



Review

Allostatic load biomarkers of chronic stress and impact on health and cognition

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ABSTRACT

The allostatic load model expands the stress-disease literature by proposing a temporal cascade of multi-systemic physiological dysregulations that contribute to disease trajectories. By incorporating an allostatic load index representing neuroendocrine, immune, metabolic, and cardiovascular system functioning, numerous studies have demonstrated greater prediction of morbidity and mortality over and beyond traditional detection methods employed in biomedical practice. This article reviews theoretical and empirical work using the allostatic load model vis-à-vis the effects of chronic stress on physical and mental health. Specific risk and protective factors associated with increased allostatic load are elucidated and policies for promoting successful aging are proposed.

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Contents

1. Introduction	2
2. Concept of allostasis	2
3. Allostatic load model	3
4. Review of studies incorporating allostatic load algorithms	3
4.1. Older and middle-aged adults	3
4.2. Working adults	13
4.3. Children and adolescents	13
5. Conclusion	13
References	14

1. Introduction

Chronic psychosocial stress and consequent physiological dysregulations are increasingly viewed as catalysts of accelerated aging and agitators of disease trajectories. Individual differences in the brain's interpretations of and the body's reactions to environmental stressors are nevertheless the ultimate determinants of either vulnerability towards or resilience against stress-related diseases (Lupien et al., 2009; McEwen, 1998b, 2009). Health and successful aging can therefore be conceptualized as

one's ability to adapt and effectively respond to the dynamic challenges of being alive. Embodying this notion is the allostatic load model, which assesses physiological dysregulations that ensue when normal homeostatic functioning is shifted towards abnormal ranges via the prolonged secretion of stress hormones and the subsequent mal-adaptations this strain exerts on interdependent systems. This review summarizes theoretical developments and studies that incorporate allostatic load algorithms used to predict health and cognitive outcomes throughout lifespan development.

2. Concept of allostasis

The term *allostasis* refers to the process whereby an organism maintains physiological stability by changing parameters of its internal milieu by matching them appropriately to environmental demands (Sterling and Eyer, 1988). Traditional homeostatic

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models define health as a state in which all physiological parameters operate within normal values, while those that do not warrant pharmaceutical intervention. In contrast, allostasis defines health as a state of responsiveness and optimal predictive fluctuation to adapt to the demands of the environment (Sterling, 2004). Allostasis differs from homeostasis vis-à-vis its emphasis on dynamic rather than static biological set-points, considerations of the brain's role in feedback regulation, and view of health as a whole-body adaptation to contexts (Schulkin, 2003b). These insights have encouraged new ways of conceptualizing complex, multi-systemic biological activities where, as Heraclitus wrote, "the only constant is change". The allostatic load model expands the theory of allostasis by applying it to the cause and effects of chronic stress.

3. Allostatic load model

Allostatic load (AL) represents the 'wear and tear' the body experiences when repeated allostatic responses are activated during stressful situations (McEwen and Stellar, 1993). Real or interpreted threats to homeostasis initiate the *sympathetic-adrenal-medullary* (SAM) axis release of catecholamines and the *hypothalamic-pituitary-adrenal* (HPA) axis secretion of glucocorticoids that mobilize energy necessary for fight-or-flight responses (Sapolsky et al., 2000). Coordination of allostasis therefore depends on the brain's evaluation of threat (hippocampal, amygdaloid, and prefrontal cortical regulation); (Herman et al., 2005; McEwen, 2007) and execution of physiological responses. The perception of threat and mobilization of these allostatic mechanisms are fundamentally shaped by individual differences in constitutional (genetics, development, experience), behavioral (coping and health habits), and historical (trauma/abuse, major life events, stressful environments) factors that ultimately determine one's resiliency to stress (Fig. 1; McEwen, 1998a).

While adaptive acutely, chronic over-activation of SAM- and HPA-axis products induce a 'domino effect' on interconnected biological systems that overcompensate and eventually collapse themselves, leaving the organism susceptible to stress-related diseases (Korte et al., 2005; Lupien et al., 2006; McEwen, 1998b). Brain changes associated with chronic stress and AL (e.g., synaptic and dendritic remodeling, suppressed neurogenesis, structural atrophy/hypertrophy) further diminish the body's ability to cognitively process and physiologically respond to stressors (McEwen, 2000b). These contribute to pathophysiological *allostatic states* (Fig. 2) that reflect response patterns in which allostatic systems are overactivated and/or dysregulated (McEwen, 2003b). These processes are rooted in biopsychosocial antecedents integrated within the AL model that postulates a sequential chain of dysregulation in multiple systemic mediators.

A key feature of allostasis, AL, and ultimately allostatic overload is that multiple mediators of adaptation are involved and

interconnected in a non-linear network. Each mediator system produces biphasic effects and is regulated by other mediators, often in reciprocal fashion, leading to non-linear effects upon many organ systems of the body (McEwen, 1998a). At first, prolonged secretion of the stress hormones epinephrine, norepinephrine, and cortisol (antagonized by dehydroepiandrosterone) can falter in their ability to protect the distressed individual and instead begin to damage the brain and body (McEwen, 2006a). Stress hormones and their antagonists, in conjunction with pro- and anti-inflammatory cytokines (e.g., interleukin-6, tumor necrosis factor- α) represent the AL biomarkers referred to as the *primary mediators* (McEwen, 2003b). Synergistic effects of these molecules exert *primary effects* on cellular activities (enzyme, receptor, ion channel, genomic) that compromise the physiological integrity of allostatic mechanisms. Over time, subsidiary biological systems compensate for the over and/or under production of primary mediators and in turn shift their own operating ranges to maintain abated chemical, tissue, and organ functions. This prodromal stage is referred to as the *secondary outcomes*, whereby metabolic (e.g., insulin, glucose, total cholesterol, high density lipoprotein cholesterol, triglycerides, visceral fat depositing), cardiovascular (e.g., systolic and diastolic blood pressure), and immune (e.g., fibrinogen, c-reactive protein (CRP)) parameters reach sub-clinical levels. The final stage of AL progression is *allostatic overload*, whereby the culmination of physiological dysregulations leads to disordered, diseased, and deceased endpoints referred to as *tertiary outcomes*.

The AL model proposes that by measuring the multi-systemic interactions among primary mediators and effects, in conjunction to sub-clinically relevant biomarkers representing secondary outcomes, biomedical advances can be made in the detection of individuals at high risk of tertiary outcomes (McEwen, 2000a; McEwen and Seeman, 1999). Physicians routinely incorporate many of these biomarkers already, except attention is largely placed on values reaching clinically significant levels. By incorporating and integrating additional biomarkers, identifying pre-clinical values, and triangulating methods with various other measures if feasible (e.g., psychosocial, genotypes, and phenotypes), greater prediction of pathologies can be achieved. Because mediators leading to AL and disease susceptibilities interact in a non-linear manner whereby fluctuations in values induce compensatory remediation over time (Fig. 3), delineating time-courses of dysregulation is difficult (McEwen, 2008). Quantifying AL at a biological level, let alone with respect to the multiplicity of psychosocial modulators has thus represented a significant challenge. Nonetheless, advances over the last decade have helped pave the way to a greater understanding of the winding road to AL.

4. Review of studies incorporating allostatic load algorithms

4.1. Older and middle-aged adults

The following sections summarize studies using composite measures of AL in relation to health and cognitive outcomes throughout the lifespan (see Table 1). The MacArthur Studies of Successful Aging have provided the first steps towards an operational definition of AL. A count-based AL index representing the following 10 biomarkers was included in preliminary validation: 12-h urinary cortisol, epinephrine, and norepinephrine output; serum dehydroepiandrosterone-sulphate (DHEA-S), total cholesterol (TC) to high density lipoprotein- (HDL) cholesterol, and HDL-cholesterol; plasma glycosylated hemoglobin (Hb_{A1c}); aggregate systolic and diastolic blood pressure (SBP and DBP); and waist-to-hip (W/H) ratio (Seeman et al., 1997a). Participants' values falling within the high risk 75th percentile with respect to the sample's biomarker distributions were dichotomized as "1"

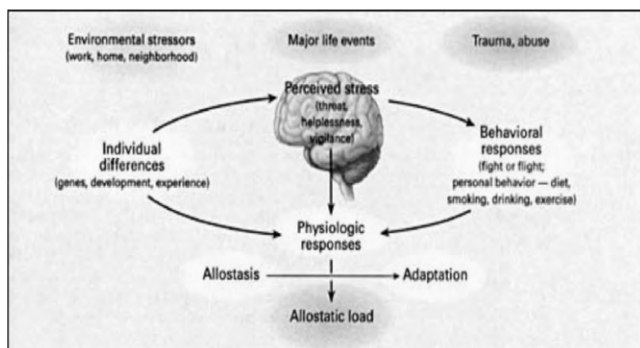


Fig. 1. The allostatic load model (McEwen, 1998a).

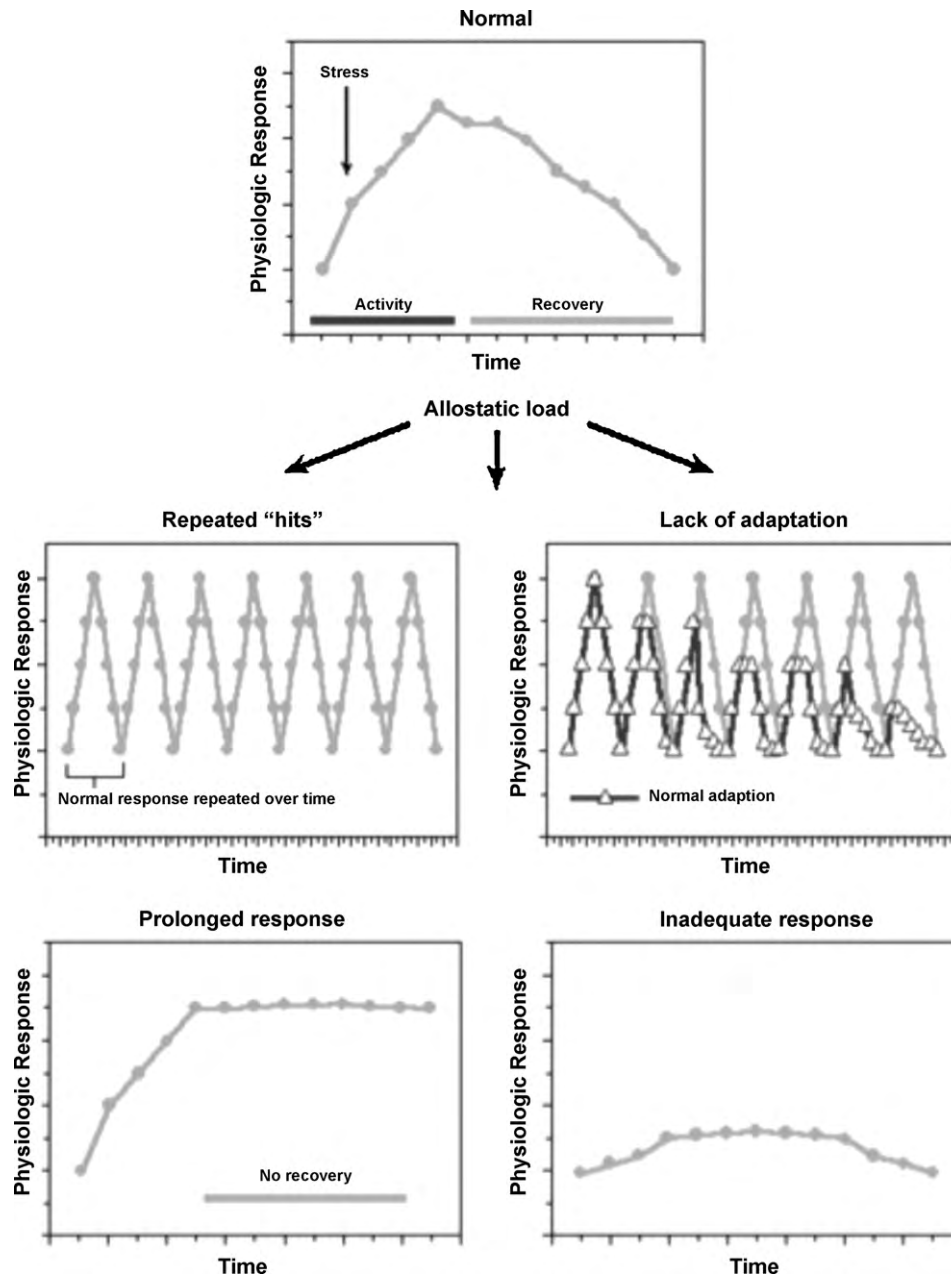


Fig. 2. Allostatic states. There are four profiles that illustrate how allostatic states deviate from healthy responses: (1) *repeated hits* from multiple stressors; (2) *lack of adaptation* reflected in a failure to habituate to stressors; (3) *prolonged response* due to impaired negative feedback; and (4) *inadequate response* or a hypoactive state (McEwen, 1998a).

and those within normal ranges as "0", then summed into an AL index (0–10). The two exceptions were DHEA-S and HDL-cholesterol whereby the lower 25th percentile signified highest risk. Using this multi-systemic index that has subsequently incorporated variant biomarker inclusions (Figs. 4 and 5; Table 2) and alternative formulations (Table 3), numerous studies have assessed the relationship between antecedents of AL and the functional significance of high AL (Stewart, 2006).

Preliminary validation of the AL model has been based on the MacArthur cohort of nationally representative, high-functioning older adults (ages 70–79) who were followed longitudinally (Berkman et al., 1993). Cross-sectional analysis revealed that even within approximately a thousand American successful agers, higher AL was related to lower baseline functioning, poorer cognitive performance (composite of language, abstraction, spatial ability, delayed spatial recognition, incidental recall of confrontation naming items after 10 min delay, delayed story recall scores),

and weaker physical performance (timed measures of balance, gait, chair stands, foot taps, and manual ability; Seeman et al., 1997a). Over 3 years, those with higher AL showed significantly greater declines in cognitive and physical functioning and augmented risk of incident cardiovascular disease (CVD) independently of socio-demographics and baseline health status. Importantly, none of the individual biomarkers comprising the AL index significantly explained these tertiary outcomes, supporting the utility of a multi-systemic composite approach to predicting tertiary outcomes in geriatric populations. These results were further substantiated after a 7-year follow-up, whereby a threshold effect was revealed in those with the highest AL levels at greatest risk of cognitive and physical declines and risk of CVD. Most importantly, higher AL was related to increased risk of all-cause mortality (Seeman et al., 2001).

Breaking the AL index down into neuroendocrine biomarkers (stress hormones, DHEA-S) versus metabolic syndrome biomarkers

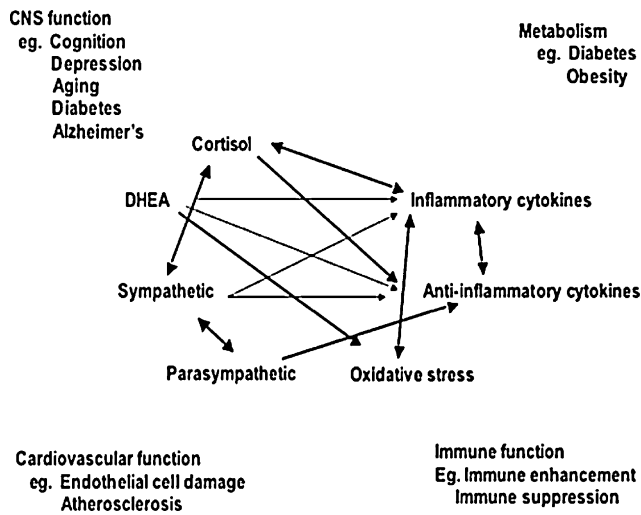


Fig. 3. Non-linear network of mediators of allostasis involved in the stress response. Arrows indicate that each system regulates the others, creating a non-linear network. Note that many body systems are influenced by the same mediator (McEwen, 2006b).

(blood pressure, lipid profiles, W/H-ratio) revealed that these clusters did not overlap, suggesting that each cluster might contribute independently to health risks. Specifically, metabolic syndrome biomarkers were largely responsible for the prediction of

incident CVD and surprisingly cognitive outcomes (Seeman et al., 2001), while both metabolic syndrome and neuroendocrine biomarkers accounted for mortality risk and only marginally to physical decline. These differential pathways provide mixed support for the inclusion of a comprehensive AL index instead of sub-categories of biomarkers. This being said, the AL index did predict mortality and physical functioning more uniformly than its clusters or constituents. Pathways leading to metabolic syndrome (obesity, hyperlipidemia, hypertension, insulin resistance) need to be distinguished from those related to AL and subsequent tertiary outcomes. Future studies will also need to decompose the temporal sequencing of neuroendocrine effects and interactions associated with metabolic syndrome aetiologies (van Dijk and Buwalda, 2008). In this endeavour, new lipidomic technologies (Oresic et al., 2008), models of glucose allostasis (Golay and Ybarra, 2005; Stumvoll and Bogardus, 2009; Stumvoll et al., 2003, 2004), and incorporation of biomarkers not currently included in metabolic syndrome nomenclature (i.e., leptin, cortisol; (Chrousos, 2000; Kahn et al., 2005; Maggio et al., 2006, 2007; Rosmond, 2005)) will be essential for research and clinical practice alike.

Using canonical correlations (Thompson, 1984) in a separate analysis, Karlamangla et al. (2002) found that primary mediators contribute independently to cardiovascular and metabolic risk factors in predicting cognitive and physical functioning declines. Specifically, epinephrine, W/H-ratio, and cortisol contributed most to higher AL prediction of physical declines, while DBP, epinephr-

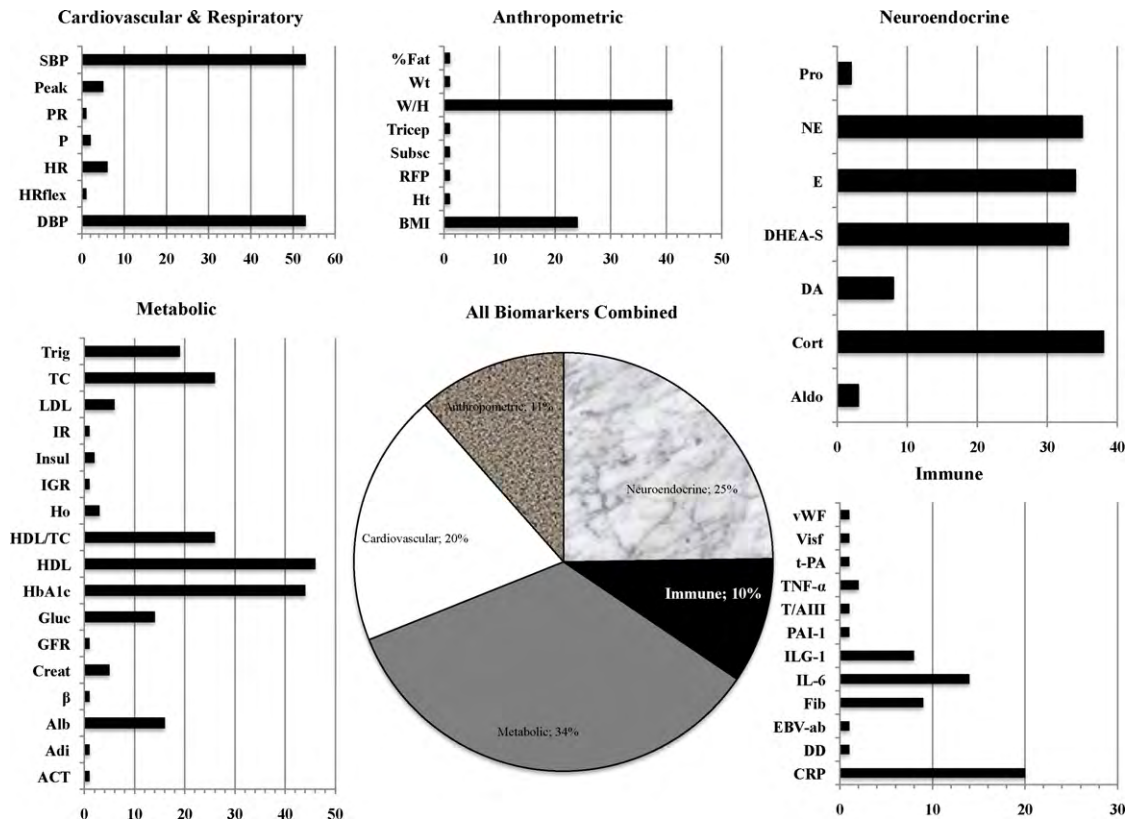


Fig. 4. Frequencies of biomarker inclusions for 58 allostatic load studies. The central pie chart illustrates the frequency for all neuroendocrine, immune (inflammatory and clotting factors), metabolic, cardiovascular/respiratory and anthropometric biomarkers combined. These are broken down into specific biomarkers for each classification in the five peripheral bar graphs where the x-axis represents frequency and the y-axis represents the biomarker abbreviations: ACT: alpha-1-antichymotrypsin, Adi: adiponectin, Alb: albumin, Aldo: aldosterone, β: beta cell functioning, BMI: body mass index, Cort: cortisol, Creat: creatinine, CRP: c-reactive protein, DA: dopamine, DD: d-dimer, DHEA-S: dehydroepiandrosterone-sulphate, DBP: diastolic blood pressure, E: epinephrine, EBV-ab: Epstein-Barr virus antibodies, Fib: fibrinogen, GFR: glomerular filtration rate, Gluc: glucose, HbA1c: glycosylated hemoglobin, HDL: high density lipoprotein cholesterol, HDL/TC: total cholesterol to HDL ratio, Ho: homocysteine, HR: heart rate, HRflex: cardiovascular physical fitness, Ht: height, IGR: insulin–glucose ratio, IL-6: interleukin-6, ILG-1: insulin-like growth, Insul: insulin, IR: insulin resistance, LDL: low density lipoprotein, NE: norepinephrine, P: pulse, PAI-1: plasminogen activator inhibitor 1 antigen, PR: pressor response, Pro: prolactin, Peak: peak expiratory flow, RFP: relative fat pattern index, SBP: systolic blood pressure, Subsc: subscapular skinfolds, T/AIII: thrombin/antithrombin III complex, TC: total cholesterol, TNF-α: tumor necrosis factor-alpha, t-PA: tissue-type plasminogen activator antigen, Tricep: triceps, Trig: triglycerides, Visf: visfatin, vWF: von Willebrand factor, W/H: waist-to-hip ratio, Wt: weight, %Fat: percent body fat.

Table 1
Allostatic load literature review.

Authors, year	Sample (nationality: type)	N	Age (mean \pm SD; range) \gg time	Sex (%)	AL #	Biomarkers	Covariates/adjustments	\uparrow AL main findings
Allsworth et al. (2005)	American: National Health and Nutrition Examination Survey	2470	23.6 (17–30)	100%	11	CRP, Alb, Peak, Creat-cl, Hb _{A1c} , HDL, TC, Trig, SBP, DBP, BMI	Race/ethnicity, age, marital status, education, poverty: income ratio, smoking history, depression	\downarrow Age of menarche
Bellingrath et al. (2009)	German: school teachers	104	45 (\pm 9.75)	100%	17	Cort, DHEA-S, E, NE, TNF- α , CRP, Fib, Gluc, Hb _{A1c} , HDL, HDL/TC, Trig, SBP, DBP, D-Dimer, %Fat, W/H	Age	\uparrow Effort/reward imbalance, \uparrow vital exhaustion, \uparrow emotional exhaustion
Clark et al. (2007)	Australian: new dementia-, veteran-, and non-caregivers	260	73.3 (\pm 7.4) \gg 2 years	66%	10	Cort, DHEA-S, E, NE, Hb _{A1c} , HDL, HDL/TC, SBP, DBP, W/H	None	\uparrow Perceived stress + dementia caregiver, relinquishing care
Crews (2007)	American: Samoans	273	55.5 (9.8; 35–88)	54%	14	Insul, Hb _{A1c} , Gluc, HDL, LDL, TC, Trig, SBP, DBP, W/H, BMI, RFP, Tricep, Subsc	None	Type II diabetes, \uparrow age + δ , \uparrow age + \uparrow
Crimmins et al. (2003)	American: National Health and Nutrition Examination Survey	22,815	20–90	?	13	CRP, Alb, Fib, Hb _{A1c} , Creat-cl, HDL, TC, Trig, SBP, DBP, Peak, Ho, BMI	None	\uparrow Age (20–60), \rightarrow age (60–90)
Crimmins et al. (2007)	American: National Health and Nutrition Examination Survey	4206	40+	?	10	CRP, Fib, Alb, Hb _{A1c} , HDL, TC, SBP, DBP, P, BMI	Age, sex, education, household income	African American, USA-born Mexican American
Crimmins et al. (2009)	American: National Health and Nutrition Examination Survey	14,912	45 (\pm 16.9; 20+) \gg 8 years	52%	9	CRP, Hb _{A1c} , Alb, HDL, TC, SBP, DBP, P, BMI	Smoking, drinking, exercise	\uparrow Mortality, \uparrow age + poverty
Dowd and Goldman (2006)	Taiwanese: Social Environment and Biomarkers of Aging Study	972	50–66	?	13	Cort, DHEA-S, E, NE, IL-6, Alb, ILG-1, Hb _{A1c} , HDL/TC, TC, SBP, DBP, W/H	Marital status, race/ethnicity, employment status, education, income	\neq Socioeconomic status
Evans (2003)	American: rural school children	339	9.2 (8–10)	49%	6	Cort, E, NE, SBP, DBP, BMI	Linear term (quadratic term)	\uparrow Cumulative risk factors
Evans et al. (2007)	American: rural middle-school children	207	13.37 (11–12) \gg 3–4 years	48%	6	Cort, E, NE, SBP, DBP, BMI	Baseline allostatic load score, sex	\uparrow Cumulative risk factors \times \downarrow maternal responsiveness
Evans and Schamberg (2009)	American: children \gg young adults	195	17.29 \gg 13 \gg 17	50%	6	Cort, E, NE, SBP, DBP, BMI	Childhood allostatic load score	\uparrow Poverty duration, \downarrow working memory
Fischer et al. (2009)	German: industrial workers	468	41.2 (18–61)	11%	9	DHEA-S, NE, CRP, HDL, LDL, DD, SBP, DBP, W/H	Age, sex	Smoking \times \uparrow AL (age 46+) = \downarrow progenitor cell counts
Geronimus et al. (2006)	American: National Health and Nutrition Examination Survey	6586	18–64	49%	10	CRP, Hb _{A1c} , Alb, Creat-cl, Ho, TC, SBP, DBP, BMI	Age, medication	\uparrow Age, \uparrow poverty, Black \uparrow
Gersten (2008a,b)	Taiwanese: Social Environment and Biomarkers of Aging Study	1021	68.3 (\pm 8.4; 54–90)	43%	4	Cort, DHEA-S, E, NE	Diet, exercise, smoking, medication	\neq Stressful life histories, \neq stress duration, \uparrow current stressful state, \uparrow age
Glei et al. (2007)	Taiwanese: Social Environment and Biomarkers of Aging Study	851	66.1 (\pm 7.8; 54–91) \gg 2–4 years	42%	16	Cort, DHEA-S, E, NE, DA, IL-6, ILG-1, Hb _{A1c} , Gluc, HDL/TC, TC, Trig, SBP, DBP, W/H, BMI	Age, sex, urban residence	\uparrow #Stressors, \downarrow locus of control, \uparrow perceived stress
Glover (2006)	American: mothers of cancer patients and controls	28	29–55	100%	10	Cort, DHEA-S, E, NE, Hb _{A1c} , HDL, TC, SBP, DBP, BMI	Age	\uparrow PTSD symptoms
Glover et al. (2008)	American: mother and primary caretakers of children with serious life-threatening illness	30	37.47 (\pm 7.2; 25–53)	100%	8	Cort, E, NE, DA, SBP, DBP, W/H, BMI	Age	\downarrow Right hippocampal volume
Goertzel et al. (2006)	American: Wichitan chronic fatigue syndrome patients and control	103	50.6 (\pm 8.7; 27–69)	82%	11	Cort, DHEA-S, E, NE, IL-6, CRP, Alb, Aldo, SBP, DBP, W/H	None	Chronic fatigue syndrome patients: \uparrow bodily pain, \downarrow physical functioning, \uparrow symptom severity, \neq fatigue ^b
Goldman et al. (2005)	Taiwanese: Social Environment and Biomarkers of Aging Study	989 (933)	68.2 (\pm 8.4; 54–91)	42%	16	Cort, DHEA-S, E, NE, DA, IL-6, ILG-1, Hb _{A1c} , Gluc, HDL/TC, TC, Trig, SBP, DBP, W/H, BMI	Age, sex	\uparrow Perceived stress, \uparrow cumulative perceived stress, \uparrow
Goodman et al. (2005)	American: 9th–12th grade students	758	16.2 (\pm 1.2; 13–19.4)	50%	9	Cort, Ins, Fib, Hb _{A1c} , Gluc, HDL, LDL, Trig, W/H	Age, sex, race/ethnicity, family structure (single vs. 2-parent home), household size, BMI	\downarrow Parent education, Caucasian, \neq sex, \neq age

Goldman et al. (2006a)	Taiwanese: Social Environment and Biomarkers of Aging Study	820	67.4 (± 8.1 ; 54–91) $\gg 3$ years	42%	16	Cort, DHEA-S, E, NE, DA, IL-6, ILG-1, Hb _{A1c} , Gluc, HDL/TC, TC, Trig, SBP, DBP, W/H, BMI	Age, sex, urban/rural, chronic conditions, mobility limitations, global self-rated health, depressive symptoms, cognitive function, pain, smoking status	Mortality, \uparrow mobility limitations, \uparrow cognitive declines, \uparrow depressive symptoms
Goldman et al. (2006b)	Taiwanese: Social Environment and Biomarkers of Aging Study	927	68.2 (± 8.4 ; 54–90) $\gg 3$ years	41%	13	Cort, DHEA-S, E, NE, DA, IL-6, ILG-1, Hb _{A1c} , HDL/TC, TC, SBP, DBP, BMI	Age, sex, urban/rural, chronic conditions, mobility limitations, global self-rated health, depressive symptoms, cognitive function, pain, smoking status	All-cause mortality
Gruenewald et al. (2006)	American: MacArthur Studies of Successful Aging	1189 (667)	70–79 $\gg 12$ years	51%	13	Cort, DHEA, E, NE, IL-6, CRP, Fib, Alb, Hb _{A1c} , HDL, HDL/TC, SBP, DBP	None	\uparrow Mortality ^c
Hasson et al. (2009)	Swedish: health care sector; IT/media sector	241; 98	46.5 (± 9.9); 41.2 (± 10.7)	100%	12	DHEA-S, Hb _{A1c} , Pro, TC, HDL, LDL, LDL/HDL, Trig, SBP, DBP, HR, W/H	Age	\downarrow Self-rated health, \downarrow education, \uparrow age, health care sector
Hellhammer et al. (2004)	German: young and elderly adults	76	25–40 and 60+ $\gg 1$ year	50%	8	DHEA-S, Fib, Hb _{A1c} , HDL, HDL/TC, SBP, DBP, W/H	None	\uparrow Age, \neq hypocortisolism, \neq stressful life events, \neq depression, \neq physical complaints
Hu et al. (2007)	Taiwanese: Social Environment and Biomarkers of Aging Study	1023	67.9 (± 8.5)	42%	10	Cort, DHEA-S, E, NE, Hb _{A1c} , HDL, HDL/TC, SBP, DBP, W/H	Age, sex, marital status, smoking, alcohol consumption	\downarrow Self-rated health, \uparrow physical activity difficulties, \downarrow education, \downarrow income, \uparrow age, no alcohol use, \neq Life career patterns, \neq occupational career patterns
Johansson et al. (2007)	Swedish: Individual Development and Adaptation program	639 (369)	43 $\gg 6$ years	100%	7	Hb _{A1c} , HDL, TC, SBP, DBP, W/H, Peak	None	\uparrow Physical functioning decline, \uparrow cognitive decline ^c
Karlamangla et al. (2002)	American: MacArthur Studies of Successful Aging	562 (251)	70–79 $\gg 7$ years	51%	10	Cort, DHEA-S, E, NE, Hb _{A1c} , HDL, HDL/TC, SBP, DBP, W/H	Baseline CVD, pulmonary peak, sex, race/ethnicity, age, years smoking, physical activity, alcohol, psychological symptoms	All-cause mortality ^a
Karlamangla et al. (2006)	American: MacArthur Studies of Successful Aging	729 (171)	70–79 $\gg 2.5$ and 4.5 years	56%	10	Cort, DHEA-S, E, NE, Hb _{A1c} , HDL, HDL/TC, SBP, DBP, W/H	Sex, ethnicity, age, smoking status, \neq chronic disease, prevalent CVD, prevalent cancer	\uparrow Career instability, \uparrow psychosomatic symptoms
Kinnunen et al. (2005)	Finnish: Jvaskylä Longitudinal Study of Personality and Social Development	117	41.7 (± 1.8)	47%	8	DHEA-S, NE, Hb _{A1c} , HDL, Trig, SBP, DBP, W/H	Sex, occupational status, binge drinking, smoking	\uparrow Hostility, \downarrow education
Kubzansky et al. (1999)	American: Normative Aging Study	818	60.8 (42–88)	0%	8	E, NE, Gluc, HDL, HDL/TC, SBP, DBP, W/H	Smoking, alcohol, physical activity, age	\neq Burnout, \uparrow age
Langelaan et al. (2007)	Dutch: telecom managers	290	43 (± 8)	0%	8	CRP, Hb _{A1c} , Gluc, HDL, TC, SBP, DBP, BMI	Smoking, physical activity	\downarrow Job control, \uparrow age, δ
Li et al. (2007)	Chinese: industrial workers	504	37.94 (± 9.47)	50%	11	Hb _{A1c} , IR, β , TC, HDL, LDL, Trig, Adi, Visf, W/H, BMI	Age, smoking, alcohol, physical exercise, marital status, education	\downarrow Meaningfulness, \downarrow sense of coherence, \uparrow clinical risk index
Lindfors et al. (2006)	Swedish: Individual Development and Adaptation program	200	43 $\gg 6$ years	100%	7	Hb _{A1c} , HDL, TC, SBP, DBP, W/H, Peak	Marital status, education, baseline sense of coherence, smoking	Chronic fatigue syndrome, \downarrow education
Maloney et al. (2006)	American: Wichitan chronic fatigue syndrome patients and control	103	50.6 (± 8.7 ; 27–69)	82%	11	Cort, DHEA-S, E, NE, IL-6, CRP, Alb, Aldo, SBP, DBP, W/H	Age, sex, education	\uparrow Chronic fatigue syndrome symptoms, \uparrow depression, \downarrow fatigue duration
Maloney et al. (2009)	American: Wichitan chronic fatigue syndrome patients and control	394	44.03 (± 9.9 ; 19–59)	78%	11	Cort AUC, CRP, Alb, Insul, Gluc, HDL, TC, SBP, DBP, HR, W/H	Age, sex, race/ethnicity, residential area (metropolitan, urban, rural), education, BMI	\uparrow Religious service attendance + \neq , \uparrow age, \neq subjective religiosity, \neq religious denomination
Maselko et al. (2007)	American: MacArthur Studies of Successful Aging	853	74.25 (± 2.72 ; 70–80)	54%	10	Cort, DHEA-S, E, NE, Hb _{A1c} , HDL, HDL/TC, SBP, DBP, W/H	Age, income, education, race/ethnicity, marital status, physical functioning, presence of CVD/diabetes/cancer	\downarrow Neighborhood SES, Black, urban Mexican American
Merkin et al. (2009)	American: National Health and Nutrition Examination Survey	13,199	20+	51%	9	CRP, Alb, Hb _{A1c} , HDL, TC, SBP, DBP, HR, W/H	Age, age ² , sex, U.S. birth, urban/rural, individual SES	Peripheral arterial disease, African American
Nelson et al. (2007)	American: National Health and Nutrition Examination Survey	5083	40+	49%	10	CRP, Alb, Hb _{A1c} , GFR, Ho, TC, Trig, SBP, DBP, BMI	Age, sex, race	

Table 1 (Continued)

Authors, year	Sample (nationality: type)	N	Age (mean ± SD; range) »time	Sex (♀%)	AL #	Biomarkers	Covariates/adjustments	↑AL main findings
Sabbah et al. (2008)	American: National Health and Nutrition Examination Survey	6847	17+	50%	7	CRP, Fib, Gluc, HDL, Trig, SBP+DBP, W/H	Education, poverty: income ratio, medical and dental insurance, sex, race/ethnicity, age, smoking	↑Ischemic heart disease, ↑periodontal disease
Schnorpfel et al. (2003)	German: industrial workers	324	40.6 (±9.3; 21–61)	16%	14	Cort, DHEA-S, E, NE, TNF-α, CRP, Alb., Hb _{A1c} , HDL, TC, SBP, DBP, W/H, BMI	Work conditions, sex, smoking, age bracket	↑Job demands x ↑age, ≠decision making, ≠social support
Seeman et al. (1997a,b)	American: MacArthur Studies of Successful Aging	904	70–79 »3 years	51%	10	Cort, DHEA-S, E, NE, Hb _{A1c} , HDL, HDL/TC, SBP, DBP, W/H	Age, sex, income, education, baseline health status, CDV status, physical activity	↓Functioning, ↓cognitive performance, ↓cognitive decline, ↓physical performance, ↓physical functioning decline, incident CVD events
Seeman et al. (2001)	American: MacArthur Studies of Successful Aging	1189 (720)	70–79 »7 years	51%	10	Cort, DHEA-S, E, NE, Hb _{A1c} , HDL, HDL/TC, SBP, DBP, W/H	Age, race, education, income, baseline CVD status, other health conditions	Mortality, incident CVD events, ↓physical functioning decline, ↑cognitive decline ^a
Seeman et al. (2002)	American: MacArthur Studies of Successful Aging; Wisconsin Longitudinal Study	1189; 106	74.2 (±2.8; 70–79); 58.5 (±0.8; 58–59)	51%; 46%	10	Cort, DHEA-S, E, NE, Hb _{A1c} , HDL, HDL/TC, SBP, DBP, W/H	None	↑Age, ↓parental care + negative social relationships + ♂, ↑criticisms/demands from spouse/children, ≠marital status
Seeman et al. (2004a)	Taiwanese: Social Environment and Biomarkers of Aging Study	950	69.2 (±4.5; 54–90) »11 years	41%	10	Cort, DHEA-S, E, NE, Hb _{A1c} , HDL, HDL/TC, SBP, DBP, W/H	Age, sex, SES, ethnicity (Fukien or Mainlander), health status, physical functioning, ill spouse	Absence of spouse + ♂, ↓social ties/support, ↓perceived quality of social environment, ↑age
Seeman et al. (2004b)	American: MacArthur Studies of Successful Aging	657	74.2 (±2.7; 70–79) »7.5 years	50%	16	Cort, DHEA-S, E, NE, IL-6, CRP, Fib, Alb, Creat-c, Hb _{A1c} , HDL, HDL/TC, SBP, DBP, Peak, W/H	Age, sex, race/ethnicity, baseline Dr. diagnosed morbidity	Mortality, ↓education
Seeman et al. (2008)	American: National Health and Nutrition Examination Survey	15,578	42 (20+)	51%	9	CRP, Alb, Hb _{A1c} , HDL, TC, SBP, DBP, HR, W/H	Age, smoking, physical activity	↓Education, ↓income, ≠ethnicity × education, ≠ethnicity × income
Seplaki et al. (2004)	Taiwanese: Social Environment and Biomarkers of Aging Study	980	68.8	41%	16	Cort, DHEA-S, E, NE, DA, IL-6, ILG-1, Hb _{A1c} , Gluc, HDL/TC, TC, Trig, SBP, DBP, W/H, BMI	Age, sex	Cognitive impairment, moderate depression, limited mobility, substantial impairment (mobility, cognition, and depressive problems) ^e
Seplaki et al. (2005)	Taiwanese: Social Environment and Biomarkers of Aging Study	958	67.7 (±8.43; 54–90)	42%	16	Cort, DHEA-S, E, NE, DA, IL-6, ILG-1, Hb _{A1c} , Gluc, HDL/TC, TC, Trig, SBP, DBP, W/H, BMI	Age, sex	↓Self-rated health, ↓activities of daily living, ↑mobility impairments, ↓cognitive performance, ↑depressive symptoms ^d
Seplaki et al. (2006)	Taiwanese: Social Environment and Biomarkers of Aging Study	972	67.7 (±8.3; 54–90)	41%	16	Cort, DHEA-S, E, NE, DA, IL-6, ILG-1, Hb _{A1c} , Gluc, HDL/TC, TC, Trig, SBP, DBP, W/H, BMI	Age, sex	↓Self-rated health, ↓activities of daily living, ↑mobility impairments, ↓cognitive performance, ↑depressive symptoms ^{a,d}
Singer and Ryff (1999)	American: Wisconsin Longitudinal Study	84	18 »59	46%	9	Cort, DHEA-S, E, NE, Hb _{A1c} , HDL/TC, SBP, DBP, W/H	None	↓Parental household income, ↓adult household income, ↑downward mobility, negative social relationships, childhood adversity + negative social relationships ^a
Smith et al. (2009)	American: Wichitan chronic fatigue syndrome patients	182	50.7 (26–69)	80%	11	Cort, DHEA-S, E, NE, IL-6, CRP, Alb, Aldo, SBP, DBP, W/H	Age, sex, BMI, fatigue status	↑#T alleles of the angiotensin-1 converting enzyme rs4968591, ↑age
Sun et al. (2007)	Chinese: industrial workers	1219	38.08 (±9.17; 23–58)	48%	13	Cort, E, CRP, Fib, IGR, Hb _{A1c} , HDL/TC, Trig, SBP, DBP, W/H, BMI	Age, sex, education, marital status, smoking, alcohol, physical exercise, type A personality	↓Decision latitude, ↑job demands, ↑age, ↓education, ↑type A personality

Author	Study	Sample Size	Age (Mean ± SD)	% Female	Variables	Outcomes
Szanton et al. (2009)	American: Women's Health and Aging Studies	728	74.2 (±0.1; 70–79)	100%	DHEA-S, IL-6, I-IGF, Hb _{A1c} , Creat-c, HDL/Tc, Trig, SBP, DBP, BMI	1 Frailty, ≠race, ≠education, ≠smoking
von Kanel et al. (2003)	American: Alzheimer caregivers	37	72 (±6)	70%	T/AIII, D-dimer, vWF, t-PA, PAI-1	1 Recent negative life events
von Thiele et al. (2006)	Swedish: public health care workers	241	45.8 (±9.75)	100%	DHEA-S, Hb _{A1c} , Gluc, Prol, TC, HDL, LDL, LDL/HDL, Trig, SBP, DBP, HR, W/H	1 Lack of recovery + fatigue, 1 age ^e
Weinstein et al. (2003)	Taiwanese: SEBAS; American: MacArthur	101; 827	72.6 (67–94); 74.2 (70–79)	47%; 51%	Cort, DHEA-S, E, NE, Hb _{A1c} , HDL, HDL/Tc, SBP, DBP, W/H	J Education, J occupational status, J finances, J demands, J widowed
Worthman and Panter-Brick (2008)	Nepalese: children (rural villager, urban-squatter, middle-class, homeless)	107	11.8 (±0.98; 10–14)	0%	Cort, Cort±, ACT, ABV-ab, PR, HRflex, Ht, Wt	Rural villager, ≠family composition

Biomarker abbreviations: ACT: alpha-antichymotrypsin, Adip: adiponectin, Alb: albumin, Aldo: aldosterone, β: beta cell functioning, BMI: body mass index, Cort: cortisol, Cort±: cortisol variability, CortΔ: cortisol area under the curve, Creat: creatinine, Creat-cl: creatinine clearance, CRP: c-reactive protein, DA: dopamine, DD: d-dimer, DHEA-S: dehydroepiandrosterone-sulphate, DBP: diastolic blood pressure, E: epinephrine, EBV-ab: Epstein-Barr virus antibodies, Fib: fibrinogen, GFR: glomerular filtration rate, Gluc: glucose, Hb_{A1c}: glycosylated hemoglobin, HDL: high density lipoprotein cholesterol, HDL/Tc: total cholesterol to HDL ratio, Ho: homocysteine, HR: heart rate, HRflex: cardiovascular physical fitness, Ht: height, IGR: insulin-glucose ratio, IL-6: interleukin-6, ILG-1: insulin-like growth, Insul: insulin, IR: insulin resistance, LDL: low density lipoprotein, NE: norepinephrine, P: pulse, PAI-1: plasminogen activator inhibitor 1 antigen, PR: pressor response, Pro: prolactin, Visf: visfatin, Peak: peak expiratory flow, RFP: relative fat pattern index, SBP: systolic blood pressure, Subsc: subscapular skinfolds, T/AIII: thrombin/antithrombin III complex, TC: total cholesterol, TNF-α: tumor necrosis factor-alpha, t-PA: tissue-type plasminogen activator antigen, Tric: triceps, Trig: triglycerides, vWF: von Willebrand factor, W/H: waist-to-hip ratio, Wt: weight, %Fat: percent body fat. AL main findings notations: 1: higher, J: lower, →: stable, ≠: not related, +: in addition to, ×: interaction, ♂: male, ♀: female.

^a Canonical correlation.
^b Genetic programming based symbolic regression algorithms.
^c Recursive partitioning techniques.
^d Group of membership.
^e k-Means cluster analysis.

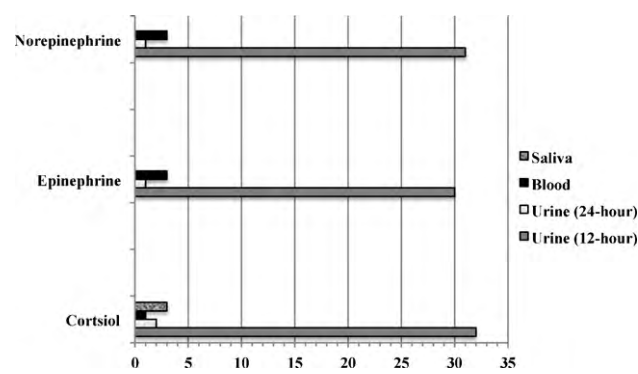


Fig. 5. Break down of stress hormone inclusions according to collection methods.

ine, and Hb_{A1c} contributed most to cognitive declines (Karlman et al., 2002). This later result extends previous work using this cohort that showed increasing cortisol levels in women to memory impairments (Seeman et al., 1997b) and increasing epinephrine levels in men to cognitive declines (Karlman et al., 2005). Moreover, these studies highlight the advantage of incorporating multi-systemic biomarkers, although specific clusters do seem to predict tertiary outcomes differentially.

In this vein, recursive partitioning techniques (Breiman et al., 1984; Zhang and Singer, 1999) have been employed to tease apart biomarker combinations demarcating 12-year mortality risk between the sexes. High risk pathways of biomarker clustering for men included epinephrine, norepinephrine, interleukin-6, CRP, and fibrinogen, while for women included IL-6, CRP, Hb_{A1c}, and SBP (Gruenewald et al., 2006). Interestingly, elevated SBP occurred in 100% of female high risk pathways but only 17% for male high risk pathways principally dominated by elevated fibrinogen, norepinephrine, and epinephrine levels otherwise completely absent for females. Such “biological signatures” demonstrate that there are multiple sex-specific routes whereby exacerbated biomarkers lead to AL and mortality risk. In an earlier analysis, however, cardiovascular biomarkers were more often dysregulated for males, while neuroendocrine biomarkers were more often dysregulated for females (Seeman et al., 2002). These findings from the same cohort measured at different time-points reveals that AL pathways indeed differ between the sexes, although sex-specific biomarker clusters depend on age.

Cross-culturally complementing the MacArthur mortality findings in a Taiwanese cohort, Goldman et al. (2006b) showed that 3-year mortality risk was largely attributable to the neuroendocrinological primary mediators, but not as strongly to the standard clinical markers of cardiovascular and metabolic systems. Specific risk factors included high Hb_{A1c} and IL-6, while both high and low values for body mass index (BMI), DBP, and epinephrine. Primary mediators did not, however, exert direct effects on secondary outcome biomarkers as theorized in the AL model (Goldman et al., 2006b). The authors state that while neuroendocrine and immune biomarkers are important predictors of future survival, little is known concerning their normal or pathological levels and processes as one ages, their different causal weight and time-courses relative to other biomarkers of health, and how practitioners can modify their functioning.

The utility of assessing multiple biomarkers, particularly primary mediators, does appear to be a powerful and practical way of improving biomedical detection strategies and eventually implementing earlier interventions to promote longevity and improved quality of life (McEwen, 2003b). In the first study assessing unaccountable changes in AL levels over 2.5- and 4.5-year risks of all-cause mortality, being older and/or a male related to higher baseline AL. Perhaps most encouragingly upon follow-up

Table 2

Example of biomarkers repeatedly used in allostatic load studies with a brief overview of their functions.

Type	Biomarker	Function
NEUROENDOCRINE	Cortisol	Glucocorticoid produced by the adrenal glands. Functions include the conversion of stored fats and proteins into carbohydrates, anti-inflammatory and immuno-suppressive effects, increased blood pressure and heart rate, suppression of digestive, growth, and reproductive activities, and modulation of limbic and prefrontal regions upon traversing the blood–brain barrier.
	Dehydroepiandrosterone	Androgen produced by the adrenal glands. Known functions include its role as a HPA-axis antagonist and its ability to convert into androgens and estrogens. It also suppresses inflammatory cytokines, improves lipid metabolism and lean muscle mass, decreases insulin resistance, and reduces oxidative brain damage.
	Epinephrine	Catecholamine produced by the adrenal glands and the brain. As part of the “fight-or-flight” response, it increases heart rate and glucose levels while decreases digestive and immune functions.
	Norepinephrine	Catecholamine produced by the brain. As part of the “fight-or-flight” response, it increases blood pressure, constricts blood vessels, and modulates brain activities.
	Dopamine	Catecholamine produced primarily in the brain and adrenal glands. It is a well-characterized neurotransmitter involved in many neurological activities (motivation, voluntary movement, cognition) and also increases blood pressure and heart rate.
	Aldosterone	Minerocorticoid produced by the adrenal glands. Functions by reabsorbing sodium, retaining water, and excreting potassium in the kidneys in order to maintain blood acidity, as well as to decrease blood volume and blood pressure.
IMMUNE	Interleukin-6	Cytokine produced by macrophages and T-cells. Functions in pro-inflammation and anti-inflammation by stimulating B cell and T cell differentiation that assist acute phase reactions to tissue damage.
	Tumor necrosis factor-alpha	Cytokine produced by macrophages. Functions in systemic inflammation by evoking mediators of acute phase reactions as well as in tumor apoptosis.
	C-reactive protein	Protein synthesized in the liver. Functions by enhancing phagocytosis during acute phase reactions that promote inflammation.
	Insulin-like growth factor-1	Polypeptide protein hormone produced primarily in the liver and pancreas. Functions as a stimulator of cell growth and as an inhibitor of cellular apoptosis.
	Fibrinogen	Protein that synthesizes into fibrin in the liver. Upon synthesis, functions as a blood clotting factor that promotes coagulation but when excessive increases risk of thrombosis.
METABOLIC	High density lipoprotein cholesterol	Lipoprotein synthesized in the liver. Transports cholesterol from tissues to the liver. Commonly referred to as “good cholesterol”, as its high protein/low cholesterol form is more easily removed by blood in the liver and excreted in bile.
	Low density lipoprotein cholesterol	Lipoprotein synthesized in the liver. Transports cholesterol to tissues that synthesize cell membranes and secretions. Commonly referred to as “bad cholesterol”, as its low protein/high cholesterol form is more likely to be deposited in the walls of blood vessels and contribute to atherosclerosis.
	Triglycerides	Glyceride formed from glycerol and three chains of fatty acids. Functions as an important source of energy and as a transporter of dietary fat.
	Glycosylated hemoglobin	Hemoglobin used to index the average glucose concentration over many days, weeks and even months. This proportion represents the amount of glucose that the analyzed hemoglobin has been exposed to during its cell cycle.
	Glucose	Monosaccharide synthesized in the liver and kidneys. Functions as our main source of energy.
	Insulin	Protein hormone produced in the pancreas. Functions by lowering glucose levels and promoting energy storage in the form of glycogen.
	Albumin	Protein produced by the liver. Functions in the maintenance of blood volume regulation and as carrier for molecules of low water solubility.
	Creatinine	Nitrogenous waste product of muscle creatine phosphate that is filtered and excreted by the liver. Creatinine clearance is a marker of glomerular filtration rate representing renal functioning.
CARDIOVASCULAR AND RESPIRATORY	Systolic blood pressure	Measured using a sphygmomanometer. Represents the maximal force exerted by blood against the blood vessel walls when the left ventricle is contracting during systole.
	Diastolic blood pressure	Measured using a sphygmomanometer. Represents the minimal force exerted by blood against the blood vessel walls when the left ventricle is relaxed during diastole.
	Peak expiratory flow	Measured using a peak flow meter. Represents the maximum speed of expiration and the degree of obstruction of airflow through the bronchi.
	Heart rate/pulse	Measured at sites where arterial pulsation can be felt. Represents the number of palpations made by the heart within a period of time.
	ANTHROPOMETRIC	Waist-to-hip ratio
Body mass index		Measure of weight and height that is then calculated into an index by dividing weight by height ² . Represents a proxy measure of an individual's relative body fat percentage ranging from severely underweight, underweight, normal, overweight, to three different classifications of obesity.

was that regardless of sex, decreases in AL were significantly related to reductions in the risk of dying (Karlman et al., 2006). These findings strongly suggest that even in older age, longer lifespans can be attained when physiological dysregulations are diminished. If higher AL is associated with tertiary outcomes like mortality, CVD events, cognitive impairments, physical difficulties, and even frailty (Szanton et al., 2009) over and beyond traditional

clinical biomarkers, it follows that identifying and addressing their antecedents can carry important biomedical implications.

Psychosocial factors contribute to differentials in AL levels between societies and sexes. By combining the MacArthur cohort and those from the Wisconsin Longitudinal Study (WLS), retrospectively reported positive parental bonding and harmonious later life relationships was related to lower AL in men, who

Table 3

Description of existing allostatic load algorithmic formulations and statistical techniques.

Formulation	Description
Group allostatic load index	Summary measure representing the number of biomarkers falling within a high risk percentile (i.e., upper or lower 25th percentile) based on the sample's distribution of biomarker values. Because each biomarker is dichotomized as 0 or 1 depending on cut-offs, each biomarker is allotted an equal weight in the index. This is the traditional count-based formulation used most often.
Norm allostatic load index	Summary measure representing the number of biomarkers falling within a high risk percentile (i.e., upper or lower 25th percentile) based on a population's distribution of normative biomarker values used in clinical practice. This count-based formulation is pending established biomarker norms and therefore not yet used in the reviewed studies.
z-Score allostatic load index	Summary measure representing the sum of an individual's obtained z-scores for each biomarker based on the sample's distribution of biomarker values. This standardized formulation allows the weight of each biomarker to be different depending on its deviation from the sample's mean.
Difference allostatic load score	Difference between two time-points for a single biomarker or an index measure of multiple biomarkers. For example, an index measure of pro-coagulation responses using several hemostatic biomarkers or two measures of cortisol before and after exposure to an acute stressor.
Dynamic allostatic load score	Repeated measures analysis or change scores between three or more time-points for single or multiple biomarkers. For example, diurnal measures of cortisol at different times of the day or an area under the curve calculation that encompasses variability in cardiovascular functioning over time.
Nominal allostatic load grouping	Dividing participants into groups based on an allostatic load index threshold (e.g., ≤ 3 or ≥ 4). The threshold cut-point can be based on previous studies with similar number of biomarkers or arbitrarily based on the sample's distribution.
Bootstrapping	Resampling technique used to make inferences about population parameters by generating multiple repetitive computations that estimate the shape of a statistic's sampling distribution (Mooney and Duval, 1993). The obtained bootstrap statistic can then be used as weights for allostatic load biomarkers and/or indices in subsequent analyses.
Canonical correlation	Multiple correlational analysis that measures the association between two sets of latent variables representing an independent set and a dependent set (Thompson, 1984). It has been used to determine the best linear combinations of weighted allostatic load biomarkers at baseline that are maximally correlated to tertiary outcomes like mortality at follow-up.
Recursive partitioning	Multivariate reduction technique that generates categories aimed at precisely classifying participants based on several dichotomous dependent variables (Breiman et al., 1984; Zhang and Singer, 1999). It has been used to classify participants into outcome risk categories by first identifying the biological markers and cut-points that best differentiate across participants. These have been used to define allostatic load categories (e.g., high, intermediate, low) and tertiary outcomes (e.g., mortality).
Grade of membership	Multivariate reduction technique that identifies heterogeneous groups of combinations and their value zones that is then used to estimate whether a participant matches a defined combination, as well as the degree of their membership into one of these combinations (Manton et al., 1994). A set of individualized weights is then used to compare participants against certain pre-defined profiles (e.g., low neuroendocrine and high metabolic combinations versus high neuroendocrine and high cardiovascular, etc.).
k-Means cluster analysis	Multivariate reduction technique that identifies homogeneous groups of cases that are then sorted into one of any specified number of clusters (Aldenderfer and Blashfield, 1991). Once sorted using a nearest centroid algorithm, these clusters serve as groups (e.g., recovered, non-recovered, and fatigued) that can then compared in terms of allostatic load levels.
Genetic programming based symbolic regression algorithms	Regression and classification technique involving an evolutionary computer simulation that processes programs built from specified primitives (logical or arithmetic operators such as "+, -, *, /") that are a good fit to a given dataset (Koza, 1998; Goertzel et al., 2006). This is a computer intensive approach ultimately used to understand the dependency of one variable on several others (e.g., allostatic load biomarkers and chronic fatigue syndrome symptoms).

benefited most from emotional support (Seeman et al., 2002). Conversely, women, but not men, who regularly attend religious services displayed lower AL levels (lower epinephrine and W/H) independently of social network characteristics or subjective religiosity (Maselko et al., 2007). Greater sense of coherence and meaningfulness in life has also been related to lower AL in a 6-year study of middle-aged female Swedes (Lindfors et al., 2006). These studies represent the positive impact that emotional, spiritual, and personal resources can have on health, well-being, and moreover resilience to stress and AL that touch societies worldwide.

The investigation of sociological dimensions in relation to traditional and alternative AL formulations have been cross-culturally corroborated in a study of near elderly (ages 54–70) and elderly (ages 71+) Taiwanese who participated in the Social Environmental and Biomarkers of Aging Study (SEBAS). In line with the results of Seeman et al. (2002), lower AL was associated with the presence of a spouse in near elderly men, but not women, while social ties with close friends and/or neighbors was protective for the elderly irrespective of sex (Seeman et al., 2004a). Using the SEBAS in a separate study, 3-year mortality risk, mobility limitations, cognitive declines, and depressive symptoms were partially predictive of higher AL; however, these outcomes were driven differentially by traditional clinical risk factors, neuroendocrine mediators, and attenuated by health controls (Goldman et al., 2006a). In similar studies, Seplaki and collaborators contributed several important methodological analyses using grade of membership techniques (Manton et al., 1994) and alternative AL indices using again the SEBAS cohort. They showed that higher AL was related to poorer health status (self-rated health, activities of daily living, mobility, temporal orientation),

depressive symptoms, and cognitive impairments (Seplaki et al., 2004, 2005, 2006). These results are largely contingent on the AL index formulation used (e.g., 2-tailed versus traditional 1-tailed, 10th and 90th versus 25th and 75th percentiles). Each formulation yields comparable results, although there are small but modest predictive differences based on the biomarkers and outcomes used. For instance, the 2-tailed formulations (high and low biomarker distributions) need to be more restrictive than the traditional 1-tailed quartile cut-points, although they might in turn have a less sensitive threshold and therefore limited ability to be used as an early warning signal of health and functional declines (Seplaki et al., 2004).

Future studies could perhaps employ AL permutations with the SEBAS and other cohorts in conjunction to *life histories* (Ryff and Singer, 2000), that is, pathways among socioeconomic mobility and social relationships at different time-points used to delineate potential interactions with impending tertiary outcomes. To illustrate, Singer and Ryff (1999) have applied such pathways and demonstrated that childhood parental bonding and household income category correspond to higher AL. Contrasting these with adult finances and relations revealed that increased downward mobility related to increased AL, as did low parental income coupled with negative social relationships (Singer and Ryff, 1999). Lifecourse changes in one's social position and the quality of social networks can therefore be used to map gradients in disease risk.

Teasing apart socio-demographic effects has demonstrated that education and poverty interact strongly with AL and associated outcomes. Previous reports of greater 7-year mortality risk in the MacArthur study of successful agers from diverse socioeconomic strata, for example, were strongly effected by the interplay

between high AL and lower education (Seeman et al., 2004b). In the SEBAS cohort, Hu and colleagues showed that higher AL as well as lower education and income were independently associated with poorer self-rated health, more difficulties in instrumental activities of daily living, and less physical activity. While bivariate analyses revealed that high AL related to older age, female sex, less education, lower income, less alcohol use, and poorer health status, the associations between education, income, and health status was not significantly mediated by the conventional AL index (Hu et al., 2007). Likewise, another study found socioeconomic status (SES) not to be mediated by AL nor cortisol (Dowd and Goldman, 2006; for a review, see Dowd et al., 2009). Conversely, combining the SEBAS and MacArthur cohorts revealed that lower SES (lower education, occupational status, finances) and greater social challenges (recent widowhood, high demands) related to higher AL (Weinstein et al., 2003). In the Normative Aging Study, lower education also related to higher AL, but was mediated by hostile personality traits that maintained an independent effect on AL (Kubzansky et al., 1999). Collectively, these studies highlight the need for more longitudinal analyses that are sensitive to the interplay between AL, SES, and even personality traits in forecasting ensuing diseases.

The large-scale American National Health and Nutrition Examination Survey (NHANES) revealed that AL attenuates the effects of education and income gradients in the prediction of ischemic heart disease and periodontal disease (Sabbah et al., 2008). Tracking about fifteen thousand participants from the same cohort over 6 years, Crimmins et al. (2009) demonstrated that those living in poverty show sharper increases in AL until middle age and then plateau around ages 70 and above. Older poor individuals with higher AL are at the greatest risk of mortality, while age attenuates the effect of poverty. Strikingly, those with high AL have a life expectancy that is 6 years shorter than those at low biological risk with similar poverty status and matched for sex (Crimmins et al., 2009).

Results of this degree represent the very real consequences of higher AL on public health, an effect that sadly transcends SES strata and infringes upon race/ethnic health disparities. For instance, African Americans with peripheral arterial disease in the NHANES have the highest AL levels (higher SBP, CRP, and homocysteine and lower glomerular filtration rates) even after controlling for age, sex, and race (Nelson et al., 2007). African American women show the most consistently elevated levels of AL across age groups, a finding supporting the “weathering hypothesis”, stating that non-Caucasian women’s health deteriorates in early adulthood as the physical consequences of cumulative SES disadvantage contributes to inter-generational reproductive complications (Geronimus et al., 2006). Substantively, poor Caucasians were less likely than non-poor African Americans to have higher AL. For individuals of lower neighborhood SES in the NHANES cohort, the risk of having higher AL is 200% for African Americans, 70% for urban Mexican Americans, and 30% for Caucasians, suggesting that neighborhoods are more deprived for non-Caucasians (Merkin et al., 2009). Similarly, USA-born Mexican Americans and African American also show higher levels of AL than foreign-born Hispanics and Caucasians. Concerning biomarker clusters, African Americans and Caucasians showed the strongest gradients in cardiovascular and metabolic pathways, while inflammatory risk factors predominated Mexican Americans (Seeman et al., 2008). Regardless of ethnic stratifications, however, lower education and income related to higher AL. Higher AL has also been found in older female American Samoans at the highest risk of diabetes, yet age was negatively related to AL in men (Crews, 2007). These studies demonstrate that lower SES incurs greater risk of increased AL (see review Szanton et al., 2005), concomitant to important race/ethnic inequalities that must be addressed in the evolution of public policies.

Regardless of one’s SES and consistent with AL theory, stressful circumstances have been reported in relation to physiological dysregulations and psychopathological sequelae. Using the SEBAS cohort, concurrent and cumulative perceived stress-related to increased AL (high and low DHEA-S, glucose, and IL-6 levels) most strongly in women (Goldman et al., 2005). Another analysis of stressful life histories (e.g., marital status, group participation, co-residence with married son) found no association with neuroendocrine AL parameters and, yet, current perceived stress was again found in women (Gersten, 2008a). This finding conflicts with AL theory stipulating that chronic stress is at the core of physiological dysregulations, but the findings may be due to limitations in the assessment of stress (Gersten, 2008b; Loucks et al., 2005) and cultural nuances (McDade, 2008). In a more comprehensive SEBAS analysis over 2–4 years, the combination of low locus of control, social networking, and social position rendered individuals more vulnerable to perceive and physiologically respond to stressors adversely, although the statistical magnitude was weak (Glei et al., 2007).

Subjective perceived stress, as opposed to objective environmental stress, was correlated to higher AL primary mediators in veteran dementia caregivers from Australia over 2 years when contrasted to new and non-caregivers (Clark et al., 2007). On the other hand, a greater number of negative life events and difficulties related to higher AL based on z-score composites of pro-coagulation dynamics before and after a 15-min speech stress task in Alzheimer’s caregivers (von Kanel et al., 2003). The inherently stressful nature of being a caregiver has also been tested in mothers of children with cancer and controls, revealing that increased AL (higher norepinephrine, BMI, and lower cortisol) is associated with intensified post-traumatic stress disorder symptoms in a dose response pattern (Glover, 2006). In a related study of thirty mothers of children with serious life-threatening diseases, Glover et al. (2008) demonstrated that higher AL was related to the number of months since the onset of the child’s disease and to significantly smaller right hippocampal volumes most prominent in PTSD symptomatic mothers (Glover et al., 2008). These pioneering studies utilized both high and low ends of cortisol variation since hypocortisolism can characterize certain syndromes and diseases (Fries et al., 2005). Along with studies by Gianaros et al. (2007) on chronic life stress and, as summarized by Sheline (2003) for mood disorders the hippocampus is a sensitive bellweather of delayed effects of chronic stress in both normal and depressed individuals.

Likewise, in a study of young and older hypocortisolemic or control adults (dichotomized according to diurnal and dexamethasone suppressed cortisol variations, psychometrics of pain, fatigue, and perceived stress), no significant group differences in relation to increased AL were found except for older age (Hellhammer et al., 2004). In several studies of chronic fatigue syndrome (CFS) patients, those with higher AL had worse health (pain, physical functioning, symptom severity, but not fatigue; Goertzel et al., 2006) and lower education (Maloney et al., 2006). The risk of developing CFS was recently shown to be three times higher in those with higher AL, which was also related to greater depressive symptoms and perplexingly shorter duration of fatigue (Maloney et al., 2009). In the first genetics study of AL, 32 candidate genes (HPA-axis, neurotransmission, immune, and metabolic systems) were assessed in 182 CFS patients, revealing that the T allele of the ACE rs4968591 gene related to higher AL (higher IL-6, CRP, and lower cortisol in women) independent of age, sex, BMI, and fatigue status (Smith et al., 2009). The relationship between this angiotensin-1 converting enzyme polymorphism and dysregulations of neuroendocrine and immune biomarkers represents a diathesis-stress effect consistent with the AL framework.

Future investigations of genetic mechanisms contributing to AL would strengthen understanding of mind–body interactions with respect to multi-systemic disease aetiologies (Epel, 2009). Furthermore, theoretical literature linking AL composites to psychopathologies like mood disorders (Kapczinski et al., 2008; McEwen, 2003c, 2004, 2005), anxiety disorders (McEwen, 2002; Schulkin et al., 1994, 1998), and substance-abuse (Koob, 2003; Koob et al., 2004; Koob and Le Moal, 2001; Schulkin, 2003a; Valdez and Koob, 2004; Zimmermann et al., 2007) have been matched by only a paucity of empirical evidence in humans, thus representing another avenue of inquiry. In sum, the aforementioned studies support the AL model vis-à-vis numerous tertiary outcomes in middle- and old-age, although they represent pathophysiological manifestations rooted in mal-adaptation to stressors from past experiences.

4.2. Working adults

Chronic stress is the most common explanation for how adverse work environments contribute to disease trajectories (Taylor et al., 1997). The first study of AL in the workplace found that older male German industrial workers (ages 21 and 61) with higher job demands had higher AL (higher SBP, DBP, CRP; Schnorpfeil et al., 2003). A subsequent study found smoking by AL and smoking by effort–reward imbalance (Siegrist et al., 2004) interaction effects in the prediction of lower bone-marrow derived progenitor cells (Fischer et al., 2009). The ground-breaking observation that smoking (which was more common in lower SES workers) interacts with greater work stress or AL strongly supports the notion that synergistic behavioural and psychosocial risk factors exhaust progenitor cells and therefore weaken vascular integrity. For Chinese industrial workers, dysregulated glyco-lipid parameters of the AL index related to increased age, being male, and lower job control (Li et al., 2007). Likewise, increased age, lower education, lower decision latitudes, higher job demands and type A personality traits related to higher AL in a larger sample (Sun et al., 2007). Using *k*-means cluster analysis (Aldenderfer and Blashfield, 1991), it was found that increased age, fatigue, and lack of recovery related to higher AL in female Swedish public health care workers (von Thiele et al., 2006). In a study of Dutch telecom managers, no significant associations to burnout (emotional exhaustion, depersonalization/cynicism, professional efficacy; Maslach and Jackson, 1981) were established with AL; however, the authors contend that participants may have been too young to detect physiological dysregulations (Langelaan et al., 2007) and none of the primary mediators were included in the AL indices. Yet, a more recent study of German female school teachers of the same age (mean 45) revealed that greater effort–reward imbalance, vital exhaustion, and burnout as measured with emotional exhaustion corresponded to slightly higher AL levels (Bellingrath et al., 2009). In an even younger Finnish sample, greater career instability between the ages of 27 and 36 increased the risk of higher AL at age 42 threefold with concurrently increased frequencies of psychosomatic symptoms (Kinnunen et al., 2005). By contrast, no associations were found among AL and life/occupational career patterns, family-to-work conflict, optimism, and well-being measured 6 years afterwards in a sample of female Swedes (Johansson et al., 2007).

These authors state that their findings collectively suggest that the Swedish welfare state's improved work–family options promote improved health in women as evidenced by their low AL. Such proposals demonstrate the implications AL research can have in assessing the effects of public policies and workplace conditions (Behrman and Juster, in preparation). For example, female Swedes working in the health care system (compared to information technologies/media), who were characterized by

increased age, lower education, and poorer self-rated health, had higher AL (Hasson et al., 2009). As working conditions exert a strong effect on SES gradients in health and differentials between sectors (e.g., manual work and musculoskeletal disorders; Lundberg, 1999), decomposing the specific physical and psychological factors that mediate and/or moderate impending diseases is imperative.

It is also important to recognize that the effects of job insecurities and adverse working conditions may not surface until much later on in life, a reality that will soon strain society further as populations worldwide retire and age (Fischer and Thayer, 2006). Regarding shifts in increasingly older American adults, a descriptive study of more than twenty-two thousand NHANES participants found that AL steadily increases with age up through the 20s–60s and then plateaus throughout the 60s–90s during the period of greatest mortality risk (Crimmins et al., 2003). This age trajectory suggests that there is, at the very least, a 40 year “window of opportunity” to intervene in escalating AL levels that stabilize around the age of retirement. This being said, allostatic load develops even earlier than adulthood.

4.3. Children and adolescents

Several studies have demonstrated that AL can be detected in disadvantaged youths. The work of Gary Evans' group has linked higher AL to greater cumulative risk factors (crowding, noise, housing problems, family separation/turmoil, violence, income-to-needs ratio, single parent, maternal high school dropout) at age 9 (Evans, 2003), and to the interaction between such adversities and low maternal responsiveness at age 13 (Evans et al., 2007). More recently, longer poverty duration has been linked to working memory impairments at age 17 (Evans and Schamberg, 2009). Similarly, lower parental education increased AL in 9th–12th grade adolescents (Goodman et al., 2005). A field study of Nepalese found that homeless and rural villagers were more susceptible to increased AL levels compared to urban squatters and middle-class 10–14 year olds (Worthman and Panter-Brick, 2008).

SES gradients such as these can carry life-long behavioral and health consequences (McEwen, 2003a). For instance, earlier age of menarche, which differs among race/ethnic/SES strata and increases the risk of future health problems, was associated with an over twofold risk of increased AL in young adult women (Allsworth et al., 2005). Accumulated damage over time and/or the biological embedding of adversities during sensitive developmental periods are nevertheless experienced and manifested in heterogeneous ways, such that the physiological expression of the stress response system to stressors is processed differently as either positive, tolerable, or toxic stress (Shonkoff et al., 2009). The aforementioned findings and frameworks strongly advocate that disease trajectories start early and carry forth until death unless addressed by harnessing factors that foster resiliency.

5. Conclusion

Decomposing which protective factors render individuals resilient to age-related health and cognitive declines depends on our conceptual definitions of successful aging and appreciation of individual differences (Lupien and Wan, 2004). Rather than being the absence of pathology or deceleration of senescence, resilience is a state of adaptation to a lifetime of stress and strain. Evidence from AL studies have clearly demonstrated that mal-adapting to stressful environments has serious consequences, yet more importantly have also shed light on the specific protective and risk factors involved. While AL does appear to increase as one ages and differs by sex (McEwen, 2000c), we can additionally proclaim associations throughout lifespan development that

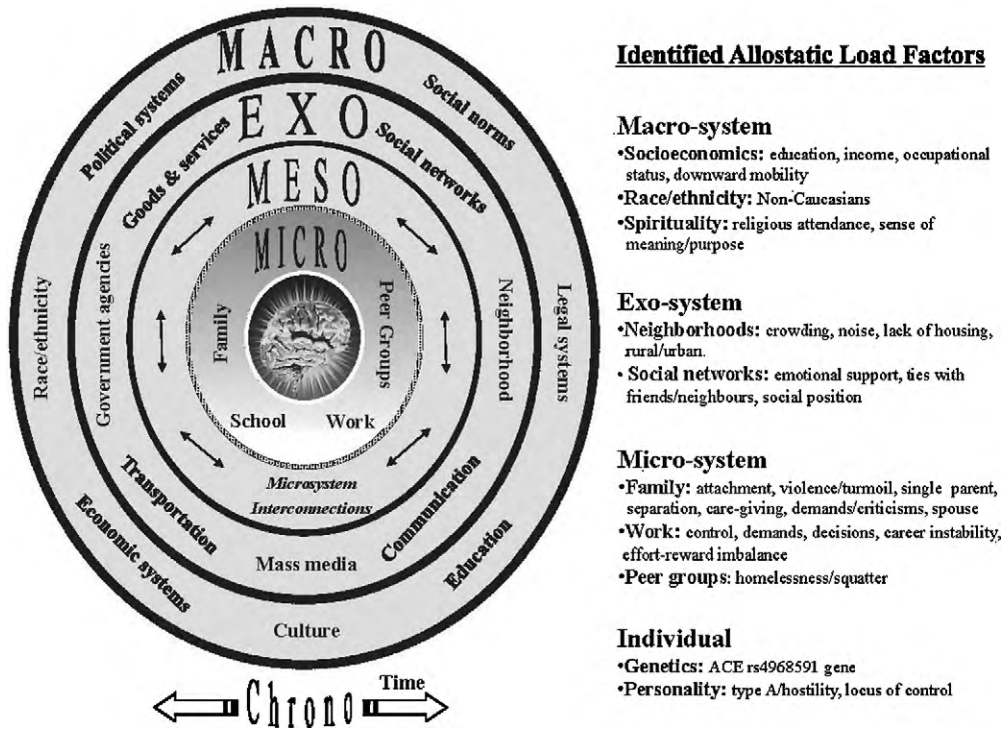


Fig. 6. An ecological systems model of identified allostatic load antecedents. The central propositions of Bronfenbrenner's general ecological model is that individuals are developmentally shaped by complex reciprocally interacting systems. These interdependent forces consist of the individual's immediate environment (micro-system), the interconnections among several individuals (meso-systems), the indirect influence of social structures and settings (exo-system), and finally the current overarching cultural and sub-cultural patterns (macro-system) over time (chrono-system). Examples are provided in the diagram to the left, with parallel risk and protective factors identified in relation to allostatic load listed on the right. Adapted from (Bronfenbrenner, 1977, 1994, 1995).

include SES, social/relationship, workplace, lifestyle, race/ethnic, and genetic factors (Fig. 6). Specific protective factors (e.g. parental bonding, education, social support, healthy workplaces, sense of meaning, etc.) are available or manifest at different time-points throughout lifespan development, and yet they each have the capacity to promote life-long resiliency against AL. Targeting the antecedents of AL at critical periods and implementing programs that cultivate resiliency is therefore essential to improving public health.

The next stage in AL research could be to assess the efficacy of interventions in reducing AL with these factors in mind. At an individual level, programs that encourage improved sleep quality/quantity, social support, sense of purpose, self-esteem, healthy diet, substance avoidance, and physical activity, while those at a social level might include policies that create incentives for beneficial practices in the workplace, cleaner and safer neighborhoods, and the motivation towards higher education are but a few examples of life-long benefits that could improve mental and physical health (McEwen, 2008). Specifically for the elderly, well-being therapy emphasizing autonomy, purpose in life, personal growth, positive relations with others, environmental mastery, and self-acceptance could be applied (Singer et al., 2005) and cognitive interventions could focus on physical and social activities (Elias and Wagster, 2007). These person-centered approaches to diminishing AL communally represent a move away from polypharmaceutical panaceas that currently plague biomedical treatment strategies.

In conclusion, the AL model has received compelling empirical support in its ability to predict a plethora of health outcomes using a multi-systemic approach, while it also conceptually extends multidisciplinary literatures on stress, SES, and successful aging that collectively carry important public policy and biomedical implications.

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