Analyzing the Impact of Stress: A Comparison Between a Factor Analytic and a Composite Measurement of Allostatic Load

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ABSTRACT

Stress is possibly the hallmark characteristic of the current conflicts confronting the United States. Extended and repeated deployments require the ability on the part of war-fighters to effectively process stress in ways never before routinely encountered. Stress is well defined as a series of psychological and physiological processes that occur in response to a stressor, or the perception of stress. The physiological response to stress follows an identified path, a robust neuroendocrine response leads to responses in the cardiovascular, metabolic, renal, inflammatory and immune systems. After a stress response, the body's natural tendency is to return to a steady state, a process called allostasis. If the body is not effective in returning to homeostasis, or if the environment is such that stress is repeated, markers of dysfunction may be apparent in the physiological systems that respond to stress. A method of measuring multiple biomarkers of stress responsive systems and determining who shows consistent evidence of dysfunction was developed by Bruce McEwen and labeled allostatic load (AL). AL is most frequently measured by developing a level of risk for each biomarker and obtaining an AL score for the number of biomarkers the criterion for risk is met. This provides a single, equal-weighted measure of AL and does not allow for the identification of multi-systems. We employed a principal component factor analysis on a set of biomarkers and scored each factor using unit weighting. We compared the predictive power of 7 obliquely rotated factors to that of a composite AL marker. The set of factors predicted more of the variance in measures of depression, anxiety, and medical outcomes, it also provided evidence of the systems most involved in the development of pathology. The results confirm that AL is best analyzed as a multi-system construct. Not only does this predict more variance, it also provides suggestions as to the mechanisms underlying stress related disorders.

ABOUT THE AUTHORS

J. Galen Buckwalter, PhD is a Research Scientist at the USC Institute for Creative Technologies. Dr. Buckwalter has had an extremely active career both as an academic research scientist and as an entrepreneur in the private sector. Dr. Buckwalter's academic career, with over 100 peer reviewed publications, has focused on psychological applications for virtual reality, psychoneuroendocrinology, advanced statistical methods, and personality. In the private sector, with two patents granted, Dr. Buckwalter has focused on the psychology of relationships and was a co-founder of eHarmony.com.

Albert "Skip" Rizzo, PhD directs the Medical Virtual Reality Group at the USC Institute for Creative Technologies. He is a Research Professor in Psychiatry and Gerontology. Dr. Rizzo conducts research on the design, development, and evaluation of Virtual Reality systems targeting the assessment, training, and rehabilitation of spatial abilities, attention, memory, executive function, and motor abilities. His latest project has focused on the translation of the graphic assets from the X-Box game, Full Spectrum Warrior, into an exposure therapy application for combat-related PTSD.

Teresa Seeman is a Professor of Medicine and Epidemiology at the University of California at Los Angeles. She also co-directs the UCLA/USC Biodemography & Population Health Center as well as the UCLA Research Operations Core. Her major research interests are the role of social and psychological factors on health risks in aging, age-related changes in physiological dysregulation and its impact on health. She is one of the leading researchers on the concept of allostatic load, directing the original empirical tests of this concept, including development of various approaches to assessment of AL as well as analyses of its relationships to various major health outcomes and its differential distribution within the population. Currently, many of her projects focus on understanding the biological mechanisms for social and psychological effects on health risks.

Bruce Sheffield John is a full-time researcher at the USC Institute for Creative Technologies. He has completed programs in Psychology and Video Game Design at, while also earning a BS in Policy, Management, and Planning from, the University of Southern California. His current work includes allostatic load, resilience, and personality.

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INTRODUCTION

Stress is a multi-faceted construct that is often conceptualized as an external force that can severely affect a person psychologically. It is not, however, a simple linear causal pattern in that the person's psychological and physiological reactions to stressors, especially if the stressors are unusual or prolonged, can in fact be the source of further stress. In this context, stress can be conceptualized as a series of psychological and physiological *processes* that occur in response to the perception of a stressor. These processes are activated as part of a systemic effort to bring a person back to homeostasis, an effort labeled allostasis when it refers to balancing the systems impacted by perceived stressors (McEwen, 1998).

Stressors can be categorized into two distinct but interdependent types: life events and contextual interpretations. Life events range from low to high intensity and have varying durations which can trigger acute or chronic stress, but the person's contextual interpretation of the stressor also affects the intensity and duration of the stress (Brown, 1989; Brown & Harris, 1989). For instance, a soldier of war who engages in a firefight, a life event of high intensity but short duration, would be expected to experience acute stress during the event (RAND, 2008), but this stress could become chronic if the soldier interprets the event in a maladaptive way (e.g. that death is constantly imminent). On the other hand, a minority child may have experiences that lead him/her to understand that people of his/her ethnic or racial background are treated unequally. This is a life event of extended duration, but its intensity is largely determined by the child's contextual interpretation (Geronimus et al., 2006; Kaestner et al., 2009). The distinction between life events and contextual interpretations illustrates the importance of the nature of the stressor and the person's perception of stressors. Both can have an influence on the persistency, or even existence, of stress. As the Ancient Greek philosopher, Epictetus, once said, "Men are disturbed not by things, but by the view which they take of them" (Monroe, 2008).

A person's stress response, or the psychological and physiological processes that are initiated by stress, also ranging in duration and intensity, is influenced by individual characteristics (vulnerability, resilience, hardiness) (Baum et al, 1993; Cohen et al., 1997). Adaptation to acute stress may strengthen a person's psychological and physiological systems, a process that has been labeled toughness (Dienstbier & Pytlik Zillig, 2002). Although stress responses can be acute or chronic, the exact time it takes for acute reactions to become chronic has not been definitively established. One of the reasons that it is important to classify stress responses is that they are prone to dysfunction, resulting in negative health consequences (Taylor et al., 1997). One of the first studies to use physiological indicators for measuring stress investigated the caregivers of family members with Alzheimer's disease. The authors classified this stress as chronic because of the long-term nature of the care, approximately eight years (Kiecolt-Glaser et al., 1987). However, assessments of stress responses were

considered chronic reactions after just nine months in a study looking at reactions to a bus disaster (Milgram et al., 1988). A diagnostic criterion for posttraumatic stress disorder (PTSD), a disorder in which the brain's stress system is constantly active after a person experiences an intense stressor (Southwick et al., 2005), requires that the stress activation continues for at least four weeks, otherwise it falls into the category of an acute stress disorder (APA, 2000). Stress disorders like PTSD are measured only through behavioral responses or self-reported behaviors. Although it has been posited that stress responses may vary depending on whether they are acute or chronic, measuring indications of stress in various physiological systems has emerged as an objective gauge (Seeman et al., 1997; McEwen & Seeman, 1999; Singer & Ryff 1999). The use of such measurements have interesting implications for discovering factors of resilience and hardiness, positive psychological and biological resolutions, as well as vulnerabilities, to stress.

Allostatic Load

The AL model can be traced back to the work of Hans Selye (1976), who suggested that stress-induced "agents" had "a general effect on large portions of the body." Sterling and Eyer (1988) developed the concept of allostasis which, in contrast to homeostasis, emphasized that the body's set points for various physiological mechanisms, such as blood pressure or heart rate, can vary in order to meet a specific external demand. McEwen and Stellar (1993) refined the construct of allostasis by broadening its scope. Instead of a single changing set point, they described allostasis as the combination of all physiological coping mechanisms that are required to maintain homeostasis. In other words, allostasis is the reaction and adaptation to stressors by multiple physiological systems, whereas homeostasis refers specifically to system parameters essential for survival (McEwen, 2002).

Chronic psychosocial stressors strain interdependent physiological systems such as the sympathetic nervous system, the neuroendocrine system (in particular the hypothalamic-pituitary-adrenal (HPA) axis), and the immune system. One's vulnerability or resilience to various stressors is thought to have both short and long-term health consequences. In fact, "successful aging" has been conceptualized as "one's ability to adapt and effectively respond to the dynamic challenges of being alive" (Juster, McEwen, & Lupien, 2009). The construct of allostatic load (AL) encompasses this view of health by combining measurements of biomarkers from various physiological systems that are impacted, to some extent, by stress.

The body's adaption to the demands of the environment is necessary, but there are different patterns of response, some of which result in physiological hardiness and psychological resilience, and some of which lead to negative outcomes. For instance, frequent stressors or prolonged exposure to stress can accumulate, resulting in an allostatic burden on the body's self-modulating regulatory systems. This can lead to an allostatic dysregulation in the form of an inability to shut off physiological responses to stress long after the stressor itself is terminated. Given the potential for the body to strengthen from stress response mechanisms, another form of dysregulation is an inadequate response to stress (McEwen, 1998). Both allostatic burden and allostatic dysregulation can lead to allostatic dysfunction in which the allostatic subsystems are temporarily, and possibly permanently, maladaptive. Calculating AL is a way to measure the "cumulative biological burden exacted on the body… when the adaptive responses to challenges lie chronically outside of normal operating ranges," (Singer, Ryff, & Seeman, 2004). Put another way, AL is a quantifiable measure of the wear and tear, a "physiologic stamp" on the body's regulatory systems that occurs when multiple acute and/or chronic stressors are experienced (Gianaros et al., 2010; Seplaki et al., 2004). From a conceptual standpoint, the construct of AL in the literature is still quite rudimentary. More recent AL models posit that biomarkers interact on multiple levels. For instance, Juster, McEwen, and Lupien (2009) theorize that by measuring multi-systemic interactions among *primary mediators* (e.g., levels of cortisol, adrenalin, noradrenalin) and relevant sub-clinical biomarkers representing *secondary outcomes* (e.g., serum HDL and total cholesterol), it is possible to identify individuals at high risk of *tertiary outcomes* (e.g., disease and mental illness). Yet this approach does not fully encapsulate the dynamic, nonlinear, evolving, and adaptive nature of the interactions between these biomarkers. Moreover, these markers are not purely physiological: psychological processes, including appraisal of and reactions to various stressors, constitute a separate but interdependent subsystem in the allostatic model. We support a case-based approach to analysis, which acknowledges that each allostatic system is unique in its configuration based on differences in (1) environmental context, including socioeconomic status and availability of psychosocial resources; (2) regulation and plasticity of bio-allostatic systems; (3) regulation and plasticity of what we term psycho-allostatic systems; (4) psychology, including personality and appraisal of stressors; (5) environmental stressors, which range from biological to sociological; and (6) health outcomes.

Measuring AL is also useful because it can provide a basis for understanding connections between the etiology of systemic illnesses such as cardiovascular disease (CVD) and mental illnesses such as depression and PTSD (McEwen, 2000). Longitudinal studies have affirmed the utility of multiple measures over and above any single biomarker in the AL index for predicting lower baseline functioning, declines in cognitive and physical functioning, increased risk of incident CVD, and all-cause mortality (Seeman et al., 1997; Seeman et al., 2001). Moreover, measurements of multiple biomarkers in AL for more specific populations show promise as a step towards promoting longevity and improving quality of life through earlier interventions (Karlamangla et al., 2006; McEwen, 2003), although the exact role of how stress increases AL is unclear (Goldman et al., 2006; Gersten et al., 2010). AL has also been shown to predict the presence of PTSD among women exposed to high stress, the mothers of pediatric cancer survivors (Glover et al., 2006). The implications of combined biomarkers predicting PTSD could have etiological significance.

A review of AL literature by Juster, McEwen, and Lupien (2009) found the number of biomarkers included in an AL composite across 58 studies ranged from 4 to 17, and that some studies made no adjustments for demographic or health-related behaviors (e.g., race/ethnicity, age, sex, education, income, smoking, and even chronic stressors such as work conditions, presence of an ill spouse) whereas other studies controlled for up to 10 factors. Other research has demonstrated that certain biomarkers cluster differentially for certain sex and age cohorts (Gruenewald, et al., 2006). Thus, particular demographic factors could become figured into formulations of specific "biological signatures" for different groups (Juster, McEwen, & Lupien, 2009). However, other factors, such as behavioral reactions to stress or personality traits, which can exacerbate or attenuate allostatic load, are more difficult to measure practically and conceptually. Although 25 different biomarkers spanning neuroendocrine, immune, metabolic, cardiovascular/respiratory, and anthropometric systems have been identified, there is no consensus on which ones should contribute to either a generic measure of AL or measures of AL which are more sensitive for certain groups or certain health outcomes.

Besides the discrepancy in what exact biomarkers should be used to measure AL, there is no agreed upon formula for combining these variables into an AL index score. Juster, McEwen, and Lupien (2009) site 11 existing algorithmic formulations and statistical techniques for calculating allostatic load. The formula used most often is a group AL index, calculated by counting the number of an individual's biomarkers which fall within a high risk percentile (i.e., upper or lower 25^{th} percentile) based on the sample's distribution of biomarker values. Each biomarker is then dichotomized as 0 or 1 depending on whether the subject's value falls within the upper/lower risk quartile, meaning that each biomarker has equal weight in the index. Other algorithms are being developed, some that include theoretical system-specific scores (Gruenenwald, et al., 2006). We propose to employ an exploratory factor analysis to both determine if the factor structure of a common set of AL biomarkers supports the conceptualization of AL as a multi-system construct and to further determine if scores derived from these factors provide an effective means of understanding AL. This paper will directly compare the most widely used method of scoring AL with a method that first captures possible groupings of biomarkers into physiological systems by utilizing factor analysis.

METHOD

Subjects

Data for the current study was obtained from the Midlife in the United States (MIDUS) Study. In 1994/95, the MacArthur Midlife Research Network carried out a national survey of over 7,000 Americans aged 25 to 74. The purpose of the study was to investigate the role of behavioral, psychological, and social factors in understanding age-related differences in physical and mental health. The study was broad in scientific scope, enrolled diverse samples (which included twins and siblings of main sample respondents) and made use of "satellite" studies to obtain in-depth assessments in key areas (e.g., daily stress, cognitive functioning). In 2002, the National Institute on Aging awarded a grant to the Institute on Aging at the University of Wisconsin-Madison to carry out a longitudinal follow-up on all original MIDUS respondents. The new initiative (MIDUS II) included five research projects. We focused on psychosocial and health variables assessed in MIDUS I and comprehensive biomarker assessments on a subsample of MIDUS respondents collected at MIDUS II. A total of 1230 participants completed both the psychosocial and health variables we used as outcome variables as well as provided specimens needed to complete assays for all biomarkers needed to calculate AL. To allow for replication of the factor structure, we randomly divided the dataset into two equal sets of 615 participants. This sample had 55.3% women (340) with a mean age of 57.3 (SD = 11.5).

Allostatic Load Markers

The markers collected for this study were more extensive than the vast majority of studies using the construct of AL. To assure comparability to the construct of AL, as it is most commonly reported, we required a biomarker to have been reported in at least two studies in the review of AL literature reported by Juster, McEwen, and Lupien (2009). The biomarkers utilized in this study are the catacholomines, **norepinepherine**, **epinephrine**, and **dopamine**. **Cortisol**, the primary glucocorticoid is also assayed. **Triglycerides**, which at very high levels are a risk for cardiovascular disease, are included, as is **insulin**, a hormone central to regulating carbohydrate and fat metabolism in the body. Body *habitus*, including **waist to hip ratio (WHR)** and **body mass index (BMI)** are measures that indicate much about a person's metabolism. WHR has been related to dysregulated HPA axis activity, elevated heart rate and blood pressure, and high glucose, insulin, and triglyceride levels. Both WHR and BMI are included in our analysis. **Total cholesterol** is the fat steroid synthesized in the liver that is at the top of the steroid chain. **HDL** cholesterol is characterized by high protein and low cholesterol structures**. LDL** cholesterol is characterized by low protein and high cholesterol. We include all three cholesterol measures. Also included are three pro-inflammatory measures: **fibrinogen**, an aid in coagulation, **C-reactive protein (CRP**), an acute phase reaction protein, and **interleukin-6 (IL-6**), which functions in the immunological response to stress or trauma. **Heart rate** accelerates with stress or trauma, depending on biological, genetic, medical, and other physiological factors, and is also included**. Systolic** and **Diastolic blood pressure**, which is highly associated with chronic stress and increased risk for cardiovascular disease are included. **Hemoglobin A1c (HbA1c**), which indicates the average amount of plasma glucose concentration over an extended period of time, is an included marker. **Dehydroepiandrosterone-sulfate (DHEA-S)** is included given its role as a steroid synthesized in the adrenal system. **Insulin-like Growth Factor (IGF-1)** reduces oxidative stress and **peak flow** is the maximum speed of expiration, both of which are included.

Outcome Measures

The MIDUS study was designed to look at a wide range of psychosocial and health-related variables. We selected a range of psychological tests, primarily those related to stress, anxiety, and depression. All of these variables are predictors of PTSD as well as being co-morbidities with PTSD. While there was no marker of PTSD available in this dataset, we feel that if AL can effectively predict these variables it is likely that it also plays a role in PTSD. We include the Center for the Epidemiological Study of Depression (CESD), the Perceived Stress Scale (PSS), the State Trait Anxiety Inventory (STAI) and the Social Anxiety Scale (SAS). On the medical variables, we analyzed the presence or absence of self-reported stroke/TIA's, diabetes, and asthma.

Analytic Strategy

The effects of AL on the separate outcome variables were analyzed in two methods. First, we calculated AL by identifying the at-risk quartile for allostasis dysregulation for each of the 22 variables we included. If a subject was in the at-risk quartile they received a 1 for that variable. The AL score was the sum of the recoded biomarkers. The revised method of analyzing AL began with a principal component factor analysis. The roots greater than or equal to one test was used to identify the number of factors extracted, confirmed by the scree test. An oblique rotational method, Promax, was employed given the obvious correlations between these factors. All items were placed on the factor on which they loaded the highest. Factors were named based on the common physiological components reflected by the items that loaded on the factor. After the factor analysis, all 22 items were converted into z-scores. Subscales were scored for each factor by taking the average of the z-scores for the items that loaded on each factor. The effects of the composite AL score and the factor identified subscales were compared with liner regressions. The effects of gender and age were first controlled for by forcing them into the regression. Then the effect of the AL composite variable was entered, the change in multiple R estimated, and the significance calculated. After the effect of the AL composite was estimated, a separate regression was conducted again forcing in gender and age. Then all seven of the factor-identified subscales were entered in a single block and the change in multiple R was estimated for the entry of all seven variables. Significance was calculated for change in multiple R. The significance level for each of the seven subscales was calculated after controlling for age and gender and the effects of the other 6 subscales. A part correlation was also estimated for each of the seven variables again controlling for age, gender, and the other six subscales.

RESULTS

Seven factors met criteria for extraction. The factors were labeled Stress Hormones, Metabolic Syndrome,

Pro-Inflammatory Elements, Cholesterol, Blood Sugars, Blood Pressure, and Anti-Age. The items loading on each factor and the factor loading values are shown on Table 1. The change in effects sizes (R) after controlling for age and gender are listed in Table 2.

Table 1: Factor Loadings

Biomarkers	Principal Component Factors						
	Stress Hormones	Metabolic Syndrome	Pro-inflam -matory Elements	Cholesterol	Blood Sugars	Blood Pressure	Anti-Age
Norepinephrine	.864						
Dopamine	.854						
Epinephrine	.824						
Cortisol	.681						
Triglycerides		.748					
Insulin		.738					
WHR		.642					
BMI		.614					
HDL Cholest.		-.758					
Fibrinogen			.784				
CRP			.756				
IL-6			.704				
Heart Rate			.332				
Total Cholest.				.962			
LDL Cholest.				.917			
HbA1c					.918		
Glucose					.915		
Systolic BP						.892	
Diastolic BP						.878	
DHEA-S							.745
Peak Flow							.648
IGF-1							.631

Table 2: Effect Sizes

Outcome Variables	Factors		Index	
	R	p	R	p
CESD	.296	<.001	.237	<.001
PSS	.305	<.001	.266	<.001
STAI	.298	<.001	.238	.002
SAS	.240	.033	.220	.002
Stroke	.275	.064	.229	.719
Diabetes	.616	<.001	.219	<.001
Asthma	.206	.032	.121	.888

The multiple R was larger for all outcome variables when the seven AL subscales were entered (labeled "Factors") than for the composite AL variable (labeled "Index"). While the R was larger for all analyses, the significance level was generally equivalent except for asthma which was non-significant when analyzed with the composite AL but significant (p = .032) when analyzed with the seven subscales. It is also noteworthy that while both methods were highly significant in predicting diabetes, the multiple R using seven subscales was nearly three-fold larger than the composite AL (.616 vs. .219).

The pattern of significance when evaluating the seven subscales across the selected outcomes may also provide relevant information for future studies. Shown on Table 3, first is the finding that the subscale that is very similar to Metabolic Syndrome, except for the exclusion of blood pressure, is the most predictive of negative outcomes. It was a significant predictor of higher depression, perceived stress, social anxiety, and diabetes. It may be relevant that it was nearly significant in predicting anxiety as well (p = .061). The subscale that was next in predicting negative outcomes was Pro-Inflammatory Elements. This subscale, comprised of the signature pro-inflammatory substances, fibrinogen, C-reactive protein, IL-6, with the less expected heart rate, was a significant predictor of greater depression, perceived stress, and anxiety. A highly notable finding is that there is one subscale, labeled Anti-Age, that has very positive effects. The combined effects of DHEA-S, peak flow, and IGF-1 appear to have protective effects on depression, perceived stress, and anxiety. Other effects that appear

Table 3: Subscales

Outcome Variables	Principal Component Factors													
	Stress Hormones		Metabolic Syndrome		Pro-inflam--matory Elements		Cholesterol		Blood Sugars		Blood Pressure		Anti-Age	
	p	cor	p	cor	p	cor	p	cor	p	cor	p	cor	p	cor
CESD	.561	.024	.016	.099	.005	.117	.859	-.007	.948	.003	.031	-.089	.008	-.109
PSS	.546	.025	.015	.100	.007	.111	.609	-.021	.743	.014	.655	-.018	.016	-.100
STAI	.861	-.007	.061	.077	.007	.112	.156	-.059	.770	.012	.306	-.042	.006	-.113
SAS	.088	.072	.017	.100	.827	.009	.280	.045	.096	-.070	.927	-.004	.100	-.069
Stroke	.003	-.124	.472	-.030	.617	.021	.165	.058	.936	.003	.098	.069	.949	.003
Diabetes	.625	.017	.014	-.084	.397	.029	<.001	.127	<.001	-.536	.323	.034	.229	-.041
Asthma	.015	.103	.113	-.067	.200	-.054	.345	.040	.936	.003	.176	.057	.400	.036

in the analysis of subscales are the Stress Hormones predicting higher presence of strokes and/or TIA's. Cholesterol and Blood Sugars (along with Metabolic Syndrome) were both factors in predicting the presence of diabetes. Finally, high blood pressure had a seemingly protective effect against depression.

DISCUSSION

The cumulative results provide strong support for not only conceptualizing AL as a multi-system construct but also for the practice of analyzing AL as a multi-system construct.

The exploratory factor analysis of this set of biomarkers that are widely used in the study of AL yielded a highly interpretable and informative set of factors comprising AL. The first factor, Stress Hormones, provides a comprehensive marker of circulating hormones related directly to current stress response. This factor is comprised of all of the catecholamines and the primary glucocorticoid, cortisol. Catecholamines are primarily secreted from the sympathetic-adrenal-medullary (SAM) axis and stimulated by the HPA axis (Juster, McEwen, & Lupien, 2009). Cortisol is produced in the adrenal glands and is regulated by ACTH. Catecholamines are the central components in the "flight or fight" reaction in the immediate response to stress. Dysfunction of catecholamines have been related to PTSD, depression, anxiety, and schizophrenia, while cortisol has been found to be a major factor related to abnormal cognitive decline.

Metabolic syndrome is a group of risk factors that have been observed to occur together. They increase the risk for coronary artery disease, stroke, and type 2 diabetes. According to the American Heart Association and the National Heart, Lung, and Blood Institute NHLBI), metabolic syndrome is present when there is three or more of the following signs: high blood pressure, high WHR, lowered HDL, and high triglycerides. Insulin resistance is also an aspect of metabolic syndrome, it results in blood sugars not being able to get into cells which in turn causes the body to produce more and more insulin. Our factor labeled Metabolic Syndrome has all of these components except high blood pressure and thus meets NHLBI criteria for metabolic syndrome.

The Pro-Inflammatory Elements factor also fits clearly with an underlying physiological system. The elements that group on this factor include acute phase proteins (fibrinogen and CRP) and an interleukin that can act both as a pro- and anti-inflammatory cytokine. Taken together these three acute phase reactants have been shown to be related to poor prognosis in unstable angina (Ikonomidis et al., 1999). This supports a strong role for inflammation in cardiovascular disorders. These three inflammatory elements have also been found to be strong predictors of both short and long-term complications in patients after a myocardial infarction (Ziakis et al., 2006).

The factors labeled Cholesterol, Blood Sugars, and Blood Pressure each represent physiological systems that have been strongly linked to distinct physiological systems, each with a clear role in stress response. The final factor, labeled Anti-Age, is less clearly linked to a stress related physiological system. DHEA-S is a ubiquitous steroid produced mainly from the adrenals. While the link to the adrenal gland is often cited as the link to stress, DHEA and DHEA-S have been reported to be protective against both depression and stress (Wolkowitz et al., 1995). IGF-1 may decrease stress in elderly men who begin resistance exercise (Cassilhas et al., 2010). The inclusion of peak flow, a marker of good health, further suggests that this factor may reflect

a positive aspect of the stress response system, if in fact this system is indicative of stress response.

The clear and compelling structure of the factor analysis of these biomarkers of AL strongly supports previous research that conceptualizes AL as a multi-system construct. The factor structure we observed using an exploratory approach shows numerous similarities to a multi-system approach that was theorized and confirmed with a structural equation model by (Seeman et al., 2010). In an unreported analysis, it is also notable that a second exploratory factor analysis, conducted on the second half of this randomly selected dataset, showed a near identical 7 factor solution. The only difference was that the heart rate variable did not load on the pro-inflammatory factor, in fact it did not load saliently on any factor. Taken together we feel there is increasing support for conceptualizing AL, much as McEwen did originally, as a multi-system array.

The predictive regressions conducted in this study further suggest that not only is AL best conceptualized as a multi-system set of functions, it is best empirically analyzed as such. The consistently higher effect sizes seen for the combined subscales formed by the factors, in comparison to the composite index score, suggests that the inclusion of system-specific scales better predicts psychological and health outcomes than does a composite that includes all systems in a single score. The information provided by considering separate scores ratings, for each of the systems that could be impacted by stress, appears to provide more useful information than a single composite. This is nowhere more clear than in the prediction of diabetes, where the effect size increases from .219, when using the composite index, to .616 when using all factors. When considering the nature of the subscales created, i.e., a Metabolic Syndrome, Cholesterol, and Blood Sugars, it is immediately apparent why use of this information is more predictive than the overall composite. These stress-responsive systems are consistently predictive of diabetes. It is our argument that continued use of a multi-system approach to the analysis of AL will identify an increasing number of stress modified outcomes.

In addition to a better overall predictive ability, the use of multi-system subscales provides suggestions on the mechanism whereby stress may impact psychological and health-related outcomes. A ready example from the current data is the finding that our subscale of a Metabolic Syndrome predicts depression, perceived stress, and social anxiety, with a near significant association with trait anxiety. Metabolic syndrome has been found to be highly common among those with severe mental illness (Newcomer, 2007). Results have been equivocal on the association between metabolic syndrome and depression and anxiety (Raikkonen et. al., 2002; Herva et al., 2006). Our findings strongly support a role for metabolic syndrome in depression and anxiety.

Other notable findings from our study suggest a role for pro-inflammatory markers in mood disorders. The human literature is scant, but the strength of current findings relevant. It should be noted that pro-inflammatory elements have been associated with metabolic syndrome, pointing out the need to explore the associations between our factors (Brunner, et al., 2002) in a case-based approach as discussed above. Our Anti-Age subscale also suggests there may be a positive role for these popular “fountains of youth” in mood disorders. While it remains to be determined if these markers do in fact belong as part of the stress response cycle, the putative decision to include these in several studies of AL give some credibility to this conceptualization. If DHEA-S and IGF-1 do, in fact, show elevations in response to stress, and they are protective against mood disorder, this suggests one mechanism whereby stress can play a positive role. While tentative at best, this does warrant a more systematic exploration.

The overall results from this study suggest that AL, as analyzed in the current study, could have remarkable implications for military training. AL could be used to understand how the war-fighter is most likely to respond to stress in the future. If the physiological systems responsive to stress indicate dysfunctions related to prior stress exposure, it is highly likely the dysfunctional responses will continue. It remains to be seen what the effect of training to cope with stress, to develop resilience, will have on AL. However, it appears that this may prove to be a physiological measure of the effectiveness of such training. And finally, given the suggestion that there may be a factor that relates to a positive system within the stress response sequence, the possibility of identifying war-fighters who may respond to stress positively should be further explored. Numerous other outcomes also need to be explored; resilience, cognitive functioning, and social skills to name a few. These preliminary results, supporting our ability to predict a range of outcomes from specific measures of biological stress responsive systems, are an encouraging continuation of previous research and offer another methodological approach to analyzing the multi-systems of AL.

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