. Three 10 mL Serum Separating Tubes were centrifuged at 4°C for 20 minutes at 2000-3000 rpm. Then, 1 mL of sera was aliquoted into separate 2 mL vials and stored at -60 to -80 °C until shipped on dry ice to the assaying lab. Samples were stored in a -65°C freezer until they were assayed.

Serum IL-6 was assayed in the MIDUS Biocore Laboratory at the University of Wisconsin, Madison using Quantikine® high-sensitivity enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, MN). The inter-assay coefficient of variance (CV) was 12.31% and intra-assay CV was 3.25%. ELISA kits (R&D Systems, Minneapolis, MN) for sICAM and E-Selectin, and immunonephelometric assays (Dade Behring Inc., Deerfield, IL) for measuring fibrinogen and CRP were assayed in the Laboratory for Clinical Biochemistry Research at the University of Vermont, Burlington, VT. Correction factors for lot-to-lot changes in sICAM and sE-Selectin assays were also applied at the Laboratory for Clinical Biochemistry Research. Inter- and intra-assay CVs were as follows: sICAM (inter: 5%), sE-Selectin (inter: 8.8%, intra: 5.0%), Fibrinogen (inter: 2.6%, intra: 2.7%), and CRP (inter: 5.7%, intra: 4.4%), all within a standard acceptable range of < 20% (DeSilva et al., 2003). Values below detectable ranges were replaced with one unit lower than the detectable range: for CRP, values below 0.15 ug/dL (N = 28) were adjusted to 0.14 ug/dL; for E-Selectin, values below 0.1 ng/mL (N = 1) were adjusted to 0.09 ng/mL; for sICAM, values below 45 ng/mL (N = 5) were adjusted to 44 ng/mL.

CRP values greater than the 10 mg/L clinical cutoff for acute infections (Pearson et al., 2003) were excluded (n=37). Including only those who also had cortisol data, the total sample sizes for each marker were $N_{IL\text{-}6}$ = 898, N_{CRP} = 895, $N_{Fibrinogen}$ = 895, N_{sICAM} =898, and $N_{sE\text{-}Selectin}$ =898. Missing cases were due to blood draw refusal or inadequate sample volume for assaying. Data for all inflammatory markers were natural log-transformed to correct for positively skewed distributions, and fibrinogen values were scaled by 100 to maintain comparable estimates with the other inflammatory measures.

Covariates

Standard sociodemographic, health, medical and behavioral information were included in analyses to control for known confounds with cortisol and inflammation (Karlamangla et al., 2013; Cohen et al., 2012; Wilson, Woody, & Kiecolt-Glaser, 2018). Participant *sex* and highest level of *education* (categorical variable converted into average years) were measured in the MIDUS baseline survey, both linked to cortisol and inflammation (Karlamangla et al., 2013; Segerstrom & Miller, 2004). *BMI* was computed from measurements taken by biomarker project laboratory staff. *Comorbidities* was a sum score of twenty self-reported physician diagnosed conditions, including heart disease, high blood pressure, circulation problems, blood clots, heart murmur, transient ischemic attack or stroke, anemia or other blood disease, cholesterol problems, diabetes, asthma, emphysema or chronic obstructive pulmonary disease, tuberculosis, thyroid disease, peptic ulcer disease, cancer, colon polyps, arthritis, glaucoma, cirrhosis or liver disease, or depression. Medication usage that affects measurement of cortisol or inflammation were included: *corticosteroids*, anti-anxiety and *anti-depressant medication*, *cholesterol medication*, and *blood pressure medication* (anti-hypertensives) were dummy coded to indicate use (=1) or non-use (=0) (Jain & Ridker, 2005; Kenis & Maes, 2002; Karlamangla et al., 2013; Tatli & Kurum, 2005).

Standard behavioral variables that influence the diurnal cortisol trajectory and inflammation include circadian sleep and cigarette smoking (Karlamangla et al., 2013; Sin et al., 2015). Hours of sleep from the night prior was recorded in each day's diary interview. I used centered, quadratic *hours of sleep*, With the expectation that too much

or too little sleep both affect the cortisol trajectory (Karlamangla et al., 2013), I used a quadratic transformation of *hours of sleep* (sleep^2) as a covariate. *Average morning wake time* was computed as the mean across reported values of first cortisol sample. Number of cigarettes smoked per day was also included in the daily interview questions and averaged across all days to form a *mean number of cigarettes smoked*. *Time interval*, computed as the number of days between biomarker and NSDE assessments was used as a sensitivity check for treating variables cross-sectionally (negative = participated in biomarker project first, positive = daily diary first).

Data Analysis

The present study's main interests were to (1) quantify individual differences in cortisol variability, (2) examine whether extent of cortisol variability is linked to inflammation above and beyond cortisol slopes, and (3) test whether that association is moderated by age.

Modeling Cortisol IIV

To begin addressing these questions, I first modeled each individual's diurnal cortisol trajectory, then compute variability from the trajectories.

Diurnal Cortisol Trajectories.

Each individual's diurnal cortisol at time, *t*, was modeled using a person-specific linear spline growth curve with knot points at .5 hours, 4.5 hours, and 15 hours from waking (Karlamangla et al., 2013):

$$\text{Cortisol}_t = \beta_0 + \beta_1 (\text{TimeSinceWaking}_t) + \beta_2 (.5\text{hrs-}4.5\text{hrs}_t)$$

$$+ \beta_3 (4.5\text{hrs-}15\text{hrs}_t) + \beta_4(15\text{hrs}+_t) + \beta_5(\text{WakeTime}) + \varepsilon_t \quad (1)$$

where β_0 indicates the individual's cortisol intercept, β_1 indicates the individual's CAR, β_2 indicates the initial DCS, β_3 indicates the (often less steep) post-lunch cortisol decline, β_4 allows for a late night upswing in cortisol, and β_5 is the effect of morning awakening time, person-mean centered, thus indicating the effect of waking earlier or later than the person's average, and ε_t is the time specific residual.

The above regression was fit separately to each individual's repeated measures to find the best fit person-specific trajectories and to avoid random slope shrinkage that would occur in a multilevel model (i.e., where slopes are pulled toward the average trend). After accounting for individual differences in intercept and slopes, a multilevel model would result in larger person-specific residuals for those with slopes further from the average trends. Thus, the present separate regression approach provides more conservative estimates of cortisol variability.

Cortisol Variability.

The cortisol trajectory was then used to de-trend each individual's time-series and obtain a residual time-series that indicated the extent that the individual's cortisol fluctuated around their typical diurnal trajectory. Each individual's cortisol variability was then quantified as the standard deviation of his/her residual time series. Specifically,

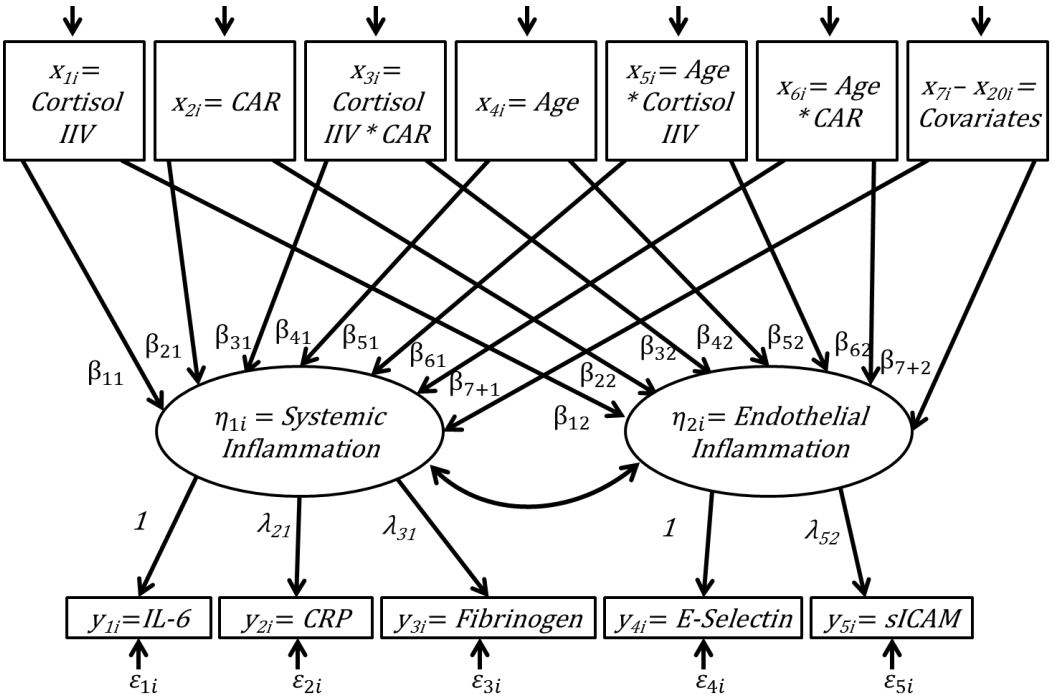
$$Cortisol\ Variability = \sigma_{\varepsilon_t} = \sqrt{\frac{1}{T-1}\sum_{t=1}^{T}(\varepsilon_t)^2}$$

where *T* is the number of cortisol samples provided by the individual. This standard deviation is a person-level indicator of day- and situation-specific *cortisol intraindividual variability (cortisol IIV)* (Marceau et al., 2013).

Cortisol Variability's Association with Inflammation across Age

I then examined how general systemic inflammation and endothelial inflammation were related to cortisol trajectory (CAR or DCS), cortisol IIV, and age using a structural equation model. Two latent factors were theoretically defined and indicated by markers of systemic inflammation (IL-6, CRP, and Fibrinogen) and endothelial inflammation (E-selectin and sICAM-1), respectively. The separation of the markers into two factors provided for specificity in measurement of individuals' inflammatory process. The measurement and structural models are depicted in Figure **4-1**:

Figure **4-1.** Structural equation model with latent factors for systemic inflammation and endothelial inflammation regressed on cortisol intraindividual variability, CAR, age, their interactions, and covariates.



The measurement model is depicted at the bottom of the diagram, where y_{1i} through y_{5i} are IL-6, CRP, Fibrinogen, E-Selectin, and sICAM-1, respectively, η_{1i} is a latent factor for systemic inflammation, η_{2i} is a latent factor for endothelial inflammation, and the variance of ε_i=Θ is a diagonal matrix, with elements θ_{11}, θ_{22}, θ_{33}, θ_{44}, θ_{55}.

In the structural model, β_{1i} is the difference in inflammation uniquely due to cortisol variability. β_{2i} is the difference in inflammation due to CAR [or DCS in its respective model]. β_{3i} is the extent that cortisol variability moderates CAR [or DCS]. β_{4i} is the difference in inflammation associated with a one year increase in age. β_{5i} reflects the extent that age moderates the association between cortisol variability and

inflammation. β_{6i} reflects the extent that age moderates the association between CAR [or DCS] and inflammation. β_{7i-20i} are the effects of the sociodemographic, medicinal, and behavioral control variables mentioned above.

The model was fit to the data using the lavaan package (Rosseel, 2012) in R (R Development Core Team, 2016), with incomplete data treated as missing at random (Enders, 2010), and all predictors grand mean centered so that parameter estimates depict effects for the average participant. Model parameters were evaluated for statistical significance at $\alpha = 0.05$.

Results

Descriptive statistics for key variables are shown in Table **4-1**. Consistent with expectations, the five inflammatory markers were all correlated (*r*s range from .07 to .50), with the strongest correlations among IL-6, CRP, and Fibrinogen. Inflammation was positively associated with age (IL-6, Fibrinogen, and sICAM-1), BMI (IL-6, CRP, Fibrinogen, and E-selectin), and comorbidities (IL-6, CRP, Fibrinogen, E-selectin, and sICAM-1). The pattern of correlations among the inflammatory markers suggested that general systemic markers of general systemic inflammation (CRP, IL-6, and Fibrinogen) reflect a different kind of inflammation than the markers of endothelial inflammation (E-Selectin and sICAM-1).

The inflammatory markers were not related to cortisol variability (*r*s range from –.01 to .05), weakly positively associated with CAR (*r*s range from .04 to .11), weakly negatively associated with DCS (*r*s range from –.03 to –.11), and not associated with

AUC (*r*s range from –.03 to .06). Cortisol IIV was not associated with CAR (*r* = .06), weakly negatively correlated with DCS (*r* = –.09), and positively associated with AUC (*r* = .28). Cortisol IIV was not associated with sex (*r* = –.02), age (*r* = .03), or BMI (*r* = .02), weakly negatively associated with education (*r* = –.07), and weakly positively associated with comorbidities (*r* = .08). Steeper CAR was weakly positively related to age (*r* = .09) sex (*r* = .08), and comorbidities (*r* = .11), weakly negatively related to education (*r* = –.09), and not associated with BMI (*r* = .05). Flatter DCS was weakly negatively associated with age (*r* = –.08) and comorbidities (*r* = –.11), weakly positively associated with education (*r* = .08), and not related to sex (*r* = –.05) or BMI (*r* = .04). The correlations suggest cortisol IIV may not uniquely relate to inflammation, though it may still moderate associations between CAR or DCS and inflammation.

Table **4-1.** *Sample-Level Descriptive Statistics and Correlations*

	M	*SD*	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)
(1) IL-6	0.76	0.74	--	.50	.39	.16	.17	.05	.09	–.11	.04	.22	.01	–.04	.35	.23	–.07
(2) CRP	0.36	1.15		--	.49	.11	.20	.03	.09	–.11	–.03	.04	.17	–.06	.43	.16	.09
(3) Fibrinogen	5.80	0.27			--	.06	.16	–.01	.11	–.10	.01	.13	.13	–.04	.29	.13	–.01
(4) E-selectin	3.58	0.53				--	.10	.02	.04	–.03	.06	–.05	–.14	.01	.22	.04	–.07
(5) sICAM-1	5.61	0.36					--	.02	.11	–.09	–.01	.14	–.02	–.07	.07	.11	.08
(6) Cortisol IIV	0.32	0.16						--	.06	–.09	.28	.03	–.02	–.07	.02	.08	–.02
(7) CAR	0.74	0.95							--	–.82	.14	.09	.08	–.09	.05	.11	.04
(8) DCS	–0.97	1.25								--	–.09	–.08	–.05	.08	–.05	–.11	–.03
(9) AUC	30.84	8.22									--	.19	–.14	–.04	–.01	.02	–.03
(10) Age (33-84)	56.50	12.11										--	–.03	–.11	–.02	.35	.02
(11) Sex (0 = men)	0.56	0.50											--	–.02	–.06	.10	–.05
(12) Yrs. of Educatic	16.18	2.41												--	–.05	–.06	–.02
(13) BMI	29.67	6.51													--	.18	.06
(14) Comorbidities	4.08	2.90														--	.00
(15) Project Lag	-0.34	1.60															--

Note: *N* = 794- 1703 (missing cases due to missing sociodemographics). *M* = Mean; *SD* = Standard Deviation. All inflammatory markers are natural log transformed

Results from the structural equation model examining how general systemic inflammation and endothelial inflammation are related to CAR, cortisol IIV, and age are shown in Table **4-2**. The same model with DCS as the cortisol slope of interest is shown in Table 3. Overall, the models fit the data reasonably well and allow for tests of the hypotheses of interest. For the SEM with CAR: χ^2 (254) =2285.97, $p < .001$; low correlations in the data are reflected in CFI = .32 and TLI= .20; while SRMR = .09 and RMSEA = .07 are within acceptable ranges. For the SEM with DCS: χ^2 (254) =2510.46, $p < .001$; low correlations in the data are reflected in CFI = .30 and TLI= .17; while SRMR = .09 and RMSEA = .07 are within acceptable ranges.

The measurement model for the two inflammation factors is shown in the bottom portion of Tables **4-2** and **4-3**. The general systemic inflammation factor was indicated by IL-6 (Standardized λ_{11}= 0.64), CRP (Standardized λ_{21} = 0.79), and Fibrinogen (Standardized λ_{31} = 0.60), reflecting the strong correlations seen in Table 1. The endothelial inflammation factor was indicated by E-Selectin (Standardized λ_{42} = 0.24) and sICAM-1(Standardized λ_{52} = 0.44). Although this factor may not be well-defined, reflecting differences between E-selectin and sICAM-1, the positive correlation is captured and invokes the intended construct.

Results from the structural model, wherein the two inflammation factors are regressed on cortisol IIV, CAR, age and covariates, are in the top portion of Table **4-2**. Contrary to our hypotheses, neither cortisol IIV (β_{11} = 0.04, p = .72) nor CAR (β_{21} = 0.03, p = .13) was associated with general systemic inflammation. Cortisol IIV also did not significantly moderate the effect of CAR on systemic inflammation (β_{31} = -0.05, p = .58). As expected, older age was associated with higher inflammation (β_{41} = 0.01, $p < .001$),

but contrary to expectations, age did not moderate the effects of cortisol IIV (β_{51} = 0.01, p = .17) or CAR (β_{61} = 0.00, p = .89) on inflammation. Of the covariates, only sex (β_{71} = 0.13, p = .003), wake time ($\beta_{10,1}$ = 0.03, p = .04), average number of cigarettes smoked ($\beta_{11,1}$ = 0.01, p = .003), BMI ($\beta_{13,1}$ = 0.04, p < .001), blood pressure medication use ($\beta_{14,1}$ = 0.10, p = .01), and cholesterol medication use ($\beta_{15,1}$ = -0.09, p = .03) were associated with systemic inflammation. In support of treating the data as cross-sectional, the time interval between the daily diary and the lab visit was not associated with systemic inflammation ($\beta_{20,1}$ = 0.0, p = .77). The same pattern of results arose when reducing the sample to only those whose cortisol was measured before their inflammatory markers. In summary, cortisol variability, CAR, and their interaction did not show expected associations with systemic inflammation across adulthood.

Results for the endothelial inflammation factor indicated that, again contrary to our hypotheses, cortisol IIV (β_{12} = 0.02, p = .68) was not associated with inflammation, and steeper CAR (β_{22} = 0.03, p = .01) was associated with higher inflammation. Cortisol IIV also moderated the association between CAR and endothelial inflammation (β_{32} = -0.18, p = .001). Displayed in Figure **4-2**, when cortisol IIV is high (dotted line), endothelial inflammation does not differ with flatter or steeper CAR. However, contrary to expectations, when cortisol IIV is low (solid line), steeper CAR is associated with higher endothelial inflammation.

Contrary to the hypotheses, age was not associated with endothelial inflammation (β_{42} = 0.00, p = .06), and did not moderate the effects of cortisol IIV (β_{52} = 0.01, p = .11) or CAR (β_{62} = 0.00, p = .59). Sex (β_{72} = -0.07, p = .01), number of cigarettes ($\beta_{11,2}$ = 0.01, p < .001), BMI ($\beta_{13,2}$ = 0.00, p = .03) and menopausal status ($\beta_{19,2}$ = -0.04, p = .02) were

associated with endothelial inflammation. Again, the time interval between the daily diary and the lab visit was not associated with endothelial inflammation ($\beta_{20,2}$ = 0.00, *p* = .61), and results did not change with a reduced sample for theoretical cortisol to inflammation effect ordering. In summary, cortisol variability moderated the effect of CAR, such that steeper CAR and low cortisol variability were associated with high endothelial inflammation.

Results from the two inflammation factors regressed on cortisol IIV, *DCS*, age and covariates, are in the top portion of Table **4-3**. Patterns of significance were the same as in Table 2 listed above, with the exception that steeper DCS (β_{21} = -0.04, *p* = .02) was surprisingly related to higher systemic inflammation. Again, contrary to hypotheses, cortisol variability (β_{11} = 0.03, *p* = .77) was not uniquely related to systemic inflammation and does not moderate the association between DCS and systemic inflammation (β_{31} = 0.05, *p* = .49). Older age was associated with higher systemic inflammation (β_{41} = 0.01, *p* < .001), but did not moderate the effects of cortisol IIV (β_{51} = 0.01, *p* = .16) or DCS (β_{61} = 0.00, *p* = .65). Cortisol IIV (β_{12} = 0.01, *p* = .82) did not relate to endothelial inflammation, but steeper DCS (β_{22} = -0.02, *p* = .04) related to higher endothelial inflammation. Displayed in Figure **4-3**, when cortisol variability is low, steeper DCS is related to particularly high endothelial inflammation (β_{32} = 0.12, *p* < .001).

Table **4-2.** *Structural Equation Model Results of Confirmatory Factors of General Systemic Inflammation and Endothelial Inflammation Regressed on CAR, Cortisol IIV, and Age*.

		General Inflammation Factor				Endothelial Inflammation Factor		
Covariates	β	B		SE	β	Est		SE
Cortisol IIV (β_{1i})	0.01	0.04		(0.11)	0.03	0.02		(0.05)
CAR (β_{2i})	0.06	0.03		(0.02)	0.23	0.03	*	(0.01)
CAR * Cortisol IIV (β_{3i})	-0.02	-0.05		(0.09)	-0.31	-0.18	*	(0.05)
Age (β_{4i})	0.15	0.01	*	(0.00)	0.15	0.00		(0.00)
Age * Cortisol IIV (β_{5i})	0.05	0.01		(0.01)	0.12	0.01		(0.01)
Age * CAR (β_{6i})	-0.01	0.00		(0.00)	-0.04	0.00		(0.00)
Sex (β_{7i})	0.14	0.13	*	(0.04)	-0.28	-0.07	*	(0.03)
Education (years) (β_{8i})	0.00	0.00		(0.01)	-0.03	0.00		(0.00)
Quadratic Sleep Hours (β_{9i})	0.04	0.01		(0.01)	0.02	0.00		(0.01)
Wake Time (β_{10i})	0.07	0.03	*	(0.01)	-0.01	0.00		(0.01)
Cigarettes (β_{11i})	0.13	0.01	*	(0.00)	0.56	0.01	*	(0.00)
Comorbidities (β_{12i})	0.02	0.00	*	(0.01)	0.03	0.00		(0.00)
BMI (β_{13i})	0.53	0.04	*	(0.00)	0.23	0.00	*	(0.00)
Blood Pressure Medication (β_{14i})	0.11	0.10	*	(0.04)	0.11	0.03		(0.02)
Cholesterol Medication (β_{15i})	-0.09	-0.09	*	(0.04)	0.03	0.01		(0.02)
Corticosteroid (β_{16i})	0.00	0.00		(0.08)	-0.12	-0.08		(0.04)
Antidepressants (β_{17i})	0.05	0.06		(0.05)	0.10	0.03		(0.02)
Hormone Treatment (β_{18i})	0.06	0.09		(0.06)	-0.10	-0.04		(0.03)
Menopausal Status (β_{19i})	-0.04	-0.03		(0.03)	-0.20	-0.04	*	(0.02)
Time Interval (β_{20i})	0.00	0.00		(0.01)	0.04	0.00		(0.01)
	Stand.	Unstand.			Stand.	Unstand.		
Factor Loadings	λ	λ		SE	λ	λ		SE
IL-6	0.64	1.00			--	--		--
CRP	0.79	1.92	*	(0.13)	--	--		--
Fibrinogen	0.60	0.35	*	(0.03)	--	--		--
E-Selectin	--	--		--	0.23	1.00		--
sICAM-1	--	--		--	0.45	1.34	*	(0.35)

Note: χ^2 (254) =2285.968, $p < .001$; CFI = .323; TLI= .201, SRMR = .09; RMSEA = .07. Time Interval indicates number of days between biomarker and stressor assessments (negative = participated in biomarker project first). *N* = 794- 1703. Stand.= Standardized. Unstand. = Unstandardized. SE = Standard Error.

Table **4-3**. *Structural Equation Model Results of Confirmatory Factors of General Systemic Inflammation and Endothelial Inflammation Regressed on DCS, Cortisol IIV, and Age*.

		General Inflammation Factor				Endothelial Inflammation Factor		
Covariates	β	B		SE	β	Est		SE
Cortisol IIV (β_{1i})	0.01	0.03		(0.11)	0.02	0.01		(0.06)
DCS (β_{2i})	-0.09	-0.04	*	(0.02)	-0.18	-0.02	*	(0.01)
DCS * Cortisol IIV (β_{3i})	0.03	0.05		(0.07)	0.29	0.12	*	(0.04)
Age (β_{4i})	0.15	0.01	*	(0.00)	0.15	0.00		(0.00)
Age * Cortisol IIV (β_{5i})	0.05	0.01		(0.01)	0.10	0.01		(0.01)
Age * DCS (β_{6i})	0.02	0.00		(0.00)	-0.02	0.00		(0.00)
Sex (β_{7i})	0.14	0.13	*	(0.04)	-0.26	-0.07	*	(0.03)
Education (years) (β_{8i})	0.00	0.00		(0.01)	-0.02	0.00		(0.00)
Quadratic Sleep Hours (β_{9i})	0.05	0.01		(0.01)	0.02	0.00		(0.01)
Wake Time (β_{10i})	0.07	0.03	*	(0.01)	-0.03	0.00		(0.01)
Cigarettes (β_{11i})	0.13	0.01	*	(0.00)	0.59	0.01	*	(0.00)
Comorbidities (β_{12i})	0.02	0.00		(0.01)	0.04	0.00		(0.00)
BMI (β_{13i})	0.53	0.04	*	(0.00)	0.25	0.01	*	(0.00)
Blood Pressure Medication (β_{14i})	0.11	0.11	*	(0.04)	0.12	0.03		(0.02)
Cholesterol Medication (β_{15i})	-0.09	-0.09	*	(0.04)	0.02	0.01		(0.02)
Corticosteroid (β_{16i})	0.00	0.01		(0.08)	-0.13	-0.08		(0.05)
Antidepressants (β_{17i})	0.05	0.06		(0.05)	0.09	0.03		(0.03)
Hormone Treatment (β_{18i})	0.06	0.09		(0.06)	-0.12	-0.05		(0.03)
Menopausal Status (β_{19i})	-0.04	-0.03		(0.03)	-0.19	-0.04	*	(0.02)
Time Interval (β_{20i})	0.00	0.00		(0.01)	0.03	0.00		(0.01)
	Stand.	Unstand.			Stand.	Unstand.		
Factor Loadings	λ	λ		SE	λ	λ		SE
IL-6	0.64	1.00			--	--		--
CRP	0.79	1.92	*	(0.13)	--	--		--
Fibrinogen	0.60	0.34	*	(0.03)	--	--		--
E-Selectin	--	--		--	0.24	1.00		--
sICAM-1	--	--		--	0.44	1.27	*	(0.34)

Note: χ^2 (254) =2510.456, $p < .001$; CFI = .30; TLI= .17, SRMR = .09; RMSEA = .07. Time Interval indicates number of days between biomarker and stressor assessments (negative = participated in biomarker project first). *N* =794- 1703. Stand.= Standardized. Unstand. = Unstandardized. SE = Standard Error.

Figure **4-2.** Cortisol variability moderates the association between CAR and endothelial inflammation.

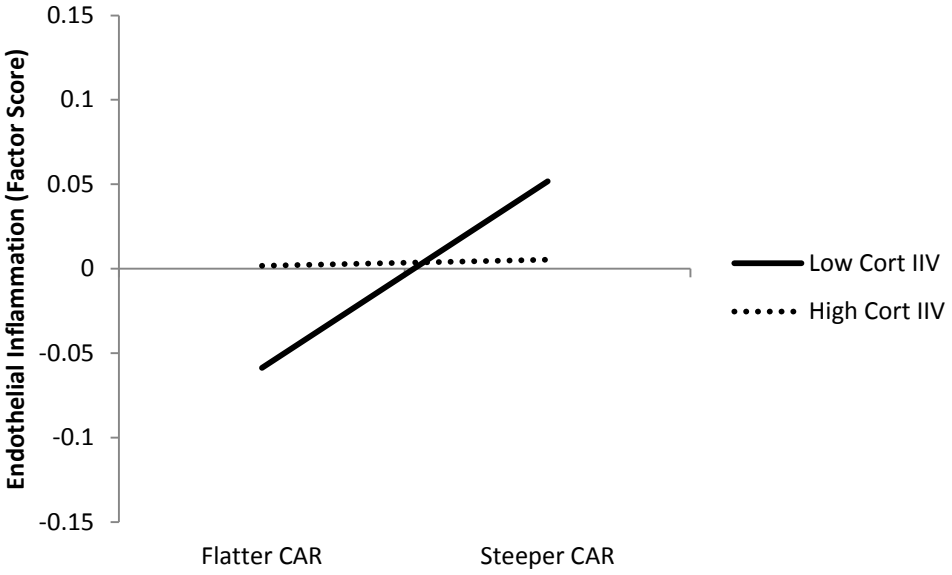
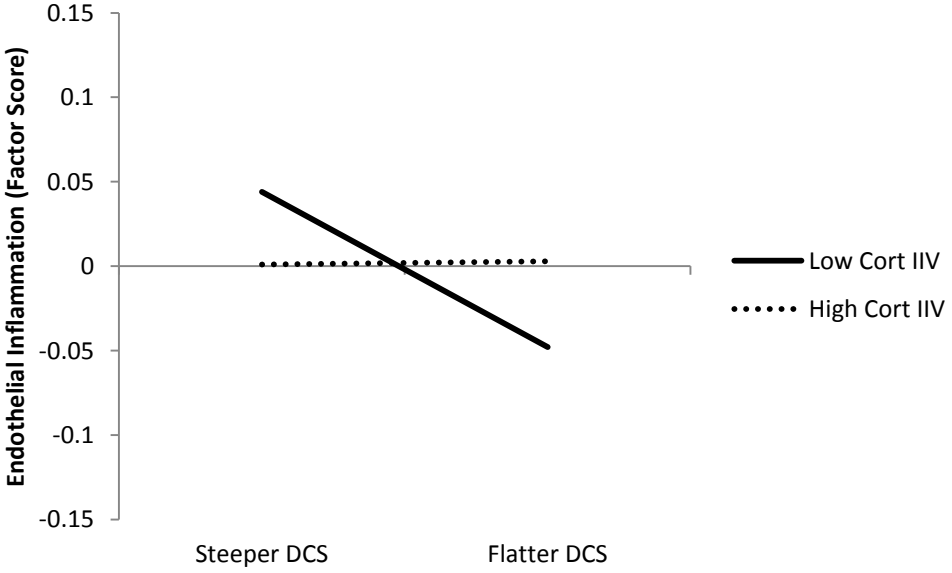


Figure 4-3. Cortisol variability moderates the association between DCS and endothelial inflammation.



Discussion

This study examined how variability in diurnal cortisol trajectory related to systemic and endothelial inflammation across adulthood using data from 895 individuals aged 34-84 years old who provided blood samples and 4 days of cortisol samples, 4 times a day. Contrary to hypotheses, cortisol variability was not uniquely associated with either systemic or endothelial inflammation. Low cortisol variability, in combination with steeper CAR or steeper DCS was related to higher endothelial inflammation. While older age was associated with higher systemic inflammation, age did not moderate the effects of cortisol on inflammation. The study provides insight into how cortisol trajectories and variability from those trajectories are related to inflammation through the adult life span.

Cortisol and Inflammation

Unexpectedly, steeper CAR and DCS were both related to higher inflammation. This is contradicts previous research that flatter cortisol trajectories indicate dysfunction in the HPA axis and are associated with higher inflammation (Cohen et al., 2012; Hackett et al., 2013; Hammer & Steptoe, 2004; Miller et al., 2002; Sephton, et al., 2000). Potential measurement and analytical reasons could account for such findings. However, several theoretical reasons for mixed findings, discussed below, suggest future work is needed to clarify associations.

Reliability of the cortisol slope estimates a necessary concern to address. There has long been debate in the cortisol literature about necessary sampling for reliably modeling cortisol trajectory (see Segerstrom et al., 2014). While Kraemer and colleagues

(2006) suggest three days of cortisol measurement is optimal for diurnal slope estimation, the MacArthur Network suggests six days, while Segerstrom and colleagues (2014) suggest at least ten days are necessary for estimating reliable between-person differences in slope. With the present study's four days of cortisol sampling, it is possible the opposite signed effects are due to lack of power (Gelman & Carlin, 2014).

However, several features of the present study lend confidence to the reliability of slope estimates. While there is plenty of heterogeneity in individuals' estimated cortisol slopes, the average trend was a rise in the morning and decline through the rest of the day, demonstrating the expected prototypical diurnal cortisol trajectory. Additionally, the percentage of individuals who had unexpected slopes (e.g., 12% experienced a rise after the first half hour of waking) was similar to other studies of cortisol slopes throughout the day (e.g. 8% of Miller and colleague's (2002) sample experienced rising DCS). Previous studies using the same sample as the current study also found expected associations among cortisol slopes and sociodemographic characteristics (Almeida et al., 2009; Dmitrieva et al., 2013; Karlamangla et al., 2013).

Theoretically, it is possible that the estimated diurnal cortisol slopes reflected day-level or within-day characteristics not controlled for in the present study; thus the associations among steeper slopes and increased inflammation may be due to a third variable confound. While the present study controlled for common covariates in cortisol-inflammation associations, other daily characteristics and within-day covariates can be examined as mediators. Particularly important for the present findings, Stawski and colleagues (2013a) found that greater frequency of stressor exposure was associated with steeper DCS. As acute stress may be associated with prolonged endothelial dysfunction

that may build over time (Poitras & Pyke, 2013), acute stress may link steeper diurnal cortisol trajectory to endothelial inflammation. Future work can examine stress as well as other potential daily and within-day links (e.g., physical symptoms) between steeper diurnal trajectories and endothelial dysfunction.

Operationalizing HPA dysfunction as Cortisol Variability

Contrary to the hypothesis that cortisol variability indicates HPA dysfunction, higher cortisol variability was not related to higher inflammation in the present study. Indeed, in the presence of *low* cortisol variability, the steeper diurnal cortisol trajectory slopes were related to higher endothelial inflammation. These findings call into question the theoretical robustness of the recent literature on cortisol variability. Certainly moment-to-moment and day-to-day fluctuation in cortisol patterns reflect important regulatory information (Marceau et al., 2013). However, it has not yet been clarified whether cortisol variability indicates lack of ability to maintain homeostasis as opposed to allostasis to changing circumstances (e.g., stressors) to which the body is responding. Cortisol variability's associations with depressive symptoms during cancer treatment (Sannes et al., 2013), caregiving stress (Sannes et al., 2016), and bipolar disorder (Havermans et al., 2010) may indicate the construct's particular usefulness in clinical samples or conditions of chronic stress. Only one recent study has implicated cortisol variability as a marker of HPA dysregulation in a community sample (Herriot et al., 2017). Considering the lack of replication in the present study, more work is needed to validate under what conditions cortisol variability is an indicator of HPA dysregulation.

Future work must also clarify the most meaningful computation(s) of cortisol variability: whether IIV in AUC, or in levels and slopes through the diurnal trajectory. While Havermans and colleagues (2011) and Sannes and colleagues (2013, 2015, 2016) used deviations from cortisol trajectories, Herriot and colleagues (2017) used variability in daily AUC. The present study was the first to compare cortisol variability from diurnal trajectory in a sample of healthy adults. It is possible that day-to-day cortisol variability in level is more indicative of issues in the general population than slopes, so future work (including extensions of the present study) should compare these different computations. Operational specificity and consistency will help clarify the meaning and bounds of the cortisol variability construct moving forward.

The Role of Aging in Cortisol Output and the Cortisol-Inflammation Association

While older adults are theoretically expected to have greater variability and HPA dysregulation than younger adults, the present study's descriptive correlations indicated age was not associated with cortisol IIV and weakly associated with CAR and DCS. Further, older age was associated with steeper CAR and DCS. Previous literature might explain such associations. Bergendahl and colleagues (2000) found compared to younger men, older men's morning peak cortisol was premature, and even earlier under conditions of fasting stress. They report complex patterns of dysregulation, including disruption of co-regulation with Luteinizing Hormone. It is possible that to capture the nuances of age differences in cortisol trajectories, it is necessary to have different knot points based on age and daily stressors. Older adults have higher cortisol levels throughout the day and

may experience greater day to day variability in CAR (Almeida et al., 2009); excluding day-level data dependency may have confounded age-based level and slope differences. Age differences in AUC (i.e., older adults tend to have higher AUC) are more well-established than age differences in other aspects of the diurnal cortisol trajectory (Karlamangla et al., 2013; Larsson et al., 2009; Van Cauter et al., 1996). Thus variability in day to day AUC, like the measure used in Herriot et al (2017), could help tease apart age differences.

In regards to inflammation, the present study found the expected inflammaging effect (i.e., higher inflammation at older ages), but no evidence for vicious cycles of dysfunction between biological systems (i.e. no age moderation of cortisol effects). This may be a product of sample selection effects, as older adults who participate in the biomarker study are notably healthier than the general population (U.S. Census, 2014). As mentioned above, it is possible that age differences in the association between cortisol IIV and inflammation are dependent on cortisol metric of use (e.g., exist for AUC-based, but not for cortisol trajectory- based variability metrics).

Limitations and Future Directions

With the robustness of a large sample, cortisol measurement across four days, five inflammatory markers, and conservative, person-specific modeling of cortisol variability from diurnal trajectories, the present study contributed contradictory findings to the new, growing literature on cortisol variability. As noted above, the unexpected findings exist in the context of several limitations, and there are many opportunities for future extensions

of this work. One of the study's strengths was the larger sample who were in better health than most studies of cortisol variability. Conversely, generalizability is somewhat limited as the individuals who participated in both the NSDE and biomarker subprojects of MIDUS are healthier and more educated than the general public (US Census, 2014).

While four days of four cortisol samples allowed for modeling a four part spline for each individual, it also presented several drawbacks. The timing of cortisol samples varied widely, and a large portion of the sample did not take their cortisol samples at the requested times (about two-thirds of participants their 30 minute post-waking sample within 10 minutes of the correct time). Though this allows examination of the general shape of cortisol trajectory at various times across the day, it is not ideal for modeling individual four-part splines with day-level variation. Thus all 16 cortisol samples were aggregated, without allowing for day-level variation. Future sensitivity checks should compare estimated slopes with averaged slopes from each separate day. Similarly, future work may wish to compare across alternative methods of modeling cortisol variability (e.g., AUC variability versus two- to four-part splines).

Though framed by theoretical associations among cortisol and inflammation, the current study did not test for underlying pathways between the biomarkers. This growing literature would benefit from examining both the biological and psychosocial mechanisms that may link cortisol trajectories and variability to inflammation. Biologically, glucocorticoid receptor sensitivity should be included in lab assays. Psychologically, daily stressor exposure and emotional reactivity to stress should be examined as possible links between the observed cortisol slopes and high endothelial

inflammation. Ample daily and within-day characteristics related to cortisol provide the opportunity for future work to parse more meaning from cortisol variability metrics.

Synopsis

The present study provided contradictory evidence to the new literature that uses cortisol variability as an indicator of HPA dysfunction. Rather than greater cortisol variability indicating HPA dysregulation, low variability in combination with steeper diurnal cortisol slopes were related to higher endothelial inflammation. Results should be interpreted with caution, as previous literature suggests flatter, not steeper, diurnal cortisol slopes should be associated with higher inflammation. Nevertheless, these findings, from a conservative approach with a large national sample, indicate greater need for specificity in operationalizing cortisol variability. Extensions of this work can examine whether cortisol slopes and variability should be interpreted in the context of additional daily circumstances, such as daily stressors.

Chapter 5 Overall Discussion

This dissertation examined associations among psychosocial stressor experiences, affect, and biological dysregulation with innovative operationalizations of major stress process theories. The first paper presented three numeric and three nominal metrics used to examine repeated measures of categorical variables, such as stressor types. These metrics offer novel ways to describe stressor exposure, and understand associations between stressor experiences and measures of successful aging. The second paper used low stressor diversity, one of the metrics from the first paper, with high stressor exposure to operationalize daily stressor chronicity. The combination of high stressor exposure and low stressor diversity was related to higher endothelial inflammation, further validating the proposed chronicity operationalization. The third paper operationalized allostatic load in the HPA system as deviations from an individual's typical diurnal cortisol trajectory. Contrary to hypotheses, higher cortisol variability was not associated with higher inflammation, suggesting a need for greater operational specificity in the new and growing literature on cortisol variability. Together, these findings highlight the usefulness of intraindividual variability approach to daily stress research across the adult life span.

Advancement of Novel Constructs and Methodological Approach to the Stress Process: Stressor Diversity, Cortisol Variability, and Latent Factors of Inflammation

This dissertation forwarded the constructs of stressor diversity and cortisol variability as part of a multiple time scale stress process, and the findings suggest further areas of development for both constructs. Stressor diversity was described as the dispersion of stressor experiences across an intraindividual distribution of stressor types. Remaining to be tested are the underlying processes that shape stressor type distributions and relate them to health and well-being. However, theories of stress and appraisal (Lazarus & Folkman, 1984) and life course theories of stress (Pearlin, 1989) guide interpretation of the stressor diversity construct and findings. Theoretically, the types of stressors an individual is exposed to are a product of: the individual's social roles (Pearlin, 1989); (perceived) lack of resources to reduce threats to values; beliefs about the self and the world; and coping patterns (Lazarus & Folkman, 1984; Pearlin, 1989). Low stressor diversity, particularly in the context of high stressor exposure, is theoretically associated with higher negative affect due to resource depletion or perceived lack of resource fit that is characteristic of chronic stressors (Hobfoll, 1989; Lazarus & Folkman, 1984). In this case, resources are the objects, environmental and social conditions, personal characteristics, and energies (e.g., time and money that are used to obtain other resources) that are used to uphold valued goal commitments (Hobfoll, 1989; Lazarus, 2001; Lazarus & Folkman, 1984). Repeated failure to cope with a stressor (i.e., ineffective use of resources) is then expected to transition allostasis to allostatic load in response to high

stressor exposure and low stressor diversity. Validation of the theoretical processes underlying stressor diversity can be achieved by including categorical resources in analyses, even potentially modeling the transaction between stressor and resources over time.

The next major construct evaluated in this dissertation was cortisol variability. Cortisol variability was hypothesized as an indicator of HPA dysregulation. However, opposing findings suggest that in such an early stage of construct development, it might be more prudent to abstain from value judgements of cortisol variability's (mal)adaptive nature. Further, researchers might consider an alternative hypothesis: that cortisol variability may, in fact, indicate HPA robustness. At its core, cortisol variability is daily and within-day deviation from a person-specific trajectory. Within-person variability *should* exist in response to varying daily and within-day circumstances (Segerstrom et al., 2014). Examples of such variation can be found in response to both daily stressors and chronic stressors (Klein et al., 2016; Stawski, Cichy, Piazza, & Almeida, 2013b). In cases of chronic caregiving stress, for example, a typical caregiving day consists of blunted cortisol trajectories (Klein et al., 2016). Nevertheless, it is considered beneficial that individuals return to a normative diurnal cortisol trajectory on days when adult day services are utilized (Klein et al., 2016). To classify cortisol variability as dysfunction instead of normative response to varying circumstances, it may be necessary to account for more day (e.g., work day, weekend day, stressor day) and within-day (e.g., stressor events, exercise) covariates in the original computation of cortisol trajectories (i.e., use multi-level modeling with sample and day levels). Relatedly, Sannes and colleagues (2013, 2015) found links between higher cortisol variability and greater distress, but this

might in fact be attributed to the severe stressors the individuals were facing on a day-varying basis, rather than regulatory problems. In light of discrepant findings for the novel construct of cortisol variability, further work is needed to determine under what circumstances and for which populations might it represent *capacity for response* to varying circumstances or *inability to maintain homeostatic* diurnal cortisol trajectories.

To examine the associations among the above constructs and inflammation, this dissertation used a novel approach of modeling inflammation with two latent factors (systemic and endothelial), based on theoretical pathways associating stress and inflammation. The stress and inflammation literature utilizes a range of inflammatory markers, and is still determining which are most useful for such research (Marsland et al., 2017). Most often, inflammatory markers are examined separately, as each has a unique role, outlined previously, in the inflammatory process. However, the theoretical foundation for such research is based in the underlying construct of systemic inflammation, best modeled as a common factor upon which each inflammatory marker loads (Friedman et al., 2015). Recent evidence suggests that systemic inflammation and endothelial inflammation are distinct pathways from stress to cardiovascular health that may function differently in the face of various stressor types (Non et al., 2014). The present studies advance this theoretical approach by modeling endothelial inflammation as a separate factor from systemic inflammation. Indeed, endothelial dysfunction is often exhibited early in the progression of chronic inflammatory diseases (Steyers & Miller, 2014). Thus, a two factor approach both enables separation of systemic and endothelial inflammation and may provide specificity of the relative timing at which chronic stress is associated with these distinct inflammatory processes.

Intraindividual Variability and Time Scale in Studying the Stress Process

Each paper highlighted the usefulness of an intraindividual variability approach, and discussed a novel method for examining the day-to-day dynamics of the stress process. Intraindividual variability is theoretically driven by short-term processes (e.g. regulation, adaptation) or dynamic characteristics (e.g., lability, plasticity). The first paper's metrics allowed us to test age-differences in stressor experiences driven by processes of selection, optimization, and compensation involved in socioemotional aging (Baltes & Baltes, 1990; Carstensen et al., 1999; Charles, 2010). The second paper demonstrated that the dynamic characteristic of chronicity is captured by low stressor diversity and high stressor exposure. The third paper tested, but did not support, the use of variability from individuals' diurnal cortisol trajectory (i.e., cortisol variability), as an operationalization of HPA axis dysregulation. With mathematical operationalizations of theoretical constructs, researchers can be more precise in determining the boundaries of theory. Further, these metrics offer interventionists more precise target populations (e.g., stress interventions can target those with high stressor exposure and low stressor diversity, then further adjust based on the specific modal stressor(s).)

The presented intraindividual variability metrics were particularly useful as moderators of individual mean levels of stressor exposure or stress-response. All three numeric metrics from the first paper moderated stressor exposure's association with negative affect. Similarly, the nominal metrics define the actual stressor types that are being described by numeric stressor exposure metrics. Future work can benefit from combining numeric and nominal metrics. Both the second and third papers also found

intraindividual variability meaningfully moderated average stressor exposure and diurnal cortisol slopes, respectively. Together, the three dissertation papers highlight the utility of examining intraindividual variability as a moderator of the effects of mean levels in future research.

Each paper additionally contributed to theoretical understanding of stressor and stress response "pile-up", as well as the time-scale of such processes, suggested in Lazarus and Folkman's (1984) psychological stress and appraisal and McEwen's (1998) allostatic load theories. The first paper suggested the distribution of one's stressor experiences across types is related to their average negative affect across a typical week. While it was tested across one week, the time-scale of the process that relates "typical" stressor experiences with average affect is likely longer, reflecting buildup of (un)successful coping over months and possibly years (Koffer et al., 2016; Lazarus & Folkman, 1984). The second paper maintained that daily stressor dynamics are indicative of longer-term (i.e., at a monthly or yearly time-scale) stressor chronicity that relates to chronic endothelial inflammation. Contrary to hypotheses, the third paper found that within person, across day deviation from diurnal cortisol trajectory might not reflect HPA dysregulation (i.e., allostatic load built up over months or years), as greater cortisol variability was related to lower inflammation. All of the presented papers used daily data, created summary statistics of the week, and used the summary statistics to assess effects of stressor/stress "pile-up" over months and/or years.

Referring back to Figure 1-1, the present dissertation contributed support for the multiple time scale pathways through which daily stress leads to health and well-being. Upholding the theoretical notion that daily stressor experiences accumulate (Column A,

moving down in time scale row; Lazarus & Folkman, 1984), these studies elucidated that both exposure to and diversity of stressor experiences are part of the accumulation process. Indeed, high stressor exposure and low stressor diversity indicate a pattern of failed psychosocial coping (Lazarus & Folkman, 1984) and repeated physiological activation (McEwen, 1998) that contributes to poorer well-being outcomes (moving across row 2 from weekly/monthly stressor experiences to weekly/monthly affect) and allostatic load (moving from row 2 weekly/monthly stressor experiences to row 3 yearly/multi-year inflammation). Likely, the allostatic load from high stressor exposure and low stressor diversity is partly related to the higher negative affect experienced, though this was not directly tested in the present studies.

The present studies also partly supported theory-based bidirectional associations among (bottom row) lifespan development and age-related biological vulnerabilities with (second row) patterns of daily stressor experiences, affect, cortisol, and (third row) yearly/multi-year inflammation. Supporting socioemotional aging theories, older age was related to differences in patterns of stressor exposure, likely due to developmental gains in socioemotional regulation and greater need to compensate for age-related biological vulnerabilities (fourth row, second and third columns: developmental/aging changes in psychology and biology related to second row, first column differences in stressor experiences) (Baltes & Baltes, 1990; Carstensen, Isaacowitz, & Charles, 1999; Charles, 2010). Surprisingly, while there is strong theoretical support for interactive vulnerability produced by chronic stressor experiences and biological cycles of senescence, this dissertation found stress processes (i.e., the association between chronic stressors and inflammation and the association among cortisol trajectories and variability with

inflammation) were age invariant. One possible reason for age invariance was selection bias, particularly within the cross-sectional design, that reduces generalizability to less healthy older adults. However, it is also possible that older adults are able to use compensatory techniques to regulate their health and well-being in the face of biopsychosocial resource losses (Baltes & Baltes, 1990). Longitudinal work would be particularly useful for testing age-based moderation of the stress process. Nevertheless, the present dissertation contributed a large, age-heterogeneous study to the stress and inflammation literature, that is often lacking in sample size and/or age range (Marsland et al., 2017; Segerstrom & Miller, 2004). Building from the present work's multiple time scale operationalizations, it may be helpful to operationalize theoretically expected developmental socioemotional gains and biological vulnerabilities to test the developmental mechanisms that may moderate faster time scale processes.

Theoretical Implications for Adult Development and Aging: Stressor Diversity in the Context of the Selective Optimization with Compensation Model

Age did not *moderate* the stress processes discussed in this dissertation, however, age differences in intraindividual variability of stressor types have important developmental and aging theoretical implications. Indeed, age differences in the categorical intraindividual stress metrics presented in this dissertation support and add nuance to tests of core theories of development and aging, particularly Baltes and Baltes' (1990) Selective Optimization with Compensation model.

The proffered numeric and nominal metrics of categorical variables provide a unique opportunity to examine the various quantitative and qualitative selection processes of aging. *Selection* is the reduction in efficacious life domains by choice or due to loss of adaptive capacity (Baltes & Baltes, 1990). Selection involves an adaptive process that considers environmental demands, motivations, psychosocial skills, and biological capacity (Baltes & Baltes, 1990). For example, with more limited resources to manage daily hassles, older adults are expected to *select* emotion-regulation goals over information-gathering goals (Carstensen et al., 1999). In the various categorical domains of life (e.g., activity types, stressor types, social partners), selection should manifest both with numeric distributional shifts toward less intraindividual variability (e.g., lower diversity and rarity, higher dominance), and nominal shifts (e.g., changes in types, spreads, and orders) that reflect positive emotion-oriented goals. Reduced stressor diversity may reflect selective engagement in certain life domains with age.

Further, higher stressor diversity's between-person association with lower negative affect and inflammation is in line with the developmental task of optimization. *Optimization* is the process by which individuals enrich their general reserves and maximize their ability to engage both quantitatively and qualitatively in their chosen behaviors and life course (Baltes & Baltes, 1990). Greater stressor diversity theoretically allows individuals to replenish resources to reduce impact of stressor exposure, thus optimizing resource use. Categorical metrics of intraindividual variability would allow future work to directly test this theoretical framing by assessing distributions of resource use and risk alongside stressor type distributions. Similarly, optimization in other life

domains (e.g., control beliefs, social engagement) is made more easily testable with the offered categorical metrics.

When certain resources are no longer available, compensation is the maintenance of desired functioning by use of alternative resources (Baltes & Baltes, 1990). With older age, compensation is typically a regulatory response to resource loss (Baltes & Baltes, 1990). For example, emotion-regulation strategies may compensate for reduced robustness of physiological response to stressful experiences. Specifically, age differences in stress variability metrics (i.e., lower stressor diversity, higher stressor dominance, higher stressor skew with age) were in line with socioemotional aging theories that older adults use avoidance and re-framing strategies to reduce exposure to stressors (Carstensen et al., 1999; Charles, 2010). To separate where this process reflects selection or compensation, future work should examine to what extent stressor diversity relates to life domain engagement goals and to emotion-regulation strategies.

Changes in stressor diversity and its stable association with psychosocial and physiological outcomes across adulthood support selective optimization with compensation. With reduced resources, older adults must be more selective of their experiences, optimize their resources toward unavoidable stressor experiences, and likely use emotion-regulation/avoidant strategies to compensate for biological vulnerability in response to stress. It follows that older adults are less able to achieve an optimal state of greater stressor diversity, as their resources are less robust and more vulnerable to "loss spirals." That age does not exacerbate the associations among stressor diversity and inflammation is an indicator that selective optimization and compensation allow older

adults to maintain similar emotional functioning in the face of stressors relative to younger adults.

Intervention

As stressor experiences and biological vulnerabilities both accumulate with age (Lazarus & DeLongis, 1983; McEwen, 2001), interventions that target stress processes are key for preventing associated long term mental health and disease risks. This dissertation's findings suggest targets of intervention (e.g., individuals with high stressor exposure and low stressor diversity) and provide metrics to test specific mechanisms on which to intervene (e.g., rank order of resource use). Further, the multiple time-scale approach clarifies at which time-scale(s) the stress processes are occurring, which is useful for the timing and time-scale of interventions (e.g., changes of daily patterns may help reduce longer term cardiovascular health risk from endothelial inflammation, which may be particularly important as risk increases with age).

Specifically, differences in the metrics of stressor type distribution were related to differences in negative affect and inflammation, pointing researchers toward individuals of interest for intervention. Additionally, development and aging-based differences in the metrics indicate that developmental timing should be considered when promoting health and well-being. For example, the combination of high stressor exposure and low stressor diversity was particularly associated with higher negative affect and higher inflammation, suggesting chronic stress interventions might target individuals with such stressor type distributions. As older age was linked to both higher inflammation and lower stressor

diversity, the interplay of stressor exposure and stressor diversity might be particularly important for interventions at midlife. Similarly, patterns of diurnal cortisol that were linked with older age (i.e., steeper CAR and DCS) were also associated with higher endothelial inflammation, even independent of age effects. The link between day-to-day cortisol and endothelial inflammation may provide targets for those at greater risk of atherosclerosis, though future work should discern whether and how daily stressor experiences might underlie such associations. Interventions targeting individuals according to numeric descriptive statistics of intraindividual stressor type and cortisol deviation distributions can be further modified using nominal metrics (e.g., of stressor types, resources, clinical risk levels of different biomarkers).

Limitations and Future Work

Although limitations specific to each paper were discussed in detail above, a few general limitations should be reiterated that affect all three papers. Crucially, though this dissertation advanced intraindividual variability methods to test multiple time-scale stress processes, it was limited in the cross-sectional nature of examining the yearly and developmental questions. With longitudinal data, it would be possible to parse age-based change from cohort effects and participation bias. Similarly, longitudinal burst data would be most appropriate for linking daily stress processes to chronic inflammation and more precise understanding of the timing of the link. This would also allow for testing of intraindividual change in the intraindividual variability metrics forwarded here.

Limitations in both time and person sampling also affect the generalizability of the presented findings. All three studies would benefit from more measurement occasions. More time sampling would allow greater separation of individuals by metrics of intraindividual variability. It would also improve reliability for the variability metrics that is still necessary to determine (Benson et al., 2017; Segerstrom et al., 2014). Though the participant sample size was robustly large in each study, participants in the subsamples consisted of less minorities, better educated, and healthier individuals than the general population of the United States. Thus the results presented here generalize to similarly racially homogenous, healthy, high SES population. Especially in understanding chronic stress and health, it is important to replicate these findings in more diverse populations.

This dissertation also forwarded net intraindividual variability metrics to summarize interindividual differences in daily stressor and cortisol time series, and these metrics come with limiting assumptions. Net IIV metrics require the assumption that the data are independent and identically distributed, and thus do not describe the underlying (time dependent) dynamic processes that create differences in net IIV. Future work that directly models time-dependence in the data can further uncover the processes that create chronicity in daily stressors and/or require allostatic deviations from diurnal trajectories of cortisol.

Future Work: Implications for Study Design, Methodological Approach, and Theory Development

The findings, limitations, and remaining questions of the dissertation offer specific direction for future work in terms of study design, methodological approach, and theoretical advances. Study designs most well-suited for associating multiple time scale stress processes are longitudinal burst designs. Reliability of variability metrics are still needed, but there is some suggestion that operationalizing diversity in categorical metrics may require anywhere from 6 to 24 occasions, depending on the diversity index used and likely also number of stressor types included (Benson et al., 2017). Of course there are financial tradeoffs of sampling people versus occasions. On the same days as stressor measurement, cortisol sampling with at least the morning peak and evening values sampled across at least 10 days would be ideal for modeling day to day cortisol trajectories, though again, reliability metrics for cortisol variability are needed (Segerstrom et al., 2014). Based on the dissertation's findings, measures of chronic systemic and endothelial inflammation could be taken at baseline and at yearly longitudinal follow-ups to capture the slower-moving associations between patterns of daily stressors and chronic inflammation. However, it is possible that the associations between chronic stress and endothelial or systemic inflammation function on different time scales (e.g., chronic endothelial inflammation may relate to patterns of daily stressor exposure faster than systemic inflammation). Developmental and aging-based changes can be incorporated in the design with longitudinal measurement, as well as explicit

measurement of underlying theoretical mechanisms of change, such as resource availability and emotion-regulation strategy use.

Methodologically, the work from this dissertation highlights explicitly modeling multiple time scale constructs of "pile-up" or "allostatic load" by net intraindividual variability metrics. Specifically, accumulation implied by these constructs may not be adequately addressed by the mean value (e.g., stressor exposure, cortisol slope), alone. Rather, consideration of the intraindividual variability distribution of the construct is useful, both uniquely and in combination with mean exposure. A variety of metrics to assess categorical intraindividual variability were also provided, and future work should look toward approaches to combining the numeric and nominal metrics. As many categorical variables are time dependent, future work is needed to insert nominal richness into time-structured models, as well. More broadly, the presented approach of modeling stressor/stress accumulation is in line with a push toward explicitly tying models of change with theories of change (Ram & Grimm, 2015).

Theoretically, the dissertation findings inform the process from daily stressors and daily functioning of biological stress systems to chronic inflammation. First, these papers pushed toward considering categorical elements of stressors that are typically either aggregated into a sum total or only examined separately. While the first two papers primarily discussed distribution across stressor type, future work may also consider distribution of resources, coping strategies, motivations, and emotions. For example, future work can make use of the nominal metrics applied to measures of resource use to examine the transactional processes that connect stressor exposure to affect. Second, these papers highlighted the importance of operational clarity in understanding biological

allostatic load. Modeling chronic systemic and endothelial inflammation as separate latent factors offers specificity of two distinct biological pathways while remaining tied to underlying theory of stress and inflammation. Discrepant findings with cortisol variability suggest a number of theoretical considerations that must be tested before assigning the (mal)adaptive nature of the construct. Considerations include whether daily and within-day variables such as stressor events should be controlled for, whether cortisol variability indicates the same (dys)regulatory construct in different populations (e.g., those with and without chronic stressors), and which cortisol measure(s) (e.g., CAR, diurnal trajectory, AUC) might be best suited for this construct. Overall, this dissertation contributed understanding of how chronicity manifests in daily stressors and (dys)regulation manifests in diurnal cortisol trajectories, so future work can better connect the stress process across multiple levels and time scales.

Conclusion

This dissertation offered novel operationalizations of daily stressor experiences and biological dysregulation to test stress process theory across the adult life span. First, a new framework of intraindividual variability metrics was presented that allowed for examining dynamic characteristics of daily stressor type experiences. This framework expanded the variety of developmental research questions that may be answered using categorical repeated measures data. Second, using this framework, the dissertation validated theoretical assumptions of daily stressor accumulation due to chronicity. Low stressor diversity and high stressor exposure were related to higher endothelial

inflammation. Third, the dissertation tested associations between inflammation and cortisol variability, a recently proposed operationalization of biological dysregulation. Results did not support the hypothesis that greater cortisol variability indicates HPA dysregulation, and subsequently highlighted need for greater specificity of the theoretical boundaries of the construct. Together, this dissertation forwarded the study of intraindividual variability in the stress process across adulthood. The provided methods can be useful for identifying intervention targets and have demonstrated utility in improving our understanding of stressor and stress response accumulation across adulthood.

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PUBLICATIONS

Koffer, R. E., Ram, N., & Almeida, D. M. (2017). More than Counting: An Intraindividual Variability Approach to Categorical Repeated Measures. *Journals of Gerontology: Psychological Sciences*. DOI: 10.1093/geronb/gbx086 [Special Issue on Innovative Methods in Gerontological Research]

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