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Physiological Dysregulation and Somatic Decline among Elders: Modeling, Applying and Re-Interpreting Allostatic Load

Rachael Leahy and Douglas E. Crews

The Ohio State University, Department of Anthropology and School of Public Health, Columbus, Ohio, USA

A B S T R A C T

Mortality rates continue to decline among post-reproductive individuals. This makes understanding long-term physiological responses to stress increasingly important. Allostatic load (AL) was developed to assess detrimental effects on the soma of responding to multiple stressors over a lifetime. AL arises from developmental experiences, genetic predispositions, environmental, psychosocial, life style and other stressors. In early life stress responsive systems are initiated that produce hormones that maintain the soma through continual allostatic responses. Later in life, systems designed to mitigate stressors may fail or be compromised, promoting unwanted somatic changes and dysregulation. This places a load on the regulatory system that impedes day-to-day stress responses, predisposing to cellular damage and degenerative diseases. Here we review 44 peer-reviewed 2005–2010 publications reportedly examining relationships between AL and risk factors, chronic diseases, morbidity and mortality in samples of elderly adults. The sum of results suggests that AL does assess aspects of physiological dysregulation and somatic decline, predicts detrimental age-related declines, and is associated with negative sociocultural attributes and psychological outcomes. Such consistent results and wide application of AL, while it is still being modeled and re-interpreted, suggest its perceived usefulness as a research and clinical tool. AL provides a possible biomarker of senescence, assessing it over the life span will aid in predicting future negative health outcomes.

Key Words: *aging, biomarker of aging, cortisol, senescence, stress*

Introduction

In modern populations, individuals are surviving into old age at unprecedented rates. For example, over the 20th century, life expectancies increased around the world as 0.076% of men and 0.338% of women attained 100 years[1]. By 2007, mean life expectancy was 77.9 years in the USA, 82.7 years in Japan, 82.2 years in Hong Kong, 81.8 years in Iceland, and 81.8 years in Switzerland[2]. As life expectancy increases and mortality rates decline among post-reproductive individuals, understanding processes of senescence leading to morbidity and mortality becomes increasingly important.

Exposures to stressors over the lifespan likely mediate aspects of senescent decline. Stressors such as work and home environments, social and community relationships, diet, exercise, physiological and psychological responses, lifestyle, and socioeconomic status alter physiological function[3]. Two concepts, allostasis and allostatic load, have been developed to model and assess effects of stressors on human well-being. Allostasis originated as a term comparing and contrasting resting and active states within the cardiovascular system and as an elaboration of the more static concept of homeostasis[4]. Allostasis refers to the soma's ability to respond with continuous change to maintain a dynamic equilibrium in response to stressors and external stimuli[3]. Physiologically, allostasis represents the soma's ability to change while maintaining overall somatic stability[4,5]. It describes the constantly changing functional relationships among chemical and hormonal responses activated and deactivated as our somas respond to stress-related signals. As an example, the hypothalamic-pituitary-adrenal (HPA) axis releases cortisol in response to perceived stress. In normal function, cortisol decreases to basal levels as the specific stress is attenuated[6]. Efficient allostasis is described as

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facile adaptation, including a quick response to stress and a rapid return to baseline following elimination of the stressor[7]. However, over time, allostasis becomes impaired by exaggerated or delayed reactivity peaks and a tendency to sluggish recoveries[5,7,8]. Wear and tear accumulate as the soma adapts to multiple and varying environments, resulting in allostatic load[5,9,10]. Returning to the example of cortisol, as allostasis becomes sluggish, exaggerated, or delayed cortisol may not be removed from the blood as rapidly. Cortisol has both cardiotoxic and neurotoxic effects; continued exposure to high titers may damage systemic physiology. Similar to the effects of cortisol, exposure to other factors such as adrenaline, noradrenaline, obesity, C-reactive protein, interleukins, hypertension, or hyperlipidemia, may lead to progressive physiological damage, functional loss, and increased allostatic load.

Stress

Multiple definitions of stress pervade the literature, suggesting variable reported associations of stress with morbid and mortal outcomes may reflect definitional disagreement[3–7,9–12]. Regardless of how stress is defined, it can be assessed and measured using a variety of methods, from self-reports and questionnaires to assessments of blood pressure, hormones and stress testing[3–5,9,10,12,13]. Stress is likely more damaging to elders than generally reported[13:295]. Many chronic degenerative diseases affecting elders may be related to physiological and psychosocial mediated stress. The somatic impact of such stress likely is influenced by personal experiences, genetics, and behaviors[13].

Stressors are everywhere in modern human life. Other people and social relationships are among the most prominent daily stressors; these may affect us at work, school, or home and include spouses and children[10–13]. Stressors also extend to care-giving, emotional support, financial situations, mental anxiety associated with performance, mental health issues (e.g. depression, isolation), public speaking, and job performance[12–17]. Our environments, including climate, radiation, temperature, hypoxia, diet, and infectious and parasitic agents all produce physiological and mental stress. Our somas are constantly exposed to oxidative stress, poor/under/malnutrition, stress responsive hormones, chronic and acute illnesses, immune responses to infectious diseases, injuries, and hunger[3–5,7–10,12–17].

Stress and anxiety secondary to multiple stressors may lead to immune and hormonal dysfunctions[5,7,9]. For example, during exams (stress) college students have lower white blood cell counts (response)[7,14]. Similarly, depression (a stress) is associated with poor immune and altered endocrine responses, and reduces one's ability to sleep[7,13]. Lack of sleep diminishes the soma's ability to repair damage to somatic cells, leading to lack of somatic recovery, poorer immune function, and increased senescence (response)[7]. Negative social relationships also accelerate senescence: for example, occupational stress is associated with increased serum MDA (malondialdehyde), higher levels of which increase oxidative stress[15], a major promoter of senescence[16]. Stress produces a physiological cascade of increasingly poor health and an increasing senescent phenotype.

Allostatic Load

Allostatic load represents a composite assessment of long-term physiological dysregulation occurring secondary to somatic responses to stress. First articulated by Sterling and Eyer during the 1980s, the conceptualization of AL has developed continually since the 1990s[3–5,9,10,15,17–19]. AL is modeled to assess wear and tear on the soma from continually responding to multiple stressors. By assessing function across multiple physiological systems, AL is constructed so as to measure dysregulation believed to result from somatic stressors[10,21].

Primary mediators of AL are hormones produced by the sympathetic nervous system (SNS), HPA, and other organs. In its original formulation, primary mediators of AL included: catecholamines (epinephrine, norepinephrine), cortisol, and dehydroepiandrosterone sulfate (DHEA-s)[21] (Table 1). Today, additional hormones and proteins are being used to assess AL: insulin-like growth factor-1 (IGF-1), interleukin-6 (IL-6), serotonin, fibrinogen, dopamine, C-reactive protein (CRP), creatanine, albumin, and thrombin[17–19]. As yet, none have produced significantly better models of AL than the original. Inclusion of different physiological measures when modeling AL suggest that the construct is still being interpreted and refined as research on applying AL proceeds.

TABLE 1
THE COMPONENTS OF ALLOSTATIC LOAD

Primary Mediators of Stress
Serum dihydroepiandosterone – sulfate
Overnight urinary cortisol, adrenaline, noradrenaline
Secondary Mediators of Stress
Systolic and diastolic blood pressure
Waist/hip ratio
HDL-cholesterol and total-cholesterol
Glycated hemoglobin

After Seeman et al.[20].

Primary stress mediators control a cascade of biochemical and physiological reactions promoting secondary physiological outcomes. These include elevating systolic and diastolic blood pressure, total serum cholesterol, HDL-cholesterol, triglycerides, fasting glucose, and glycosylated hemoglobin, along with increasing aspects of body habitus such as skin folds, body mass index (BMI) and waist-to-hip ratio[18]. Tertiary or disease outcomes of elevated AL are chronic degenerative diseases: atherosclerosis, cardiovascular diseases, and diabetes mellitus[3,16,18,20]. In the near future AL or a construct thereof will provide

a useful clinical and research tool for predicting, and eventually mitigating, secondary and tertiary outcomes.

Loss of allostasis and subsequent increase in allostatic load likely reflect a number of underlying cellular senescent processes. Over the past century and a half, senescence has been defined in a variety of ways (*e.g.* 21–23). Today, general senescence is viewed as a biological process characterized by an accumulation of metabolic byproducts leading to cellular dysfunction and a decreased probability of reproduction and survival[17]. Senescence is an age-independent, individualized, progressive, multifactorial, deleterious and irreversible cellular process that leads to an increased probability of death over time by affecting all organs and physiological systems[22,23]. Since Sterling and Eyer introduced allostasis and AL in 1988, research exploring relationships of AL with losses of functions, frailty and higher morbidity and mortality in elders has exploded[4]. In 2005, Stewart reviewed existing research on AL listed in the ISI »Web of Science« and published between January 2000 and June 2005[19]. In this review, we examine articles reporting on AL and its correlation with aspects of somatic decline. We restricted our review to research published between July 2005 and December 2010 and indexed in the ISI »Web of Science«. As part of discussing these papers we also explore directions for further application of AL in clinical and research settings.

Methods

The SCI indexes over 10,000 unique titles from scientific, social science, art, and humanities journals (ISI Web of Knowledge 2009). The database is updated weekly. Restricting our review to papers published July 2005 to December 2010 prevented overlap with Stewart's 2006 review[18]. We review 44 publications indexed with the key words-allostatic load, senescence, and aging. The majority were analyses of new data (27 of 44; 60%). Of the remaining, 13 were reviews and 4 were papers suggesting improvements to mathematical modeling of AL.

Results

Several points about these papers are salient. First, many applications of AL do not use the specific 10 physiological measures enumerated by McEwen and Stellar[10] and Seeman et al.[20]. In fact many applications are attempting to either re-model or re-interpret the original construction. Second, although there is wide consistency in the way AL is assessed (measuring physiological parameters and summing across risk factors in the highest quartile of risk), there is little consistency in how many or which aspects of physiology are included. In several cases, it seems authors went to previous or current research and whatever risk factors were available and constructed their own idiosyncratic model of AL. Lack of consistency due to particularistic operationalization of AL constructs makes comparing across studies difficult. These inconsistences are highlighted to some degree in this review by discussing common and alternative constructs of AL and variable types of AL, such as those based on a single variable (*e.g.*: cortisol), just neurological variation, or past diagnoses of a mental or physical illness. Additionally, these various constructs of AL have been associated with a variety of potential outcomes – chronic diseases, physical activity, cognitive disorders, post-traumatic stress disorder (PTSD), and depression or with social support and SES.

Modeling Allostatic Load

Calculating AL

In its original formulation AL was measured by summing 10 biological variables (see Table 1) for which an individual falls into the highest risk quartile of each measurement's distribution[10,18,21]. This is the upper quartile for all of McEwen, Seeman and colleagues' original primary and secondary mediators, except DHEA-s and HDL for which the 25th percentile and below is considered the highest risk quartile[3,5,10,15,20,25,27–29]. Original counts of AL are one-tailed and range from 0–10, leading to an AL of 0–10.

Alternative methods for determining AL

In recent years, several authors have questioned the validity of this simple procedure (*e.g.* 7, 28, 30). For one, physiological reactions to stressful experiences may lead to either elevated or decreased chemical and hormonal levels[30]. For example, both high and low cortisol may increase physiological wear-and-tear[31–33]. Additionally, symptoms of conditions such as PTSD are linked to low, not high, cortisol levels[28]. Such results suggest future assessments of AL may need to incorporate risks with two-tailed criteria[30]. For example, Seplaki et al. evaluated different constructs of AL, but their alternative biomarkers only moderately influenced predictability of morbid outcomes[17]. They conclude that »…count-based summary measures incorporating risk at both high and low tails and measures that preserve the continuous properties of the biological variables are strategies that may yield stronger predictions of a wider array of health outcomes than other measures…«[18:445].

To compare different estimates of AL, Seplaki et al. computed AL for an elderly Taiwanese sample combining between 10 and 16 biomarkers, one- and two-tailed risk categories, and different percentile cut points (<10% and >90% as compared to <25% and >75%)[17]. All AL scores were then compared to self-reported health, activities of daily living (ADL), reported mobility, the Centers for Epidemiologic Study of Depression Scale (CES-D) score, and an assessment of temporal orientation. Number of biomarkers and different percentile cut points only modestly affected AL's correlation with proposed dependent outcomes[17]. Conversely, AL constructs incorporating risks at both high and low levels better predicted an array of health outcomes than did constructs with only unidirec-

tional risk[17]. Such two-tailed analyses are becoming increasingly prevalent in published reports (*e.g.* 23, 34–35).

Karlamangla et al. proposed another alternative method for scoring AL[35]. Data were collected on a cohort of high-functioning 70–79 year-olds from the 1988, 1991, and 1995 rounds of the MacArthur Successful Aging Study. Change in AL over time was assessed and used to predict all-cause mortality over 2.5 and 4.5 years follow--up. The ten original primary mediators were evaluated for each. Next, to account for two-tailed risk as well as possible non-linear relationships with coronary heart disease and mortality, Karlamangla et al. added a term assessing each biomarker's deviation from the mean[35]. These values were weighted according to their independent associations with 7-year all-cause mortality[35]. Next, a bootstrapping technique was used to identify each component's contribution to the AL model; elements not contributing were eliminated[35]. Among participants with the same baseline AL, women were less likely to die than men[35]. Those with lower baseline AL tended to have a greater increase in AL over time[35]. Increases in AL over 2.5 years were predictive of all-cause mortality over the following 2 years. These results show that even among high-functioning elders increased AL is associated with increased risk for mortality[35].

While many authors continue to evaluate AL by using the 10 biomarkers originally proposed by Seeman et al.[20], others have had success utilizing different formulations of AL. The present review provides evidence that numerous variations of the AL calculation correlate with undesirable outcomes. Because of AL's intrapersonal and intrapopulational specificity, it is formulated solely for the sample examined and is not comparable among samples.

Critiques of AL

AL has been critiqued as static because it does not account for intrapersonal stressor reactivity. Individual temperament influences emotional reactions to stressors. In turn, genetic predispositions, lifestyle choices, social context, and environment impact physiological responses to emotions[7]. For example, an exaggerated cortisol response to stress seems to be typical in individuals with a »…cognitive style characteristic of greater trait anxiety…«[7:14]. Those with greater social support tend toward lower cortisol reactivity to social stressors[7]. To tailor AL to individual reactivity, Piazza et al. suggest participants' record stressors and associated emotional reactions in daily diaries and that these data be examined for correlation with biomarkers[34].

Applying Allostatic Load

Allostatic load and chronic disease

Most studies of AL have been conducted on US samples. However, several authors are attempting to determine the applicability of AL in non-Western populations (i.e. 17, 27, 33, 37–40). Crews assessed distributions of stress using four models of AL combining different physiological measures and their possible associations with sex, age, and diabetes in a Samoan sample[16]. Assessed first were the ten primary mediators proposed by McEwen and Stellar as well as fasting insulin[10]. Model 2 eliminated measures of glycated hemoglobin (HbA1c) and fasting insulin. Model 3 added tricep and subscapular skinfolds, body mass index (BMI), and relative fat pattern index measures to Model 1. Model 4 combined Model 1 with LDLc and measures of triglycerides and fasting glucose[16]. Diabetes was assessed by a fasting or 2-hour post-load glucose level at or above 140 mg/dl[16]. Among older Samoans, age was poorly correlated with AL, although there was a positive association for women[17]. For men, models 3 and 4 were significantly associated with diabetes. For women, all four models were significantly associated with diabetes[16]. Results suggest that regardless of the method used for measurement, stress load composites tend to show predictive value for diabetes morbidity among women and to some degree among men, but were not significantly related to chronological age[16].

Allostatic load and physical activity

The association between AL, mobility, and healthy senescence was evaluated utilizing data from NHANES 3 participants. Mobility was assessed by self-reports of difficulty of walking (none, some, much, or unable). AL was calculated according to Crimmins et al.[40], incorporating measures of diastolic and systolic blood pressure, HbA1c, BMI, triglycerides, HDL cholesterol, total cholesterol, albumin, C-reactive protein, fibrinogen, peak respiratory flow, creatinine clearance, and homocysteine[41,42]. Controlling for age, sex, race, disability (assessed by ADLs), and years of education, lower AL was associated significantly with higher mobility, suggesting that mobility plays an important role in healthy aging[42].

Based on a sample of elderly but active ballroom dancing participants, Strahler et al.[8] suggest no physiological association between AL and age. Rather, they suggest physical activity helps individuals maintain a healthier AL. However, these authors seem to confuse age with senescence. In general, active individuals tend to be healthier than their chronologically identical inactive peers. Strahler et al.'s results support the hypothesis that old but active individuals experience less senescence and show lower AL than their less active counterparts[8].

AL and cognitive disorders

Individuals suffering bi-polar disorder (BD) may experience more rapid senescent decline than healthy individuals[39]. To assess how BD associates with senescent decline, Cacilhas et al. evaluated AL in 100 Brazilian outpatients with BD[39]. AL was not assessed using biomarkers, but rather responses to the Functioning Assessment Short Test (FAST). FAST evaluates disability using questions about autonomy, work, cognitive functioning, financial issues, and interpersonal relationships[39]. Lower FAST scores are associated with greater functional impairment. BD patients reported significantly more

impairment than did controls. Cacilhas et al. suggest this supports their hypothesis that BD accelerates senescent decline[39]. However, as AL was not assessed using biomarkers, their research is difficult to integrate into the current AL paradigm and illustrates non-traditional constructs are being applied without adequate interpretation.

AL and socioeconomic status

Using another non-traditional construct, Kahn and Pearlin measured AL based on a participant's past diagnoses of 5 chronic conditions (cancer, stroke, heart disease, high blood pressure and diabetes) and 9 common symptoms (headaches, back pain, muscle aches, indigestion, constipation/ diarrhea, incontinence, feelings of weakness, heart palpitations, shortness of breath, and ranking on a depressive symptoms scale)[42]. They compared this index to retrospective data on participants' long--term financial hardship. Controlling for current economic situation, results indicate long-term financial hardship is associated with higher rates of chronic conditions and symptoms[42].

Poverty may have its greatest influence on biological risk early in life. Life expectancy at age 20 differs markedly by biological risk and poverty status suggesting that extreme poverty yields higher risk at younger ages[34]. Among older individuals, biological risk secondary to poverty may be mitigated, most likely because higher risk individuals have died and only less at-risk individuals survive[34].

AL and PTSD

To ascertain physiological effects of PTSD on women, Glover et al. assessed AL in a sample of 29–55 year-old mothers of childhood cancer survivors from California using the Posttraumatic Stress Diagnostic Scale (PDS)[27,43]. Chronic stress and recent stress history were evaluated using the Life Experience Survey (LES), AL was assessed using the model originally proposed by Seeman et al. 1997 with one difference; cortisol was counted when a participant scored in either the lowest or highest 12.5% of the sample distribution because either low or high cortisol may be detrimental[10,27]. Interestingly, mothers with PTSD showed the highest norepinephrine titers, but lowest cortisol[27]. AL significantly correlated with PTSD symptoms reported on the PDS, showing a dose--dependent association. Women with the highest AL exhibited PTSD, those in the middle range of AL scores showed some PTSD symptoms, while the low AL group showed no PTSD symptoms[27]. AL did not correlate significantly with traumatic events experienced in the past as measured by LES scores[27]. These results demonstrate the usefulness of AL in middle-aged adult women, while validating the hypothesis that a composite AL score is a more effective predictive tool than any single biomarker.

AL and depression

Previously depressed individuals tend to show early signs of physical decline, suggesting that depression may accelerate senescence[7, 44]. Catecholamines and cortisol likely mediated this effect[7]. In addition, absence of or low depression corresponds with higher levels of self-perceived health. For example, significant positive association is seen in polio patients between having a clear purpose in life and less self-perceived decline in health over time[46].

Cho et al. assessed the effect of prior depression on senescence[44]. Using an abbreviated version of the CES-D and two questions about prior depression, senescent decline was assessed at 6 weeks, 1 year, and 2 year follow--up using the Chronic Disease Score (CDS) and Physical Component Summary (PCS) of the 36-Item Short-Form Health Survey[44]. After adjusting for age and education, measured senescence was significantly worse in the depressed sample as compared to a control group[44]. Overtime, both CDS and PCS scores declined significantly more in the prior depression group, independent of current depression level[45]. This suggests that, despite a general opinion that once depressive symptoms are controlled risk for adverse outcomes is reduced, negative effects of depression endure beyond resolution and predict senescent decline among elders[44]. Although Cho et al. measured physical decline using CDS and PCS as proxies, they suggest that system dysregulation as assessed by AL is the likely physiological pathway mediating observed senescent decline[44–46]. Besides depression, self-perception may mediate senescent decline. For example, individuals from high stress environments tend to perceive themselves as less healthy[46]. Additionally, individuals who are better equipped to handle stress may self-select into higher stress jobs[47].

AL and social support

Maselko et al. evaluated the relationship between religious service attendance and AL using data from the 1988 wave of the MacArthur Successful Aging Study[48]. Religious activity was assessed through questionnaires and confounding with social interactions was controlled by assessing only attendance at weekly church services[48]. AL was assessed according to the original model[3,46]. Women with lower AL attended religious services significantly more frequently and demonstrated lower epinephrine and waist-hip ratio[48]. However, variability in AL was not solely due to these two factors[48]. Among men, no significant association between AL and religious activity was identified. This finding is consistent with other studies wherein gender differences influenced associations between religious participation and health[48]. AL was independent of social network/support levels, participants' subjective religiosity, and congregation[48]. Analyzing an elderly sample, Pruessner et al. reported that cortisol decreases as individuals age[49]. They also show that self-esteem is both age- and cortisol-independent in these elders.

Interpreting/Re-Interpreting Allostatic Load

Neuroendocrine allostatic load

Another way of assessing AL is now known as neuroendocrine allostatic load (NAL)[27,33]. Proponents suggest

that because NAL evaluates only catecholamines, cortisol, and DHEA-s it is based on a »…physiologically coherent class of markers representative of the neuroendocrine stress response«[27,37–39]. NAL represents activity in both the HPA-axis (cortisol and DHEA-s) and SNS-axis (catecholamines)[24]. Different percentiles for NAL have been used to delimit »high risk« percentiles (i.e.75th, 85th, 90th, and 10th, 15th, 25th). As with AL, participants are assigned one point for every biomarker in the »high risk« category. NAL also can be measured »…on the basis of a summed z score for respondents in which the score is the total number of standard deviations from the mean in the direction of high risk for each biomarker…«[27:512]. Among elderly Taiwanese, no measure of NAL predicted lifetime stress evaluated as »…widowhood, not living with a married son, living alone, and not participating in groups…«[27:509]. In contrast, both age and women's current stress-levels were positively correlated with NAL[27].

Associations between NAL and stressors also were examined in a Costa Rican sample. Stressors included household wealth, economic and health problems early in life, present economic situation, total monthly income, cumulative adversity (measured through a questionnaire), marital status, participation in church, personal loss (assessed as loss of a child or widowhood), employment, malnutrition, and caregiver status[33]. NAL biomarkers were analyzed individually and as a cumulative index[33]. Being female and advancing age both were associated with higher risks for all individual biomarkers and the NAL index[33]. However, individually, NAL hormones did not associate with stressors in a predictable manner. For example, poor health was linked significantly to more favorable cortisol values, epinephrine level was not associated significantly with any stressors, nor was early childhood adversity correlated with any biomarker[33]. The NAL index significantly correlated only with SES, but correlated positively, although not significantly, with social deprivation and loss indices[33]. Similar results occurred regardless of risk quantile examined (10th and 90th percentiles vs. 25th and 75th percentile), whether or not NAL was tallied as a z-score counting each biomarkers' standard deviations from the mean in the direction of high risk, or if NAL was analyzed as a binary variable[33]. NAL does not associate significantly with most stressors, showing significant correlation only with current stress levels in Taiwanese women and SES in Costa Rican individuals. Instead of representing long-term, cumulative stress, NAL may reflect only more recent stressors.

The best measure of AL is still to be determined, thus many studies utilize more than one method or unconventional assessments[17,18,21,27,33–36,40]. Such unconventional measures include Cacilhas et al.'s evaluating responses to a Fitness Assessment Short Test and calling it AL to Kahn and Pearlin's use of participants' past diagnoses of chronic conditions as AL[40,43]. In general, data published from 2005–2010 suggest that multiple health outcomes are associated significantly with AL; these include chronic disease, stress, frailty, mobility, SES, and physical functioning of bi-polar patients. Several studies report significant associations only among women, including correlations with church attendance, PTSD, and self-appraised memory loss.

Cortisol

In addition to cumulative measures of AL, cortisol has been proposed as a single measure of AL and senescent decline[33,50–53]. Cortisol is released in response to stress, and mediates immune system reactivity, along with glucose, protein, fat metabolism, and cardiovascular reactivity[53]. Despite being commonly used to assess physiological decline, indexes of AL generally are more effective and significant predictors of outcomes than cortisol alone[28,32,35,54-59].

To ascertain how cortisol associates with mortality and chronic diseases, serum cortisol (including measures of total cortisol, corticosteroid-binding globulin (CBG), and serum free cortisol) and salivary cortisol were assessed in two different cycles of the Longitudinal Aging Study Amsterdam[53]. The number of CDCs was assessed as a count of chronic nonspecific lung disease, diabetes mellitus, cancer, heart disease, peripheral arterial disease, hypertension, arthritis, and stroke[53]. No significant associations were found between serum cortisol and mortality for men or women. In men, higher mortality risk was associated with the third tertile of salivary morning cortisol, for women higher mortality risk was associated with the third tertile of salivary evening cortisol[53]. No significant association was reported between cumulative number of CDCs and cortisol level[53]. Although not significant, odds ratios associated with several CDCs increased with higher levels of cortisol. An index measure of AL may have been a more effective approach to predicting mortality and risk of CDCs in this study.

Allostatic load, biological age and biomarkers

Biomarkers are defined as any »biological indicator – such as blood or saliva – that reflects underlying physiological processes, including both normative processes and pathogenic states«[35:513,60]. Biomarkers of senescence should, alone or in some multivariate composite, predict functional capability at later ages better than chronological age[61]. Criteria of American Federation for Aging Research suggest biomarkers of senescence should predict the rate of senescence, monitor basic processes underlying senescence (not disease), must be repeatedly testable without harm to the subject, and must have an animal analog[61]. Accordingly, AL is expected to be a biomarker of senescence.

Biological age (BA) is a measure expected to estimate »…the functional status of an individual with reference to his or her chronological peers on the basis of how well he or she functions in comparison with others of the same chronological age…«[62:780]. BA was developed in hopes of improving on chronological age in assessing senescence[63]. Unfortunately for such methods, assessing BA using only survivors at any given chronological age considers

only genetically homogenous individuals who share longevity genes[62]. Also, large samples of octogenarians or centenarians are difficult to obtain. Furthermore such samples suffer from selection bias and selective survival and in addition, obtaining control samples of individuals who did not survive is problematic. BA often is estimated as deviation between actual age and age predicted from measured biomarkers, but remains closely correlated with chronological age. Like AL, BA differs between men and women and should be assessed separately[62]. Biomarkers commonly used to estimate biological age include systolic blood pressure, grip strength, forced expiratory volume, cholesterol, glucose, and cognitive or neuropsychological factors, overlapping with AL[62,63]. Skeletal biomarkers, scored using the Osteographic Scoring System, also have been proposed to assess senescence. Initial results using biological age measured by OSS from Framingham Heart Study data suggest this measure predicts mortality in both sexes across age groups[62].

Summarizing methods of biological age assessment, Karasik et al. conclude that in the future, BA estimates will be useful in directing health interventions[61:574]. However, they note, there is no single set of agreed on biomarkers for determining BA. Nor is it clear how external factors like sex, ethnicity, and lifestyle contribute to senescence. Caution in using BA to influence policy matters is advised until techniques are more standardized, not to mention accurate[61]. Juster et al. find AL to be a better predictor of morbidity and mortality than other measures of biological age[63].

Our prevailing health paradigm focuses on treatment rather than altering causative factors underlying health and well-being[64]. Following Koch, Bortz identifies the traditional health paradigm of interactions between host, agent, and environment[65]. However, Bortz argues this conceptual framework lacks interactions with genes, external agency, internal agency, and aging, concepts that must now be incorporated into medical models[65]. Most chronic degenerative diseases are epigenetic and even common neurological diseases show low concordance among twins. External agency encompasses infection, injury, and malignancy, while internal agency focuses on stress and disuse of physiological systems resulting in AL and increased morbidity[65]. Bortz finds the medical field generally emphasizes external over internal agency and that the latter may need more attention to improve future health[65]. The importance of genes is stressed because they interact with all other health affecting factors. Depp et al., like Karasik et al., differentiate between chronological aging and biological aging[61,66:532]. Their primary example of a quantitative method for assessing BA is AL. Depp et al. clearly believe AL is a primary paradigm for determining BA, citing the successful use of AL to predict mortality in the MacArthur Study of Successful Aging cohort[66].

Piazza et al. and Johnson et al. reviewed biomarkers used to assess AL and BA[34,60]. Piazza et al. differentiate between two types of stressors, relatively rare stressors that mark major life events and quotidian stressors, noting that interactions among and accumulation of both lead to increased morbidity and mortality[34]. Recent research on the sympathetic-adrenal-medullary axis (SAM), which is activated in response to immediate threats, shows that catecholamines are short-lived and released in a fluctuating daily pattern[34]. Age-associated changes in SAM activity are debatable but may include higher norepinephrine reactivity to stressors, higher average levels of norepinephrine, and/or reduced basal epinephrine activity[34]. In addition, chronicity of stress increases frequency and length of SAM activation, possibly resulting in tissue damage[34].

The HPA axis, in contrast to the SAM-axis, responds to longer term stress through release of corticosteroids such as cortisol, corticotrophin-releasing hormone, adrenocorticotropin hormone, and arginine vasopressin[34]. Research has focused on cortisol because it is easily obtained and assayed from saliva, has a diurnal rhythm, and is associated with physiological stress[34, 53–58]. As HPA reactivity increases with age, the negative feedback loop controlling the HPA-axis becomes impaired, and average cortisol may increase or decrease while diurnal fluctuations flatten[7,34]. Elevated cortisol leads to increased insulin and in turn may lead to increased abdominal fat stores[7]. Prolonged stress appears to depress physiological responses to cortisol eventually resulting in cortisol overproduction, an outcome detrimental to health[34]. With age the HPA changes, producing less IGF-1, growth hormone (GH), and DHEA. Low IGF-1 and GH are linked to muscle atrophy (sarcopenia) and risk of breast cancer. Low GH also predicts insulin resistance, increased adiposity and incidence of cardiovascular disease, while decreased basal levels of IGF-1, GH, and DHEA are associated with early mortality in men[7]. Such a cascade effect supports the derivation of AL as a multifactor construct connecting stress to unwanted outcomes.

AL and the Senescing Soma

Immune system

Around age 40, the immune system begins to decline[34]. Phagocytosis becomes less efficient, macrophages decrease, natural killer cells become less effective, the thymus shrinks and fewer T cells are formed, while decreased production of lymphocytes, and increased production of inflammatory biomarkers (*e.g.* IL-6, tumor necrosis factor-alpha (TNF-α), C-reactive protein (CRP), and interleukin-1β (IL-1β)) weaken responses to new immunologic threats. These changes result in »…concomitant age-related diseases associated with inflammation, such as osteoporosis, osteoarthritis, and atherosclerosis…« and perhaps even Alzheimer's disease[34:517,60]. Increase of IL-6, TNF-α, and IL-1β may be related to decreased testosterone production which predicts mortality in male veterans and a higher incidence of diabetes and metabolic diseases in women[7,60]. Links of increased IL-6 and CRP with sarcopenia vary across samples[60].

Similar to age-related changes, chronic exposure to stressors decreases lymphocyte concentrations, leading to weaker vaccine responses, slower wound healing, decreased adaptive immunity and loss of natural killer cell functionality, as well as increases in production of inflammatory biomarkers[34]. Chronic stress appears to accelerate SAM-axis, HPA-axis, and immune system declines. Stressors appear to have a greater negative effect on older individuals who tend to have higher cumulative AL which impedes efficient responses to chronic and rare life-event stressors[34].

Cognitive Decline

Antioxidants such as β-carotene may protect from cognitive decline in individuals identified as at-risk by APOE 4 alleles[58]. Production of reactive oxygen species (ROS) increases with age, leading to cross-linking of macromolecules, lipid peroxidation and impaired antioxidant activity[7]. Among the aged, such oxidative stress can lead to cognitive decline, loss of autonomy, loss of ability to perform daily activities, institutionalization, and depressive symptoms[7]. ROS accelerate tissue damage and cell aging, especially in cardiac and brain cells[7]. Healthy elders show oxidative stress similar to young adults and show comparable antioxidant defenses, suggesting that oxidation may not be an inevitable aspect of aging[7]. Lifestyle, including sedentariness, high fat diets, and insufficient sleep, are linked to oxidative DNA damage, as are smoking and alcohol use. Associations of stressors with systemic free radicals appear to be mediated by overproduction of cortisol, insulin, and glucose, and thus linked to AL[7].

Telomere shortening, mtDNA, and telomerase activity

Telomeres are the protective nucleoprotein structures capping the ends of eukaryotic chromosomes. Telomeres shorten during each cell division. This has led to proposals that telomere attrition is a biomarker of senescence[60]. Shortened telomeres are linked to CVD risk factors including pulse pressure, obesity, insulin resistance, and diabetes. They are also associated with excess adiposity, insulin resistance, and increased leptin levels. Shorter telomeres predict mortality in non-clinical samples, and among patients with chronic kidney disease, Alzheimer's, and stroke[7]. Shorter telomere lengths are linked to higher ROS levels within cells, perhaps because oxidation decreases protein activity and damages telomeric DNA[7]. Cross-sectional studies demonstrate individuals with higher oxidative stress *in vivo* show shorter telomere lengths[7]. In cell cultures the addition of antioxidants decelerates telomere shortening[7]. Chronic stress may lead to diminished telomerase activity, subsequent telomere shortening, and a biochemical cascade (including release of cortisol) resulting in increased disease susceptibility and early cell senescence. These results support the hypothesis that chronic stress produces a biochemical cascade that increases AL and the rate of senescence[63].

AL, Environments, and Stress

Protective social environments and sociality may mediate physiological responses to stress and influence individual risk of morbidity and mortality. Among animals' prosocial behaviors, »…stimulate the release of the neuropeptide oxytocin, which in turn inhibits the stress-induced activity of the HPA-axis, suggesting an inhibitory influence of oxytocin on stress-responsive neurohormonal systems…«[67:S117]. Oxytocin injections in rats also led to decreased blood pressure and cortisol, as well as increased levels of insulin and cholecystokinin, illustrating how low sociality may increase AL[67]. Among humans, higher AL occurs among those with lower SES and associates with greater dysregulation of major biological systems suggesting that social and economic environments influence stress and its outcomes[67].

An adverse environment early in life may produce physiological responses to stress leading to lower cognitive abilities and mental health in later life[12,69]. Luecken proposes »…a lifespan developmental approach…« postulating that adverse early family experiences change the setpoint for physiological stress responses contributing to the rate of cognitive decline of older adults[69:34,72]. Both rodent and human studies suggest prolonged early-life exposures to glucocorticoids accelerate senescence, cognitive impairments, neuronal damage in the hippocampus, and (for humans) poorer performance on hippocampus-driven cognitive tasks[69–71]. Dysregulation of the cardiovascular system also associates with cognitive decline in adulthood, supporting the AL model that suggests assessing dysregulation across multiple systems is necessary for understanding senescent decline[69].

The brain is a target of stress. Specifically, the hippocampus, amygdala, hypothalamus, and prefrontal cortex change in response to chronic stress[72]. Alterations in brain physiology primarily result from release of stress-responsive glucocorticoids. Loizzo differentiated two components of AL: allostatic lift (cognitive enrichment), and allostatic drag (aversive effects linked to stress)[73]. Increasing allostatic lift through medication and psychotherapy may mitigate effects of allostatic drag by »…minimizing wear-and-tear and optimizing plasticity and learning…«[34:186].

Statistical modeling of allostatic load

Due to problems inherent in longitudinal data on aging, several research groups targeted modeling techniques to improve empirical measures of AL[18,74–76]. Yashin et al. addressed the lack of a mathematical framework of AL that would account for physiological changes due to aging, stress, adaptive capacity, and environmental differences, ultimately suggesting a stochastic process model[74–75]. They note that unobserved factors generate »…hidden variability to susceptibility to diseases and death in populations…«[75:1]. They propose a model accounting for hidden heterogeneity in measures of AL, stress, and age-dependent physiological changes to improve longitudinal data analyses. Arbeev et al. focused on models incorporating missing data sets and improving genetic models of aging, health, and longevity[76].

Discussion

Biological anthropology and human biology have long term interests in assessing life styles, stress and physiological responses as predictors of morbidity, disability and mortality among elders. Although AL does not measure the dynamic nature of allostasis or interindividual variation, it does assess within individual loss of function and variation when measured over time[3–5,9,10,14–18]. AL estimates losses in physiological function due to stress-related responses across multiple domains: cardiovascular, metabolic, endocrine and energy storage[3]. Allostasis is an intraindividual process whereby internal systems reset in response to changing environmental, somatic, or mental conditions[4]. AL is associated significantly with future morbidity, disability, mortality, physical and cognitive function among elders, morbidity among Samoans of the South Pacific, days of school missed by children and varies across elderly Japanese living more traditional versus more modern life styles[7–9,12–18]. Results from case studies reviewed in this article suggest that index measures of AL also correlate with morbidity in South Pacific islanders, cognitive disorders, level of physical activity, socioeconomic status, post-traumatic stress syndrome, depression and social support in the form of church attendance. AL correlates better with these variables than do individual biomarkers such as cortisol. Summaries of reviews covering additional aspects of AL, including advances in biomarker research, how senescence affects the soma, and progress in statistical modeling applicable to AL, provide a broader understanding of the paradigm.

Theoretically, allostatic load assesses somatic wear and tear experienced over time as the body continuously adapts to changing environments and situations. Since its inception, AL has become increasingly popular for measuring the effects of senescence on the human body and mind[10]. From 2005–2010, 47 articles indexed in the ISI database included both »allostatic load« and »aging« as key words. Of these, 44 specifically examined AL in humans. Among these were 27 case studies, 13 reviews, and 4 articles pertaining to mathematical modeling. Case studies primarily were epidemiological and cross-sectional, although several prospective and retrospective cohort studies were also published. Cross-sectional studies likely are most prevalent because of their ease to effectuate and low costs. However, unlike retrospective and prospective cohort studies, cross-sectional studies cannot establish causality.

Several clear themes emerged from the fourteen reviews of AL published between 2005 and 2010. First many questioned proposed qualitative and quantitative measures of age and/or the efficacy of age-related biomarkers used in such models. Two also broached questions of future health policies concluding that AL will impact how health policy is formulated in the future, although current applications are not yet definitive. A second group focused on relationships among AL, health, and environmental variation (*e.g.* SES, stress, or protective social environments), while the final group addressed cognitive performance and AL.

Case studies of AL utilized a broad array of physiological biomarkers. However, the majority focused on the ten biomarkers originally proposed by Seeman et al. and McEwen or these ten plus additional biomarkers[10,20]. Other studies utilized NAL biomarkers or focused solely on cortisol. Two studies suggested they were examining allostatic load, but used only nontraditional measures in their evaluations[39,42]. Results from case studies support previous findings suggesting AL is a predictor of morbidity, mortality, and chronic degenerative diseases. In addition, chronic stress, PTSD, self-appraised memory and socioeconomic status are now reliably linked to differentials in AL. In some cases, positive associations were observed only in women while the opposite was never true. Only two studies failed to report an association between AL and SES, both in Taiwanese populations. Perhaps different biomarkers or thresholds are needed to evaluate AL in Taiwanese and other non-Western/European populations, or the model may not fit some cultural settings.

Several reviews examined the usefulness of AL and biomarkers for determining BA, senescent decline, and cognitive performance. Those focusing on policy agreed there is no agreement as to a definitive measure of AL and therefore currently no way to incorporate this paradigm into public health planning or policy. Reviews regarding health differences and variable environments reinforced findings that physical and mental stressors as well as lower SES can lead to higher AL, higher morbidity, and higher mortality. Only three papers focused on problems inherent in longitudinal studies, reflecting the paucity of longitudinal studies concerning AL.

Future Directions

Over the coming decades, we can expect the older population to continue to expand as age-specific mortality rates continue their current worldwide decline. This transition suggests that understanding physiological responses of elders to stress and chronic degenerative conditions will become increasingly important. Currently, one of the most promising paradigms for studying senescent change is allostatic load. Research published 2005–2010 indicates that AL provides a viable model for assessing physiological dysfunction. Across a broad array of research areas, recent results show that AL is a useful measure of cumulative somatic stress and a relatively more accurate predictor of senescent decline, morbidity, and mortality than other current methods.

In addition to assessing senescence, we propose that allostatic load will aid in assessing historical trauma among American Indians, African Americans and others, in elucidating the male-female morbidity-mortality paradox, assessing clinical, diagnostic and monitoring of geriatric patients and residents in nursing home and ambulatory care settings, and understanding problems in child growth and development. Historical trauma includes the lasting effects of post-traumatic stress disorder in survi-

vors of catastrophic events and their descendants (*e.g.* children, grandchildren, *etc.*). Transgenerational increases in mental and physical illnesses, post-traumatic stress disorder, obesity, diabetes, hypertension, and cardiovascular disease have been observed in multiple populations, including Native Americans from the European invasion, African Americans following slavery and segregation, European Jews who suffered the Holocaust, the Japanese who have been the sole victims of atomic warfare, and multiple groups such as Somalis, Tutsi, and Croatians who experienced brutality and torture by their neighbors and countrymen. In such cases, every age group and both sexes of survivors collectively endured a common thread of trauma. In the past, researchers have had a difficult time quantifying historical trauma in epidemiological research as historical trauma is a life-long population-level stressor. Historical trauma results from unresolved grief and loss passed across multiple generations and lifetimes by the original sufferers to their progeny. AL may provide a quantitative assessment for measuring physiological loses caused by historical trauma in survivors and their descendants.

Across populations and in data from multiple longitudinal epidemiological studies men self-report fewer health problems than do women, however these same men die at a faster rate than women. This has become known as the male-female morbidity-mortality paradox and has not been resolved using standard epidemiological designs[71,77–79]. Applications of AL likely will aid in resolving this paradox as it is an objective (as opposed to subjective) assessment of current function and health that may be juxtaposed with self-reports and clinical assessments of health. AL is likely to aid this research, for example AL is significantly higher among elderly men than women in both Samoan and Japanese samples, although in both cases men report better health than do women[80,81]. Similarly, as mentioned earlier, women were less likely to die during follow-up than were men with the same AL at baseline in the McArthur Study Cohort[36]. Another interesting finding is that some associations are observed only among women, for example of AL with church attendance, PTSD and self-reported memory losses.

AL also may be useful as an adjunct to the standard clinical examination. Standard clinical protocols assess multiple risk factors (*e.g.* blood pressure, glucose, lipids, *etc.*) as single, independent contributors to risks. However, AL combines multiple such risk factors from multiple domains into a single clinical measure that assesses overall somatic condition. AL may then be monitored for change over time and for evaluating responses to treatment protocols. This information is likely to improve patient compliance with prescribed treatments, be useful in monitoring improvements and loses of health status over time, and assessing improvements or declines in patient health over time serving as a basis to alter treatments. Ongoing monitoring of AL may improve all individuals' physiological well-being. Using AL, doctors can monitor patients to reduce and delay onset of chronic degenerative diseases and improve capacity to complete activities of daily living. AL has »…prospectively predicted clinically relevant outcomes including incident cardiovascular events, physical function, cognitive decline and mortality. Such findings provide evidence that AL captures physiological changes preceding the occurrence of clinical disease and, hence that AL represents a meaningful step in the disease development process…«[48:465]. Additionally, results show depression positively correlates with higher rates of senescence suggesting physicians pay closer attention to current and past depression as a »…marker for physical health decline even when there has been a sustained full remission of depressive symptoms«[45:450]. Furthermore, improving AL reduces risk of morbidity and mortality, and risk factor change plays an important role in mortality even among high-functioning elderly[36].

No reports yet show that AL is being utilized in clinical settings. As biomarkers to evaluate AL are standard in clinical practice, AL should be used as a diagnostic tool for assessing senescent decline. Because numerous studies demonstrate the strong association between AL and chronic stressors, moving AL from passive laboratory settings to clinical applications should be a major future goal. Finally, AL likely will be useful for examining child growth and development. AL already is known to be associated with illness and days of school missed by children. It also is clear that stress is associated with telomere length in both children and adults. Higher AL likely is associated with growth failure and slow maturation of children, such as sub-standard attained height. Thus, unexplained instances of subpar child growth may be directly evaluated by assessments of AL.

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D. E. Crews

The Ohio State University, Department of Anthropology and School of Public Health, 4004 Smith Laboratory, 174 W. 18th Ave., Columbus, OH 43210, USA
e-mail: crews.8@osu.edu

FIZIOLOŠKA DISREGULACIJA I SOMATSKI PAD MEĐU STARIJOM POPULACIJOM: MODELIRANJE, PRIMJENA I REINTERPRETACIJA ALOSTATSKOG OPTEREĆENJA

S A Ž E T A K

Stope smrtnosti nastavljaju se smanjivati među post-reproduktivnim pojedincima. To čini sve važnijim razumijevanje dugoročne fiziološke reakcije na stres. Alostatsko opterećenje (AL) razvijeno je kako bi procijenilo štetne učinke somatskog odgovora na više stresora tijekom života. AL proizlazi iz razvojnih iskustava, genetskih predispozicija, okoliša, psihosocijalnog i životnog načina života te drugih izvora stresa. U ranim životnim stadijima sustav stresa inicira proizvodnju hormona koji održavaju kontinuirani alostatski odgovor organizma. Kasnije u životu, sustav dizajniran za ublažavanje stresa može uspjeti ili biti ugrožen, izazivajući neželjene somatske promjene i disregulacije. To stavlja opterećenje na regulatorni sustav koji ovisi o dnevnoj bazi odgovora na stres, stvarajući predispoziciju za stanična oštećenja i degenerativne bolesti. U ovom radu donosimo 44 publikacije od 2005. do 2010. godine istražujući povezanost

između AL i faktora rizika, kroničnih bolesti, morbiditeta i mortaliteta u starijih osoba. Zbroj rezultata sugeriraju da AL utječe na aspekte fiziološke disregulacije i somatski pad, predviđa štetni pad s obzirom na godine, i povezan je s negativnim sociokulturnim atributima i psihološkim rezultatima. Takvi konzistentni rezultati i široka primjena AL, dok se još uvijek modelira i ponovno interpretirati, ukazuju na njegovu korisnost kod istraživanja i kao klinički alat. AL pruža mogućnost biomarkiranja starenja, a procjenjivanje tijekom životnog vijeka će pomoći u predviđanju budućih negativnih zdravstvenih ishoda.