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A Systematic Review of Allostatic Load, Health, and Health Disparities

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Abstract

The theoretical constructs of allostasis and allostatic load (AL) have contributed to our understanding of how constantly changing social and environmental factors impact physiological functioning and shape health and aging disparities, particularly along socioeconomic, gendered, racial, and ethnic lines. AL represents the cumulative dysregulation of biological systems with prolonged or poorly regulated allostatic responses. Nearly two decades of empirical research has focused on operationalizing the AL construct for examining the antecedents and health outcomes accompanying multisystem biological dysregulation. The purpose of this systematic review is to examine the empirical literature that quantifies the AL construct; the review also evaluates the social, environmental, and genetic antecedents of AL as well as its predictive utility for a variety of health outcomes. A total of 58 articles published between 1997 and 2012 were retrieved, analyzed, and synthesized. The results revealed considerable heterogeneity in the operationalization of AL and the measurement of AL biomarkers, making interpretations and comparisons across studies challenging. There is, however, empirical substantiation for the relationships between AL and socioeconomic status, social relationships, workplace, lifestyle, race/ethnicity, gender, stress exposure, and genetic factors. The literature also demonstrated associations between AL and physical and mental health and all-cause mortality. Targeting the antecedents of AL during key developmental periods is essential for improving public health. Priorities for future research include conducting prospective longitudinal studies, examining a broad range of antecedent allostatic challenges, and collecting reliable measures of multisystem dysregulation explicitly designed to assess AL, at multiple time points, in population-representative samples.

Keywords

allostasis, health, allostatic load

Mounting evidence supports the notion that chronic life stress, whether environmental or psychosocial, contributes to physiological dysregulation, poor mental and physical health, chronic disease, and diminished longevity, particularly in vulnerable or disadvantaged individuals (Cohen, Janicki-Deverts, & Miller, 2007; Groer, Meagher, & Kendall-Tackett, 2010). Yet, chronic ill-health need not be an inevitable outcome of chronic stress. Stress-related vulnerability or resiliency is determined by interacting genetic, environmental, and individual factors that influence risk trajectories over the life span (McEwen & Gianaros, 2010). In addition, prevention can preempt the effects of stress, and interventions can mitigate the negative outcomes of disease trajectories (Juster, McEwen, & Lupien, 2010). Most chronic diseases are substantially preventable and amenable to improved health outcomes when early warning signs or biological signatures are heeded (Gruenewald, Seeman, Ryff, Karlamangla, & Singer, 2006).

Escalating health care costs and illness burden of chronic diseases lend urgency to the scientific inquiry of stress and disease. Because of the complex nature of this relationship, a multidisciplinary, theory-driven approach holds the most promise. The concepts of allostasis and allostatic load (AL) provide multidisciplinary researchers a framework for studying both the protective effects of stress mediators during acute stress encounters and the detrimental effects of chronic or repeated stress exposure (McEwen & Stellar, 1993). Allostasis, the dynamic, adaptive regulatory process that maintains homeostasis during exposure to physical and behavioral stressors (McEwen & Gianaros, 2010), is an innovative lens through which to view health and disease (Groer, Beckie, et al., 2010) and represents a multifaceted mind–body approach for both psychopathological and pathophysiological research to articulate dynamic processes that can destabilize into maladaptive trajectories. AL is the consequence of regulatory wear and tear on the body and brain, which can lead to illness (McEwen, 1998a; McEwen & Wingfield, 2003).

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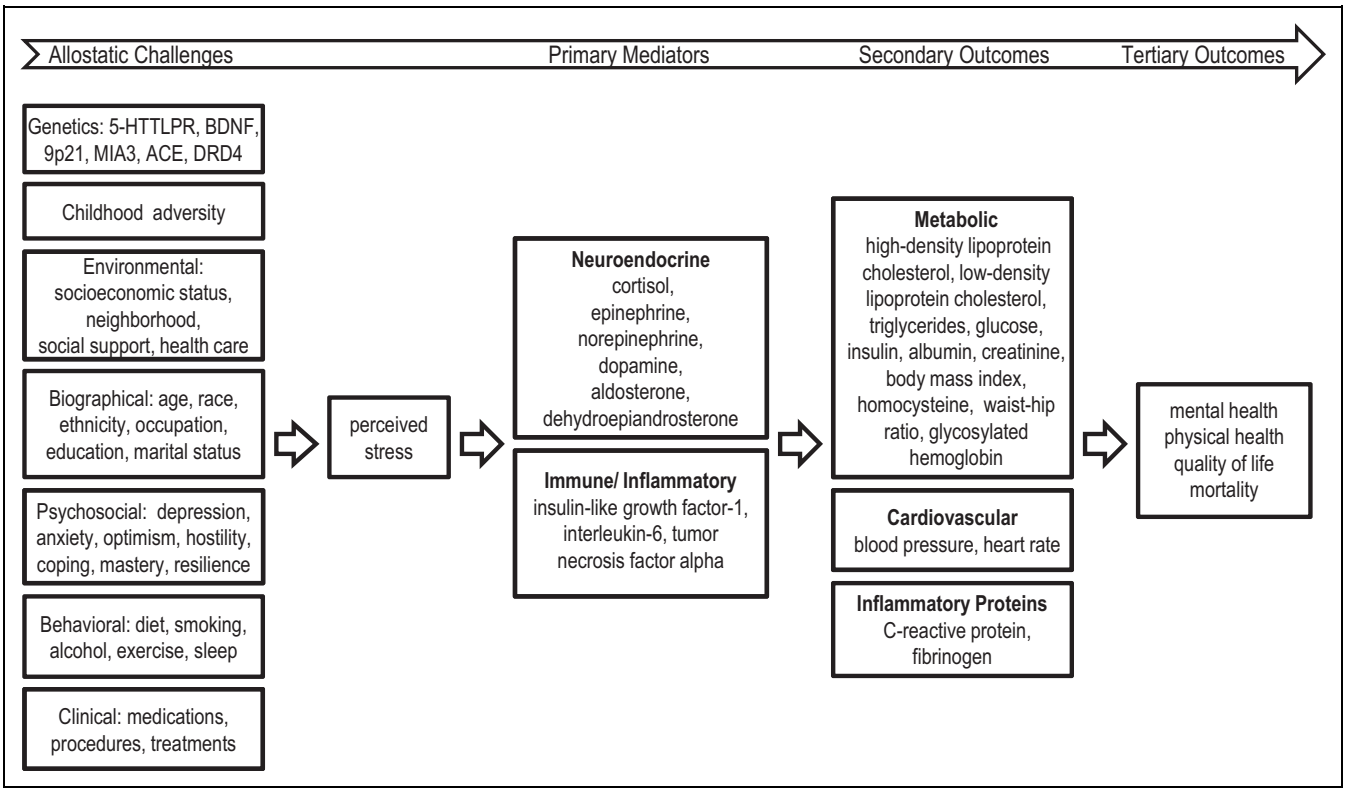

Figure 1. Heuristic model: allostatic load, health and health disparities.

The purpose of this review is to explore the utility of the AL framework for examining the dysregulated physiological responses to behavioral, genetic, psychosocial, physical, and environmental challenges and for predicting diverse health outcomes. Improved understanding of how individuals process stress is critical for translating research findings into personalized interventions for improved physical and mental health and quality of life.

Allostasis, the AL Framework, and Measurement of AL

Allostasis, a concept for understanding the prolonged effects of stress on morbidity and mortality, was first described as the regulatory process of approximating biological functioning to environmental demands to preserve physiological stability (Sterling & Eyer, 1988). The hypothalamic–pituitary–adrenal (HPA) axis and sympathetic–adrenal–medullary (SAM) systems are the cornerstones of the allostasis construct. Exposure to stressful environmental demands activates these systems, signaling changes in multiple interdependent physiological systems in a generalized stress response (McEwen, 1998a, 1998b). The individual differences as well as behavioral and historical factors that determine responses to stress shape perceptions of threat and mobilization of allostatic mechanisms (McEwen, 1998a). Control of the stress response by the central nervous system (CNS) allows the regulatory set points to vary in response to environmental demand, with the brain as the central mediator between the environment and the physiological response (Karatsoreos & McEwen, 2011).

Allostasis also addresses how the adaptive effects of these physiological systems can exact a toll when overused (McEwen, 2004). AL represents the cumulative, multisystem physiological dysregulation resulting from repeated cycles of activation and deactivation of allostasis over the life span in response to stressful life demands (McEwen & Gianaros, 2010; McEwen & Stellar, 1993; McEwen & Wingfield, 2003). This cumulative, multisystem framework for understanding health differentials and physiological predictors of health risk sets AL apart from the more common approach of concentrating on risks associated with individual systems. McEwen and colleagues have placed allostasis in a prominent position for use in the multidisciplinary study of stress and health (McEwen, 2006a; McEwen, Eiland, Hunter, & Miller, 2012; McEwen & Gianaros, 2010; McEwen & Seeman, 1999; McEwen & Tucker, 2011). Figure 1 presents a heuristic depiction of the AL model.

The allostatic process begins with the release of chemical messengers in response to stressors. Termed primary mediators, these messengers exert effects on tissues and organs via cellular activities called primary effects (McEwen, 2003, 2006a). Primary mediators regulate each other in a nonlinear network, permitting rapid adjustment to demands that compromise the physiological integrity of allostatic mechanisms. Primary mediators, adaptive when rapidly mobilized and terminated, include norepinephrine (NE), epinephrine (EPI),

cortisol, and dehydroepiandrosterone sulfate (DHEA-S; Juster et al., 2010; McEwen, 2003; McEwen & Seeman, 1999). Chronic or frequent demands for adaptation or inefficient production or suppression of these mediators, however, jeopardize health (McEwen & Gianaros, 2011). Four hypothesized neuroendocrine profiles, occurring separately or in combination, describe ways in which stress hormone responses deviate from healthy responses: repeatedly activated, nonhabituating, prolonged, and inadequate responses (McEwen, 2006b; McEwen & Gianaros, 2011).

The primary allostatic effects of the primary mediators give rise to secondary outcomes of systemic dysregulation of metabolic, inflammatory and cardiovascular (CVS) biomarkers in attempts to compensate for dysregulated stress hormones (Juster et al., 2010). Finally, tertiary outcomes of AL emerge with clinical manifestations of an array of health outcomes such as cardiovascular disease (CVD) and mortality (McEwen & Stellar, 1993). AL compromises health, not only because of the stress experiences themselves but also because of damaging behaviors such as tobacco and alcohol abuse that frequently accompany chronic stress states (McEwen & Tucker, 2011). A growing empirical literature employs the AL model for determining relevant antecedent environmental and individual correlates and numerous health consequences of AL.

The original operationalization of AL (hereafter referred to as the "10 original AL") includes a composite score of 10 markers of multisystem biological dysregulation (Seeman, Singer, Rowe, Horwitz, & McEwen, 1997). The 10 original AL comprises measures of four primary mediators—DHEA-S, urinary free cortisol, EPI, and NE—plus secondary outcome measures. The secondary outcome measures, which reflect wear and tear on the CVS and metabolic systems, include systolic blood pressure (SBP), diastolic blood pressure (DBP), waist–hip ratio (WHR), high-density lipoprotein cholesterol (HDL-C), the ratio of total cholesterol to HDL-C (TC/HDL-C), and glycosylated hemoglobin (Hb_{A1c}). In their study, Seeman et al. (1997) classified participants into quartiles based on the distribution of biomarker scores and the AL index comprised summing or counting the number of biomarkers for which participants fell into the highest-risk quartile, or in the case of HDL-C and DHEA-S, the lowest quartile. Of the 10 original AL biomarkers, 6 share similarities with indices reflecting the metabolic syndrome (Seeman, McEwen, Rowe, & Singer, 2001). Metabolic syndrome (MetS), a constellation of CVS risk factors, includes atherogenic dyslipidemia (elevated triglycerides and decreased HDL-C), hypertension, abdominal obesity, hyperglycemia, insulin resistance, and a proinflammatory state (Grundy et al., 2005). The 10 original AL improved the prediction of mortality and declining physical functioning compared to the MetS and the primary mediators alone (Karlamangla, Singer, McEwen, Rowe, & Seeman, 2002; Seeman et al., 2001) and has subsequently undergone numerous permutations and combinations using alternative scoring algorithms. The multisystem index has been utilized in a rich array of studies assessing the relationship between the antecedent correlates and tertiary outcomes of AL included in this review.

Method

I conducted the literature search using PubMed (1966–2011), CINAHL (1994–2011), and PsycINFO (1985–2011) databases with the key terms "allostasis" or "allostatic load." After excluding editorials, book chapters, and commentaries, I retrieved 148 English-language published abstracts describing human studies for potential inclusion in the review. A manual search of references added 37 additional publications, for a total of 185. I included studies exploring ethnic/racial, age, socioeconomic status (SES) and gender differences in AL as well as studies examining the influence of AL on health outcomes and excluded conceptual/review articles ($n = 38$), studies lacking multisystem physiological AL measures ($n = 33$) or AL scores ($n = 35$), studies involving children or adolescents ($n = 10$), and experimental stress response studies ($n = 11$). I did include multiple publications from particular study cohorts to highlight methodological issues and synthesize a broader range of health outcomes.

Where possible, I categorized the 58 studies comprising this review according to the cohort under study. There are 8 publications reporting findings of the MacArthur Study of Successful Aging (MSSA), another 8 reporting on the Taiwanese Social Environment and Biomarkers of Aging Study (SEBAS), 2 discussing the Northern Swedish Cohort (NSC), and 11 exploring the National Health and Nutrition Examination Survey data (NHANES). An additional 10 studies focused on American older and middle-aged adults, 9 concentrated on specific clinical conditions, and 10 centered on working adults.

AL Measurement in the MacArthur Studies of Successful Aging

The MacArthur cohort of 70- to 79-year-old primarily high-functioning, predominantly White American adults was the first with a range of physiological markers available for assessing the antecedents and longitudinal consequences of AL (Table 1). The longitudinal study design offered the advantage of allowing researchers to infer a causal association between AL at baseline and functional decline over the follow-up period. Investigators of the MacArthur cohort developed the 10 original AL to summarize physiological activity across multiple regulatory systems related to disease risks (Seeman et al., 1997). Using the original index, they found that higher AL was associated with CVD, cognitive and physical decline, and all-cause mortality over 12 years of follow-up (Gruenewald et al., 2006; Seeman, Crimmins, et al., 2004; Seeman et al., 1997) and that metabolic biomarkers were the best predictors of CVD (Seeman et al., 2001). Higher AL was also associated with increased frailty 3 years later in these elders (Gruenewald, Seeman, Karlamangla, & Sarkisian, 2009), even when investigators accounted for co-occurring physical disability and comorbidity potentially associated with alterations in biomarkers. Each unit increase in AL was associated with 10% greater odds of developing frailty. AL, measured as continuous canonical scores, was superior to any single biomarker for

Table 1. Allostatic Load Measurement in the MacArthur Study of Successful Aging

		Sample			Allostatic Load Measures		
Author, Year	Purpose and Design	*N*	Age	Sex, Race/ Ethnicity	Operationalization	Cutoff	Findings
Seeman et al., 1997	Examine relationship between AL & CVD & cognitive & physical functioning in subsample of MSSA of the EPESE; CVD events evaluated 2.5-year follow-up 1988–1991. Longitudinal	874; HF = 765, IF = 59, LF = 50	70–79 years	F = 50.8%, W = 82%, B = 18%	10 original (NF) Count in HR quartile of sample distributions. PMed DHEA-S (ng/dl) Urine cort (ug/g cr) Urine NE (ug/g cr) Urine EPI (ug/g cr) SecO SBP & DBP (mm Hg) HDL-C (mg/dL) TC/HDL-C (mg/dL) Hb_{A1c} (%) WHR	Extreme quartile (25/75 & 10/90): ≤350.0 ≥25.7 ≥48 ≥5.0 ≥ 148/83 ≤ 37 ≥5.92 ≥7.10 ≥0.94	AL in HF cognitive (2.58 ± 1.52) < AL in IF (3.14 ± 1.54) or LF (3.1 ± 1.73) subjects. Findings similar using z scores or equally weighted counts of the extreme decile. Individual parameters not related to outcomes. ↑ AL= ↑ incident CVD (self-reported MI, stroke, HTN, diabetes) & ↓ cognitive & physical functioning during follow-up
Seeman et al., 2001	Examine effect of AL on 7.5-year mortality & disease outcomes in MSSA cohort. BL: 1988–1989 Follow-up: 1991, 1996 Longitudinal	720	70–79 years	F = 51%, W = 81%, B = 19%	10 original. AL categorized as 1–2, 3–4, 5–6, 7+. MetS (BP, TC/HDL-C, WHR, Hb_{A1c}) & PMed (cort, NE, EPI, DHEA-S) subscales	As in Seeman et al., 1997	Total AL better predictor of 7.5-year mortality & ↓ physical functioning than MetS or PMed subscales alone.↑ AL = ↑ mortality independent of age, sex, ethnicity, education, income. MetS subscale better predictor of incident CVD than total AL and PMed subscale
Karlamangla et al., 2002	Examine association between AL & 7-year changes in physical & cognitive functioning in MSSA cohort; examine alternative summary AL scores. Longitudinal	251–592	70–79 years, mean = 74.1 ± 2.7	F = 51%, W = 81%, B = 19%	10 original. Compared CCs (to allow for nonuniform weights for AL components) to summary of dichotomized score (0 or 1) based on baseline cohort distributions. Compared PMed & SecO (MetS) subscales for predictive ability	As in Seeman et al., 1997	Stronger associations between BL AL & both short-term & long-term physical & cognitive functional declines independent of CVD in CC analyses than count score of AL; AL biomarkers contribute differently to future health & function. ↑ DHEA-S & DBP = ↑ functional decline; EPI has largest contribution to AL for predicting functional decline. PMed subscale predicted functional outcomes independent of MetS subscale
Seeman et al., 2002	Compare the influence of social relationships, social integration, & support on AL in midlife WLS & older MSSA cohorts. Cross-sectional	MSSA: 765; WLS: 106	MSSA: 70–79 years, mean: 74.2 ± 2.8; WLS: 58–59 years, mean 58.5 ± 0.8	MSSA: F = 50.8%, W = 81.7%, B = 18.3%; WLS: F = 53.8%, W = 100%	10 original. Used full range of AL scores & dichotomized into high (≥3 for WLS cohort & ≥5 for MSSA cohort) and low AL	As in Seeman et al., 1997	Median AL = 2 (both cohorts). MSSA: range 0–8, *SD* = 1.52; WLS: range 0–6, *SD* = 1.36. M AL (MSSA: 2.68 ± 1.58; WLS: 2.61 ± 1.46) > F AL MSSA: 2.47 ± 1.46; WLS: 2.04 ± 1.17). CVS AL biomarkers contributed more for M, neuroendocrine contributed more for F. ↑ AL = ↓ social relational measures. WLS: positive relationships = ↓ AL. MSSA: socially integrated M with support = ↓ AL. ↑ family criticisms = ↑ AL. Marital status ≠ AL

(continued)

Table 1. (continued)

		Sample			Allostatic Load Measures		
Author, Year	Purpose and Design	*N*	Age	Sex, Race/ Ethnicity	Operationalization	Cutoff	Findings
Weinstein et al., 2003	Compare AL in SEBAS Taiwanese (1997–1998) & MSSA cohorts; compare associations between social factors & challenges & AL. Cross-sectional	SEBAS: 101; MSSA: 827	SEBAS: 67–94 years, mean = 72.4; MSSA: 70–79, mean = 74.4	SEBAS: F = 47, M = 54; MSSA: F = 424, M = 403; Race NR	10 original analyzed as count-based & as continuous variables	NR	AL score NR. SEBAS F BP > MSSA F BP; SEBAS M TC/HDL-C, $Hb_{a1c,}$ NE < MSSA M TC/HDL, Hb_{A1c}, NE. F DHEA-S < M DHEA-S for both cohorts. AL biomarkers similar across populations. ↓ AL = ↑ position in social hierarchy (income, education, sex, & occupation). ↑ challenge, widowhood, ↑ demands = ↑ AL
Seeman, Crimmins et al., 2004	Determine whether AL mediates SES (education) differences in 7-year mortality in MSSA cohort (1988–1995). Longitudinal	657	70–79 years	F = 50.4%, W = 82.2%, NW = 17.8%	10 original + the following: CRP (ug/ml) IL-6 (pg/ml) Peak flow (l/min) Fib (mg/dL) cr cl (ml/min) Alb (mg/dL) Subscales: CVS, inflammatory, & PMed	Cutoffs as in Seemen et al., 1997 + the following: ≥3.19 ≥4.64 ≤300.0 ≥336.0 ≤44.63 ≤3.90	AL similar for 16 vs.10 parameters. AL: 3.9 ± 2.1. AL = 4.28 for <8 years education vs. 3.53 for ≥12. 35.4% of SES effect on mortality mediated by AL.↑ education = ↓ AL. ↑ AL = ↑ gradient of 7.5-year mortality. Three biomarkers (CRP, peak flow, Cr cl) & CVS & PMed (stress hormone) subscales were associated with mortality
Gruenewald et al., 2006	Predict mortality over a 12-year period in MSSA cohort from 1988 BL AL data. Longitudinal	667	70–79 years	F = 339, Race = NR	9 original + 4 others (NF): DHEA-S (mg/dl) Urine cort (ug/g cr) Urine NE (ug/g/cr) Urine EPI (ug/g cr) SBP & DBP (mm Hg) HDL-C (mg/dL) TC/HDL-C (mg/dL) Hb_{AIC} (%) Others CRP (mg/l) IL-6 (pg/ml) Fib (mg/dL) Alb (mg/dL) RP for M & F to determine groups of biomarkers related to mortality	Sex-based HR cut points: M < 43.5, F < 17.5 M > 37.3, F NR M > 64.2, F > 26.5 M > 4.3, F NR M > 159/73, F > 141/91 M < 27.5, F NR M & F > 5 M > 7, F > 7.5 M > 1.6, F > 3.6 M > 2.7, F > 4.5 M > 235, F NR NR	F: ↑ HDL-C, cort, NE, & EPI; M: ↑ DHEA-S, IL-6 & TC/HDL. 11/13 biomarkers (not alb or TC/HDL ratio) in HR pathways (≥ 70% dead) for 10 RP trees for M. Only 6/13 biomarkers (SBP, DBP, Hb_{A1c}, CRP, IL-6, DHEA-S) in HR pathways (≥ 60% dead) in 3 RP trees for F.

(continued)

Table 1. (continued)

		Sample			Allostatic Load Measures		
Author, Year	Purpose and Design	*N*	Age	Sex, Race/ Ethnicity	Operationalization	Cutoff	Findings
Gruenewald et al., 2009	Examine association between AL & frailty development over 3 years in MSSA cohort. BL: 1988–1989; Follow-up: 1991–1992. Longitudinal	803	Not frail = 73 ± 2.7 years, IntF =74.4 ± 2.7 years, frail = 75.4 ± 2.9 years	Not frail: F = 191, M = 163, W = 297, B = 57 IntF: F = 229, M = 172, W = 325, B = 76 Frail: F = 26, M = 22, W = 41, B = 7	10 original + 3 others (NF): Fib CRP IL-6 AL score count of dichotomous risk scores (range 0–13).	Extreme quartile cutoff as in Seeman, Crimmins, et al., 2004	AL range 0–9.1 (mean = 3.2 ± 2.0; median = 3). Quintile ranges: lowest = 0.0–1.3, 2nd =1.4–2.9, 3rd = 3.0–3.9, 4th, = 4.0–5.0, & highest ≥ 5.1. ↓ prevalence not frail & ↑ prevalence of intF & frail related to ↑ AL. ↑ AL = ↑ frailty 3 years later. Controlling for SES, health & health behaviors, 1 unit ↑ AL = 10% ↑ in odds of frailty in 3 years

Note. 10 original = original operationalization of AL includes a composite score describing the levels of 10 markers of multisystem biological dysregulation: Primary mediators—DHEA-S (ng/dL), urine cort (ug/g cr), urine NE (ug/g cr), urine EPI (ug/g cr); Secondary outcomes—SBP & DBP (mm Hg), HDL-C (mg/dL), TC/HDL-C (mg/dL), Hb_{A1c} (%), WHR.
AL = allostatic load; Alb = albumin; B = Black; BL = baseline; BP = blood pressure; CC = canonical correlation; cort = cortisol; cr = creatinine; cr cl = creatinine clearance; CRP = C-reactive protein; CVD = cardiovascular disease; CVS = cardiovascular; DBP = diastolic blood pressure; DHEA-S = dihydroepiandrosterone sulfate; EPI = epinephrine; EPESE = Established Populations for the Epidemiologic Study of the Elderly; F = female; Fib = fibrinogen; Hb_{A1c} = glycosylated hemoglobin; HDL-C = high-density lipoprotein cholesterol; HF = high functioning; HR = heart rate; HTN = hypertension; IL-6 = interleukin-6; IF = intermediate functioning; IntF = intermediate frail; LF = low functioning; M = male; MetS = metabolic syndrome; MI = myocardial infarction; MSSA = MacArthur Study of Successful Aging; NE = norepinephrine; NF= nonfasting; NR = not reported; NW = non-White; PMed = primary mediators; RP = recursive partitioning; SBP = systolic blood pressure; SEBAS = Social Environment and Biomarkers of Aging Study; SecO = secondary outcomes; SES = socioeconomic status; TC = total cholesterol; W = White; WLS = Wisconsin Longitudinal Study; WHR = waist-hip ratio; ↑ = higher or increased, ↓ = lower or decreased.

predicting health outcomes over a 7-year period (Karlamangla et al., 2002). While composite AL, but not individual markers, was linked to health and mortality (Karlamangla et al., 2002; Seeman et al., 2001), plausible alternative explanations include the summation of small effects yielding a larger one or measurement error in the biological measures. Critics thus argued that such data neither refuted nor supported the construct validity of AL (Goldman, Turra, Glei, Lin, & Weinstein, 2006).

The MacArthur Studies also highlighted the significant influences of SES, psychosocial environment, and sex differences in AL. Supplementing the AL index with inflammatory, renal and lung function biomarkers resulted in findings of a modest relationship between SES (education attainment) and AL (Seeman, Crimmins, et al., 2004). The AL index mediated 35% of the SES gradient in mortality, while none of the component biomarkers or subscales accounted for more than 15%. The CVS, inflammatory, and lung function parameters were stronger mediators of the SES–mortality relationship than the neuroendocrine biomarkers (Seeman, Crimmins, et al., 2004). Cross-sectional comparison of data from the MacArthur and the Wisconsin Longitudinal Study cohorts revealed that, although marital status was unrelated to AL, participants with less social integration and social support and more judgmental family members had higher AL (Seeman, Singer, Ryff, Dienberg Love, & Levy-Storms, 2002). Neuroendocrine biomarkers were more dysregulated in women while CVS biomarker dysregulation predominated in men. Similar comparisons of the MacArthur cohort with a Taiwanese cohort found links between increased AL and lower income, education, occupational status and finances and exposure to greater social demands (Weinstein, Goldman, Hedley, Yu-Hsuan, & Seeman, 2003).

Researchers used recursive partitioning techniques to identify a set of pathways composed of combinations of AL biomarkers that predicted sex-specific 12-year mortality in the MacArthur cohort (Gruenewald et al., 2006). This classification system exposed preclinical levels of biomarker combinations that defined elevated health risks. The high-risk pathways of AL biomarker clustering for men included NE, EPI, interleukin-6 (IL-6), C-reactive protein (CRP), and fibrinogen, whereas for women they included IL-6, CRP, Hb_{A1c}, and SBP. Substantial heterogeneity was evident in the sex-specific patterns of biomarkers predicting mortality, highlighting the observation that diverse patterns of physiological dysregulation predicted adverse health outcomes. Gruenewald et al. (2006) proposed that multiple measures of biomarkers over time would lead to more sensitive mortality predictions. The MacArthur studies have contributed to our understanding of health outcomes by examining biological risk from a cumulative, multisystem view, by exploring alternative scoring methods to create AL indices, and by investigating the mediating effect of AL in SES differentials in health outcomes. The MacArthur studies were cross-culturally augmented by the SEBAS investigations of Taiwanese aged 54–91 that included the 10 original AL biomarkers.

AL Measurement in Taiwanese and Swedish Aging Studies

The Taiwanese studies examined relationships between AL and perceived stress, the social environment, and SES as well as the consequences of increased AL on mortality and physical and mental well-being. More recently, another research group investigated the influences of SES and social adversity on AL over the life span in the Northern Swedish Cohort. These studies, presented in Table 2, contributed valuable evidence of construct validity of AL across additional Western and non-Western cultures. Most studies used the 10 original AL biomarkers, some with sex-specific high-risk cutoffs and several novel scoring algorithms. Collaborators of the Taiwanese studies expanded the existing methodological repertoire for investigating the relationship between the 10 original plus supplementary AL biomarkers and health profiles constructed using grade of membership (GOM) multivariate methods (Seplaki, Goldman, Weinstein, & Lin, 2004, 2006). They found that increased AL was associated with poorer health status (self-rated health, activities of daily living [ADL], mobility, and temporal orientation), more depressive symptoms, and cognitive impairments (Seplaki et al., 2004). Extending this work, they evaluated several approaches for measuring 16 AL biomarkers with sex-specific cutoffs and the cross-sectional relationship with physical and mental functioning (Seplaki et al., 2006). They found that the GOM-based AL score using extreme quartile cutoffs was significantly associated with all health measures, while the GOM-based score using extreme deciles was related to all but the cognitive score. The 10-item AL index was associated with all outcomes except for ADL and depressive symptoms. Hence, compared to the 10 original AL, the GOM-based measures accounted for more variance in health outcomes. These studies provide support for distinguishing primary mediators from secondary outcomes and for the importance of both distribution extremes of AL biomarkers. They also highlight the lack of robustness in the relationships between various health outcomes and particular AL cutoff choices.

Using a longitudinal design and continuously measured AL biomarkers, investigators ascertained that neuroendocrine biomarkers (EPI and IL-6) were better predictors of 3-year mortality than CVS (DBP) and metabolic (body mass index [BMI]) biomarkers in Taiwanese participants (Goldman, Turra, Glei, Lin, et al., 2006; Goldman, Turra, Glei, Seplaki, et al., 2006). The data failed to support the theoretical hypothesis that primary mediators exert direct effects on secondary outcomes because the association between the nonclinical biomarkers and mortality was relatively unchanged after adjustment for the clinical biomarkers. However, IL-6, insulin-like growth factor-1 (IGF-1), and dopamine were included as primary mediators in this study so direction comparisons to the primary mediators of the 10 original AL are questionable. Using a count-based scoring algorithm with three additional biomarkers (fasting glucose, WHR, and triglycerides), investigators found that higher AL was associated with increased 3-year mortality risk,

Table 2. Allostatic Load Measurement in Taiwanese and Swedish Aging Studies

		Sample			Allostatic Load Measures		
Author, Year	Purpose and Design	*N*	Age	Sex, Race/ Ethnicity	Operationalization	Cutoff	Findings
Seplaki et al., 2004	Determine relationship between AL & physical & mental well-being in Taiwanese elders of SEBAS 2000. Cross-sectional	980	68.8 years	F = 402, M = 578, Taiwanese	10 original + 6 others (fasting):	Extreme decile & quartile:	AL scores NR. Sensitivity analyses with other cut points did not alter results. GOM profiles of functioning related to AL. GOM profiles: 27% of M & 14% of F fully functioning. Distinctions revealed between the substantially impaired & fully functioning GOM profiles in their associations with PMed & SecO. ↑ AL = ↑ cognitive impairment, moderate depression, limited mobility, substantial impairment (mobility, cognition & depressive symptoms). Covariates: age, sex
					PMed		
					DHEA-S (ng/dL)	20.9/152.4	
					Urine cort (ug/g cr)	8.75/48	
					Urine NE (ug/g cr)	11.2/34.7	
					Urine EPI (ug/g cr)	2/5.63	
					SecO		
					SBP & DBP (mm Hg)	114/166 & 70/97	
					HDL-C (mg/dL)	153/252	
					TC/HDL-C (mg/dL)	2.81/6.14	
					Hb_{A1c} (%)	4.8/7.10	
					WHR	0.80/0.96	
					Others		
					Dopamine (ug/L)	43.7/264.1	
					IGF-1 (ng/mL)	53/168	
					IL-6 (pg/mL)	–/3.40	
					FG (mg/dL)	84/138.0	
					BMI (kg/m^2)	20/28.9	
					Trig (mg/dL)	54/204	
					GOM model estimated 5 scores of AL risk for poor health outcomes		
Seeman, Glei, et al., 2004	Examine relationship between social environment & AL in NEL (54–70 years) & elderly (71+ years) in SEBAS. Longitudinal	950 total, NEL = 531, elderly = 419	54–90 years, mean 69.2 ± 4.5	F = 395, M = 555, Taiwanese	10 original (fasting):	Extreme quartile, sample-based:	AL: elderly vs. NEL (2.7 ± 1.6 vs. 2.4 ± 1.6). Using dichotomous scores of social environment & AL: in NEL absence of spouse ↑ AL only in M. In elderly, ↑ AL = ↓ social ties/support, ↑ age. Perceived quality of social environment not associated with AL in either group. In elderly, presence of spouse not associated with AL. Covariates: age, sex, ethnicity, health status, physical functioning, ill spouse
					PMed		
					DHEA-S (ug/dL)	<40.8	
					Urine cort (ug/g cr)	>30	
					Urine NE (ug/g cr)	>27.1	
					Urine EPI (ug/g cr)	>3.7	
					SecO		
					SBP & DBP (mm Hg)	>150/89	
					HDL-C (mg/dL)	<39	
					TC/HDL-C (mg/dL)	>5.1	
					HbA1c (%)	>5.7	
					WHR	>0.93	
					Count in HR quartile (0–10)		

(continued)

Table 2. (continued)

		Sample			Allostatic Load Measures		
Author, Year	Purpose and Design	*N*	Age	Sex, Race/ Ethnicity	Operationalization	Cutoff	Findings
Seplaki et al., 2006	Examine association between GOM model of AL & physical, psychological & cognitive function in older Taiwanese in SEBAS (2000). Cross-sectional	972	54–90 years, mean 67.7 ± 8.3	F = 401, M = 571, Taiwanese	Same as Seplaki et al., 2004, with sex-specific cutoffs: PMed DHEA-S (ng/dL) Urine cort (ug/g cr) Urine NE (ug/g cr) Urine EPI (ug/g cr) SecO SBP & DBP (mm Hg) HDL-C (mg/dL) TC/HDL-C (mg/dL) Hb_{A1c} (%) WHR Others Dopamine (ug/L) IGF-1 (ng/mL) IL-6 (pg/mL) FG (mg/dL) BMI (kg/m^2) Trig (mg/dL) GOM model estimated 5 scores of risk for poor health outcomes	10/90 percentiles: M > 172, F > 118 M > 43, F > 54 M > 33, F > 36 M > 5, F > 6.6 166/97 M > 242, F > 263 M > 6, F > 6 M > 6.5, F > 8.10 M > 0.97, F > 0.94 M > 265, F > 259 M > 174, F > 152 M > 3.1, F > 3.8 M > 127, F > 164 M > 28, F > 30 M > 199, F > 209	Using 10/90 vs. 25/75 cutoffs = ↑ proportion with ↓ risk profile. Using 25/75 cutoff resulted in ↑ number with ↓ or ↑ SecO values combined with extreme PMed values. ↑ 10-item AL = ↓ self-rated health, ↑ mobility limitations & ↓ cognitive scores but not ↓ ADL or ↑ depressive symptoms. GOM using 10/90 cutoff significantly related to 4/5 (not cognitive score) health measures; GOM using 25/75 cutoff significantly related to all outcomes. Most HR scores significantly related to ↑ mobility limitations & ↑ depressive symptoms, but only profile reflecting ↑ SecO related to cognitive performance
Goldman, Turra, Glei, & Lin, 2006	Examine the relationship between AL & health outcomes over 3 years in SEBAS. Longitudinal	820	54–91 years, mean 67.4 ± 8.1	F = 346, M = 474, Taiwanese	Same as Seplaki et al., 2004. Nonclinical subscale (EPI, NE, cort, dopamine, DHEA-S, IL-6, IGF-1), range 0–7. Clinical subscale (BMI, WHR, SBP, DBP, TC, TC/HDL-C, Trig, FG, Hb_{A1c}), range 0–9	Same as Seplaki et al., 2004. Count in HR deciles (0–16)	Health outcomes (n = 820): AL = 3.3 ± 1.8 (range 0–10). Nonclinical subscale: 1.6 ± 1.2; clinical subscale: 1.7 ± 1.4. ↑ AL = ↑ mortality (n = 935), ↑ mobility limitation, ↑ cognitive decline, ↑ depressive symptoms (n = 820). 1 unit ↑ in AL = 39% ↑ odds of dying over 3 years; similar effects for clinical & nonclinical subscales. Coviariates: age, sex, urban/rural, limited mobility, self-rated health, chronic conditions, cognitive function, pain, smoking

(continued)

Table 2. (continued)

		Sample			Allostatic Load Measures		
Author, Year	Purpose and Design	*N*	Age	Sex, Race/ Ethnicity	Operationalization	Cutoff	Findings
Goldman, Turra, Glei, Seplaki, & Lin, 2006	Examine relationship between nonclinical & clinical biological risk factors & all-cause mortality over 3 years in SEBAS 2000–2003. Longitudinal	927	54–91 years, mean 68.2 ± 8.4	F = 384, M = 543, Taiwanese	9 original + 4 others (fasting): PMed DHEA-S (ug/dL) Urine cort (ug/g cr) Urine NE (ug/g cr) Urine EPI (ug/g cr) SecO SBP & DBP (mm Hg) TC (mg/dL) TC/HDL-C (mg/dL) Hb_{A1c} (%) Others Dopamine (ug/g/cr) IGF-1 (ng/mL) IL-6 (pg/mL) BMI (kg/m^2)	Biomarkers measured as continuous variables. Nonclinical (EPI, NE, cort, dopamine, DHEA-S, IL-6, IGF-1) & clinical (BMI, SBP, DBP, TC, TC/HDL-C, Hb_{A1c}) subscales	Clinical biomarkers related to mortality = BMI & DBP; nonclinical biomarkers related to mortality = EP, IL-6. Both subscales related to mortality with nonclinical superior to clinical subscale. Covariates: age, sex, urban/rural, chronic conditions, mobility limitations, self-rated health, depressive symptoms, cognitive function, pain, smoking status
Dowd & Goldman, 2006	Examine relationships between SES (education & income), AL & self-reported health outcomes in SEBAS. Cross-sectional	972	50–66 years	NR, Taiwanese	10 original + 3 others (fasting): PMed DHEA-S (ug/dL) Urine cort (ug/g cr) Urine NE (ug/g cr) Urine EPI (ug/g cr) SecO SBP & DBP (mm Hg) HDL-C (mg/dL) TC/HDL-C (mg/dL) Hb_{A1c} (%) WHR Others IGF-1 (ng/mL) IL-6 (pg/mL) Alb (mg/dL) Count in HR quartiles (0–13). Neuroendocrine (0–4), immune (0–3) & CVS subscales (0–6).	Extreme quartile: ≤ 40.8 ≥ 30 ≥ 27.1 ≥ 3.7 150/90 ≤ 38 ≥5.1 ≥5.8 ≥0.93 ≤69.5 ≥ 1.41 ≤4.4	↑ AL not related to SES. AL did not explain the SES gradient in health in M or F. For F, ↓ education = ↓ health, ↑ AL & CVS subscales but not neuroendocrine or immune subscales. For M, ↑ education related to ↑ Hb_{A1c}. Covariates: marital status, race/ethnicity, employment status, education, income
Glei et al., 2007	Examine whether perceived stress mediates the association between stressors & AL in SEBAS 1996–2000. Longitudinal	851	54–91 years, mean 66.1 ± 7.8	F = 356, M = 495, Taiwanese	Same as Seplaki et al., 2004	Same as Seplaki et al., 2004	AL: 3.4 ± 1.9 (0–10). 1 SD ↑ in stressors (+ 2.1 stressors) related to 0.09 SD ↑ in AL (0.17). Combination of ↓ social position, weak social networks & limited internal resources (↓ locus of control, optimism, engagement) = ↑ AL with small magnitude. Covariates: age, sex, urban residence.

(continued)

Table 2. (continued)

		Sample			Allostatic Load Measures		
Author, Year	Purpose and Design	*N*	Age	Sex, Race/ Ethnicity	Operationalization	Cutoff	Findings
Hu et al., 2007	Explore whether AL is associated with self-rated health & ADL & whether it mediates association between SES & health in SEBAS. Cross-sectional	1,023	67.9 ± 8.5 years	F = 430, M = 593, Taiwanese	10 original (fasting)	Extreme sample-based quartile. Same as Seeman et al., 2004. Count of biomarkers in HR quartile (0–10).	AL: 2.5 ± 1.6 (range 0–7). ↑ AL = ↑ age, ↓ self-rated health, female sex, ↓ education, ↓ income & ↓ alcohol use. ↑ AL & ↓ SES associated with ↓ self-rated health & more difficulties with physical activity & ADL. AL did not mediate SES–health relationship
Gustafsson et al., 2011	Examine the influence on AL at age 43 (2008) of SES (occupation) over life course from 16 years of age (1981) in 27-year NSC. Longitudinal	855	Evaluated at ages 16, 21, 30, & 43 years	F = 412, M = 443, Swedish	5 original + 7others (fasting): Sal cort (log nmol × h) SBP & DBP (mm Hg) TC (mmol/L) HDL-C (mmol/L) Others BMI (kg/m^2) WC (cm) CRP (mmol/L) FG (mmol/L) Trig (mmol/L) Apo A1 (mmol/L) Apo B (mmol/L) CVS (0–2), body fat (0–2), lipid metabolism (0–5), gluc (0–1), inflammation (0–1), & neuroendocrine (0–1) subscales. (AL range 0–12). AL tertiles: 0, 1, 2	Sex-specific: F < 15 or > 26, M < 17 or >29 F ≥ 125/80, M ≥ 134/86 F > 5.5, M > 5.8 F < 1.31, M < 1.05 F ≥ 26.8, M > 28.7 F > 89, M > 101 3–10 F > 5.5, M > 5.4 F > 1.18, M > 1.81 F < 1380, M < 1274 F > 979, M > 1,120 Medications coded as 2 in specific system	AL at 43 years: F = 5.5 ± 2.5; M = 5.7 ± 2.4. ↓ SES at 43 years related to ↑ AL. Adjusting for tobacco & alcohol use & physical activity attenuated the effect of SES in M but not F. ↓ SES related to ↑ AL in both sexes. Association explained by physical inactivity in M. In F, adolescent SES associated with AL; in M only current SES related to AL independent of current behaviors. ↓ SES not related to CRP or cortisol. Results unchanged when 25/75 percentile cutoffs used
Gustafsson et al., 2012	Examine influence of social (e.g., parental loss) & material adversities (e.g., income, employment) at 16, 21, 30, & 43 years on AL at age 43 (2008) in NSC. Longitudinal	822	Mean age at 16, 21, 30 & 43 years	F = 494, M = 428, Swedish	Same as Gustafsson et al., 2011	Same as Gustafsson et al., 2011	AL: F 5.43 ± 2.49, M 5.65 ± 2.42. Life course social & material adversity > in F vs. M. ↑ social adversity over life course = ↑ AL in both sexes independent of SES. ↑ social adversity in adolescence (F) & young adulthood (M) related to ↑ AL independent of SES & of later adversity during adulthood

Note. 10 original = original operationalization of AL includes a composite score describing the levels of 10 markers of multisystem biological dysregulation: Primary mediators—DHEA-S (ng/dL), urine cort (ug/g cr), urine NE (ug/g cr), urine EPI (ug/g cr); Secondary outcomes—SBP & DBP (mm Hg), HDL-C (mg/dL), TC/HDL-C (mg/dL), Hb_{A1c} (%), WHR.

AL = allostatic load; ADL = activities of daily living; Alb = albumin; Apo = apolipoprotein; BMI = body mass index; BP = blood pressure; cr = creatinine; cort = cortisol; CRP = C-reactive protein; CVS = cardiovascular; DBP = diastolic blood pressure; DHEA-S = dihydroepiandrosterone sulfate; EPI = epinephrine; F = female; FG = fasting glucose; Gluc = glucose; GOM = grade of membership; Hb_{A1c} = glycosylated hemoglobin; HDL-C = high-density lipoprotein cholesterol; HR = high risk; IGF-1 = insulin-like growth factor-1; IL-6 = interleukin-6; M = male; NE = norepinephrine; NEL = near elderly; NF = nonfasting; NSC = Northern Swedish Cohort; PMed = primary mediators; SBP = systolic blood pressure; SD = standard deviation; SEBAS = Social Environment and Biomarkers of Aging Study; SecO = secondary outcomes; SES = socioeconomic status; TC = total cholesterol; Trig = triglyceride; WC = waist circumference; WHR = waist–hip ratio. Notations: ↑ = higher or increased, ↓ = lower or decreased.

cognitive decline, depressive symptoms, and mobility limitations (Goldman, Turra, Glei, Lin, et al., 2006). These outcomes were differentially associated with total AL and the neuroendocrine and traditional clinical biomarkers. Cognitive decline was associated with the clinical biomarkers but not total AL when investigators controlled for health at baseline. Enhancing previous research, they examined immune function biomarkers, assessed risk in both tails of the distribution to capture extreme values, and used deciles rather than quartiles to denote extreme values (Goldman, Turra, Glei, Lin, et al., 2006).

Contrary to the MacArthur studies (Seeman, Crimmins, et al., 2004), researchers in the Taiwanese studies found little evidence that 13 AL biomarkers explained the SES gradient in health (Dowd & Goldman, 2006), plausibly suggesting a different biological pathway linking SES and health in Taiwan than in Western countries. Education was associated with AL for women but not men. Elderly Taiwanese with substantial social ties demonstrated lower AL, but marriage was unrelated to lower AL in women (Seeman, Glei, et al., 2004). The perceived quality of social relationships was not consistently associated with AL, perhaps reflecting the influence of cultural norms on the importance of different aspects of the social environment. Further, the combination of weak social networks, low social position, and poor coping ability was linked to greater AL (Glei, Goldman, Chuang, & Weinstein, 2007), but perceived stress did not mediate the relationship between chronic stressors and AL. Although advanced age, less education, lower income, poor health status, less alcohol use, and female sex were related to higher AL, the 10 original AL score did not mediate the relationship between SES and self-rated health (Hu, Wagle, Goldman, Weinstein, & Seeman, 2007*)*.

Gustafsson, Janlert, Theorell, Westerlund, and Hammarstrom (2011, 2012) examined the influence of SES and social adversities over the life span on AL in a longitudinal Swedish cohort of individuals aged 43 years. Cumulative SES disadvantage was related to AL in both sexes, with health behaviors explaining the relationship in men but not in women. SES in adolescence (measured by parental occupation) was related to AL in midlife for women, whereas only current SES was associated with AL in men independent of current health behaviors (Gustafsson et al., 2011). Thus, adolescence might be a critical period for women with latent effects spanning decades. For both sexes, social adversity, such as parental loss, accumulated over the life span was related to AL independent of SES disadvantage. Social adversity during adolescence for women and during young adulthood for men was also associated with AL independent of SES and of adversity in adulthood (Gustafsson et al., 2012).

Collectively, researchers in the studies displayed in Table 2 evaluated several methods of combining AL biomarkers including 10- and 16-item count scores, one- and two-tailed risk categories, summed GOM scores, and various percentile cutoffs defining risk categories (Seplaki, Goldman, Glei, & Weinstein, 2005). The two-tailed 16-count AL scores performed somewhat better than the one-tailed count scores for examining associations with health outcomes. The best performing two-tailed measure was a continuous score summing the absolute standardized differences of each biomarker from its respective mean (Seplaki et al., 2005). Cross-sectional analyses demonstrated that associations between AL and health impairments were generally robust to the choice of relevant biomarkers included, the use of different types of measures, or alternative cutoffs defining extreme biomarker values. Researchers cautioned that including irrelevant biomarkers only served to increase measurement error. These studies also emphasize the utility of longitudinal examination of the relationships among SES, the social environment, individual characteristics and AL and point to a need for defensible measures of AL, SES, health, and functioning. Assessing AL at earlier ages is as important as doing so later in life, and in this vein, I now turn to a discussion of literature representing a younger population cohort.

AL Measurement in the NHANES

Investigators conducting surveys for the National Center for Health Statistics used probability sampling to provide estimates of health and nutrition status for the U.S. civilian population. Table 3 summarizes 11 publications that utilized these data to examine AL using cross-sectional designs, with sample sizes ranging from 4,140 to 22,815. Comparing results from these studies with others in this review is complicated because measures of primary mediators were unavailable in the NHANES data. Researchers measured only 4–6 biomarkers of the 10 original AL, but they included up to 10 additional dichotomized biomarkers in the AL index, using both sample distributions and clinical criteria to define high-risk cutoff categories. The NHANES studies focused on the relationships between sociodemographic characteristics such as age, race and ethnicity, sex, SES, and neighborhood SES (NSES) and heterogeneous representations of AL. Two reports examined the cross-sectional association between AL and all-cause mortality.

Among more than 22,000 NHANES participants, AL progressively increased among those aged 20–60 years and then leveled off up through the ninth decade during the period of greatest mortality risk (Crimmins, Johnston, Hayward, & Seeman, 2003). Examining the additional influences of race, sex, and poverty status on AL in an NHANES subsample, researchers unearthed stark racial disparities in AL among young through middle-aged adults (Geronimus, Hicken, Keene, & Bound, 2006). AL was higher in Blacks than in Whites at all ages, and the score differentials increased with age adjusted for SES. The finding that AL decreased with medications removed from the algorithm highlighted the greater burden of chronic disease in Blacks aged 35–64 years compared to their White counterparts. Black women across all age groups had the highest AL, supporting the ''weathering'' hypothesis of early health deterioration due to SES disadvantage. Further, Blacks with peripheral arterial disease (PAD) had the highest AL scores (increased SBP, CRP, and homocysteine and lower glomerular

Table 3. Allostatic Load Measurement in the National Health and Nutrition Examination Survey

		Sample			Allostatic Load Measures		
Author, Year	Purpose and Design	*N*	Age	Sex, Race/Ethnicity	Operationalization	Cutoff	Findings
Crimmins et al., 2003	Examine relationship between age and AL in NHANES III (1988 –1994). Cross-sectional	22,815	20–90 years	NR	5 original + 8 others (NF):	Extreme quartile (indicated with *) & clinical criteria:	AL: 2.24 (range: 0–11). AL ↑ to age 60 years & then leveled off until age 90+. Measures of primary mediators of AL unavailable for analysis. Covariates: age, medications
					SBP & DBP (mm Hg)	≥ 140/90	
					HDL-C (mg/dL)	≤ 40	
					TC (mg/dL)	≥ 250	
					Hb_{A1c} (%)	≥ 5.6*	
					Others		
					Trig (mg/dL)	≥ 150	
					BMI (kg/m^2)	> 30	
					Alb (g/dL)	≤ 3.9*	
					CRP (mg/dL)	> 0.33*	
					Fib (↑ value, mg/dL)	> 336*	
					peak flow (ml)	< 5922*	
					cr cl (ng/dL)	≤ 44.64*	
					Ho (umol/l)	> 10.9*	
					Count in HR quartile (0–13)		
Geronimus et al., 2006	Examine relationships between age, race, gender, & poverty status & AL in NHANES IV (1999–2002). Cross-sectional	4,140	18–64	F = 2,008; M = 2,132; W = 2,800; B = 1,340	4 original + 6 others (NF):	Extreme quartile:	AL: range from 1.14 for W M aged 18–24 to 4.99 for B F aged 55–64. Sensitivity analysis of AL cutoff did not change results. AL > for B than W & > for B F than B M. B vs. W: ↑ probability ↑ AL (≥ 4) at all ages especially 35–64 years. W F vs. W M > 45 years more likely to have ↑ AL. Racial differences not explained by poverty. Poor & nonpoor B F had highest & second highest AL
					SBP & DBP (mm Hg)	> 127/80	
					TC (mg/dL)	> 225	
					Hb_{A1c} (%)	> 5.4	
					Others		
					BMI (kg/m^2)	> 30.9	
					Alb (g/dL)	< 4.2	
					Cr cl (mg/dL)	< 66	
					Trig (mg/dL)	> 168	
					CRP (mg/dL)	> 0.41	
					Ho (umol/L)	> 9	
					Count in HR quartile (0–10). ↑ AL = ≥ 4. 1 point added to score for medications affecting biomarkers		
Nelson et al., 2007	Examine the association between race/ethnicity & AL in patients with & without PAD in NHANES (1999–2002). Cross-sectional	*N* = 5,083, PAD *n* = 369, no PAD *n* = 4,714	40 to 80+	F = 2,491; M = 2,592; W = 2,755; B = 944; MA = 1,384	4 original + 6 others (NF):	Extreme quartile:	PAD: AL = 3.3 ± .08; AL ≥ 4 = 49%. No PAD: AL = 2.2 ± .05; AL ≥ 4 = 23%. PAD > in B (7.8%) than W (3.4%) or MA (5.1%). B with PAD more likely to have ↑ AL than W or MA with PAD. Those with PAD had ↑ AL scores with ↑ SBP, ↓ GFR, & ↑ Ho & CRP. Covariates: age, sex, race
					SBP & DBP (mm Hg)	> 138/81	
					TC (mg/dL)	> 234	
					Hb_{A1c} (%)	> 5.6	
					Others		
					BMI (kg/m^2)	> 31.2	
					Alb (g/dL)	< 4.47	
					Cr cl (m/min/1.73m^2)	< 78.5	
					Trig (mg/dL)	> 189.5	
					CRP (mg/dL)	> 0.49	
					Ho (umol/L)	> 10.1	
					Count in HR quartile. High AL considered ≥ 4.		

(continued)

Table 3. (continued)

		Sample			Allostatic Load Measures		
Author, Year	Purpose and Design	*N*	Age	Sex, Race/Ethnicity	Operationalization	Cutoff	Findings
Seeman et al., 2008	Examine relationships between education, income & ethnicity & AL in NHANES III (1988–1994). Cross-sectional	15,578	20 + years, median = 42	F = 7,991; M = 7,587; W = 11,979; B = 1,620; MA = 779; O = 1,200	6 original + 3 others (NF): SBP & DBP (mm Hg) HDL-C (mg/dL) TC (mg/dL) Hb_{A1C} (%) WHR Others CRP (mg/dL) Alb (g/dL) Heart rate (bpm) Count in HR category (0–9). AL≥ 3 vs. < 3, top quartile vs. lower 3 quartiles & continuous variables. Subscales: inflammation, metabolic, & CVS.	Clinical cutoffs: ≥ 140/90 < 40 ≥ 240 ≥ 6.4 M > 0.9, F > 0.85 ≥ 0.3 < 3.8 ≥ 90 Scores with/without points for medications.	Total AL: mean = 1.6, median = 1.0. Inflammation: (range 0–2) mean = 0.25, median = 0. Metabolic: mean = 1.1, median = 1.0. CVS: mean = 0.28, median = 0. ↓ education & income gradients = ↑ AL. 80% in ↓ AL range. For W & B, strongest gradients in metabolic & CVS subscales. For MA, strongest gradient in inflammation subscale. AL flattened in older age. Ethnicity: sig. ↑ risk for B & marginal ↑ for MA vs. W independent of education & income. Ethnic-by-education or -income interactions NS. Covariates: age, smoking, physical activity
Kaestner et al., 2009	Examine relationship between nativity & time in United States & AL in MA-US & MA-FB in NHANES III (1988–1994). Cross-sectional	6,161	30–60 years	Sex NR; W = 2,502; B = 1,899; MA-US = 924; MA-FB = 836	4 original + 6 others (NF): Same as Geronimus et al., 2006	Sample-based extreme quartile: Same as Geronimus et al., 2006	AL = 3 for ages 30–44 years (W = 2.5, B = 3.23, MA-US = 3.15, MA-FB = 2.92). AL = 4.5 for ages 45–60 (W = 4.14, B = 4.75, MA-US = 4.62, MA-FB = 4.46). MA-FB 45–60 years had < AL (4.46) on arrival than MA-US (4.62) & B (4.75); the difference was attenuated with increasing duration of U.S. residence. No relationship between time in U.S. & AL for ages 30–44 years. B highest AL
Merkin et al., 2009	Examine race/ethnic-specific patterns of association between NSES & AL in NHANES III (1988–1994). Cross-sectional	13,199	Median: W = 42 years, B = 38 years, MA = 34 years	F = 6,850, M = 6,349, W = 5,225, B = 4,005, MA = 3,969	Same as Seeman et al., 2008. High AL defined as score ≥ 3	Same as Seeman et al., 2008	W AL: mean = 1.5, median = 1, 25/75 percentile = 0, 2. B AL: mean = 1.6, median = 1, 25/75 percentile = 0, 3. MA AL: mean = 1.6, median = 1, 25/75 percentile = 1, 2. AL ≥ 3: W 22.8%, B 25.4%, MA 21.9%. ↑ AL = ↓ NSES adjusting for age, sex & U.S. birth in all races but only sig. for B (↑ 200%). Adjusting for education & urban location, trends remained for B & MA
Crimmins et al., 2009	Examine relationships between SES, age, mortality & AL in NHANES III (1988–1994, 1999–2004). Cross-sectional	1988–1994: 14,912. 1999–2004: 12,752	1988–1994: 44.4 ± 18.5, range ≥ 20 years. 1999–2004: 45.6 ± 15, range ≥ 20 years	1988–1994: F = 7,775, M = 7,137, W = 12,012, B = 1,584, MA = 1,316. 1999–2004: F = 6,621, M = 6,131, W = 9,683, B = 1,323, MA = 1,746	5 original (same as Crimmins et al., 2003) + 4 others (NF): Others BMI (kg/m^2) CRP (mg/dL) Alb (g/dL) heart rate (bpm) Count in HR quartile (0–9). Scores NR	Same as Crimmins et al., 2003, except BMI ≥ 30. 0 points assigned for medications	↑ AL = ↑ mortality with ↑ age + poverty. ↑ mortality by income for individuals < 70 years. Those with ↑ AL, poverty, & age had ↑ mortality; age attenuated effects of poverty. Poverty had > influence on mortality than sex. ↑ AL resulted in life expectancy ↓ by 6 years. Covariates: smoking, heavy drinking, inactivity

(continued)

Table 3. (continued)

		Sample			Allostatic Load Measures		
Author, Year	Purpose and Design	*N*	Age	Sex, Race/Ethnicity	Operationalization	Cutoff	Findings
Bird et al., 2010	Assess association between NSES & AL in NHANES III (1988 –1994). Cross-sectional	13,184	20–90 years, mean = 45 years	F = 6,842; M = 6,342; W = 10,679; B = 1,701; MA = 804	Same as Seeman et al., 2008	Same as Seeman et al., 2008	AL: 1.56 ± 1.35 (range: 0–5). Subscales: inflammation = 0.25, metabolic = 1.09, CVS = 0.28. ↓ NSES = ↑ AL controlling for individual SES, age, sex, & race; consistent across ethnic, sex, & IPR groups. Only metabolic & CVS subscales related to NSES
Borrell et al., 2010	Assess the association between AL & all-cause mortality in NHANES III linked to 2007 National Death Index. Cross-sectional	13,715	25 to 65+ years	F = 7,187; M = 6,528; W = 11,466; B = 1,565; MA = 684	Same as Seeman et al., 2008. Used sample tertiles; categorized AL as ≤ 1, 2, & ≥ 3	Same as Seeman et al., 2008	AL in survivors: 1.83 ± 0.04; AL in deaths (n = 2,491): 2.9 ± 0.05. AL of 2 & ≥ 3 = 40% & 88% ↑ mortality compared to AL of 1. All races 25–44 years: ↑ mortality = ↑ AL. No interaction between race & AL; AL ≥ 3 vs. ≤ 1 in W = 205% ↑ mortality. AL ≥ 3 vs.≤ 1 in B = 147% ↑ mortality. AL of 2 or ≥ 3 in MA = 3-fold ↑ mortality. Effect of AL on mortality depended jointly on race & age. Only W ≥ 65 years with AL ≥ 3 = ↑ mortality. Covariates: age, gender, race, education, & income
Chyu & Upchurch, 2011	Examine relationships between age, SES (education & income), ethnicity, & AL in women in NHANES (1999–2004). Cross-sectional	5,765	18 to 70+ years; <40 years n = 2,194; 40–59 years n = 2,147; ≥ 60 years n = 1,424	F = 5,765; W = 4,645; B = 700; MA = 420	5 original + 5 others (NF): SBP & DBP (mm Hg) HDL-C (mg/dL) TC (mg/dL) Hb_{A1c} (%) Others BMI (kg/m^2) Ho (umol/L) Alb (mg/dL) CRP (mg/dL) Heart rate (bmp) Count in HR quartile. Sample- based vs. clinical HR cutoffs	Extreme quartile: ≥132/78 <46 ≥228 ≥5.5 >31.93 >9.02 <4.5 ≥0.57 ≥82 No points for medications	AL = 2.71 ± 1.54 (range 0–9), mode = 2. 13% had AL of 0. ↑ AL = ↑ age, ↓ education, ↓ income & separated or divorced. AL ↑ in U.S.-born > in foreign-born. AL: B = 3.33, MA = 2.42, W = 2.65. Blacks > AL vs. other races & a marked Black/White gap in AL across all ages. Greatest disparity in AL between B & W at age 40–49 years (3.73 vs. 2.66). B accrued ↑ AL at younger ages than other racial groups. MA-FB vs. MA-US had < AL across all ages

(continued)

Table 3. (continued)

Author, Year	Purpose and Design	Sample			Allostatic Load Measures		
		N	Age	Sex, Race/Ethnicity	Operationalization	Cutoff	Findings
Yang & Kozloski, 2011	Examine sex and age differences in AL & in inflammation and MetS subscales in NHANES (1988–2006). Cross-sectional	14,485	17–85 years	F = 7,710; M = 6,775; W = 6,375; B = 4,490; MA = 3,620	4 original + 10 others (NF): SBP & DBP (mm Hg) HDL-C (mg/dL) Hb_{A1c} (%) Others BMI (kg/m^2) WC (cm) Trig (mg/dL) FG (mg/dL) CRP (mg/ml) Peak flow (mL, largest value) Fib (mg/dL) Cr cl (mg/dL) Urine Alb (mg/dL) Ho (umol/L) Count in HR quartile (excluded Fib). Inflammation (0–3) & MetS (0–5) subscales	Extreme quartile & clinical criteria: 130/85 ≤40 ≥6.4 ≥30 M > 102, F > 88 ≥150 ≥110 >3.0 <2113 M≥ 341, F≥ 411 <66.7 ≤ 3.5 ≥15	AL: M = 2.3 ± 1.9; F = 2.6 ± 1.9. Inflammation AL: M = 0.7, F = 1.0. MetS AL: M = 0.2; F = 0.1. M vs. F: ↓ inflammation, but sex gap ↓ with ↑ age. F vs. M: ↑ AL holding age constant. AL ↑ more for F than M leading to a large F excess postmenopause that persisted after adjusting for other covariates. F had > levels of inflammatory markers & overall burden but slower rates of ↑ inflammation with age

Note. 10 original = original operationalization of AL includes a composite score describing the levels of 10 markers of multisystem biological dysregulation: Primary mediators—DHEA-S (ng/dL), urine cort (ug/g cr), urine NE (ug/g cr), urine EPI (ug/g cr); Secondary outcomes—SBP & DBP (mm Hg), HDL-C (mg/dL), TC/HDL-C (mg/dL), Hb_{A1c} (%), WHR.
AL = allostatic load; Alb = albumin; B = Black; BMI = body mass index; BP = blood pressure; bpm = beats per minute; Cr cl = creatinine clearance; CRP = C-reactive protein; CVS = cardiovascular; DBP = diastolic blood pressure; F = female; FG = fasting glucose; Fib = fibrinogen; Hb_{A1c} = glycosylated hemoglobin; HDL-C = high-density lipoprotein cholesterol; Ho = homocysteine; HR = high risk; IPR = income-to-poverty ratio; M = male; MA = Mexican Americans; MA-FB = Mexican Americans foreign born; MA-US = Mexican Americans born in U.S.; MetS = metabolic syndrome; NF = nonfasting; NHANES = National Health and Nutrition Examination Survey; NR = not reported; NS = nonsignificant; NSES = neighborhood socioeconomic status; O = other; PAD = peripheral arterial disease; SBP = systolic blood pressure; sig. = significant; TC = total cholesterol; Trig = triglyceride; W = White; WC = waist circumference; WHR = waist–hip ratio; Notations: ↑ = higher or increased, ↓ = lower or decreased.

filtration rates) compared with Whites or Mexican Americans with PAD (Nelson, Reiber, Kohler, & Boyko, 2007).

Lower education and income gradients were also related to higher AL across all ethnic groups (Seeman et al., 2008). Despite 80% of individuals in the survey having low AL, U.S.-born Blacks and Mexican Americans (MAs) had higher AL compared to foreign-born MAs and Whites. Whites and Blacks showed stronger gradients for the metabolic and CVS subscales, while MAs showed the the strongest gradient for the inflammatory subscale. Using two NHANES data sets, one to determine cross-sectional SES and age differentials in AL and one linked to the National Death Index (NDI) to examine mortality over 8 years, collaborators found that living in poverty was linked to increased AL up until middle age, which then plateaued around 70 years of age (Crimmins, Kim, & Seeman, 2009). Individuals with high AL versus those with low AL, matched for sex and poverty status, had a life expectancy that was 6 years shorter. Although age attenuated the effect of poverty, poor elders with higher AL had the greatest mortality risk.

Examination of the stressful influence of immigration on AL revealed that U.S.-born and foreign-born MAs had significantly higher AL than U.S.-born Whites, with Blacks having the highest AL of any group (Kaestner, Pearson, Keene, & Geronimus, 2009). Middle-aged MAs were healthier upon arrival to the United States than U.S.-born MAs, Whites, or Blacks. Immigrants who had been in the United States for at least 20 years exhibited twice the probability of high AL of U.S.-born Whites and about the same probability as U.S.-born MAs and Blacks. For immigrants aged 30–44 years, time in the United States was unrelated to AL, conceivably because the influences of unhealthy assimilation might not yet have manifested.

Researchers extended previous work by examining the relationship between NSES, over and above individual SES, and AL in the NHANES cohort (Bird et al., 2010; Merkin et al., 2009). After adjusting for age, sex, and U.S. birth, investigators found an inverse relationship between NSES and AL (Merkin et al., 2009). Additionally adjusting for urban location and education, they found that these trends remained significant for Blacks and MAs, with the odds of having high AL with inferior NSES the strongest for Blacks. When living in the lowest NSES compared to an advantaged neighborhood, Blacks had a 200% increased odds and MAs a 70% increased odds of having high AL. Further adjusting for race/ethnicity and individual SES, investigators confirmed a strong inverse relationship between NSES and AL in the same NHANES cohort (Bird et al., 2010). The metabolic and CVS, but not the inflammatory, AL subscales were associated with NSES. Contrary to Merkin et al. (2009), Bird and colleagues, using the same measures of AL and NSES, found that the link between NSES and AL was consistent across all ethnic and racial groups. Clearly, the temporal association between NSES and AL will require substantiation with longitudinal data.

Linking NHANES data to the NDI revealed that increasing AL was associated with increased mortality regardless of race, ethnicity, income, or education (Borrell, Dallo, & Nguyen, 2010). Using the same AL index as other authors listed in Table 3 (Bird et al., 2010; Merkin et al., 2009; Seeman et al., 2008), Borrell et al. (2010) found that participants with high AL had mortality rates that were 40–88% greater than those with low AL. The mortality rates associated with AL varied by age for each racial/ethnic group, with mortality rates increased in association with high AL only beyond age 65 years in Whites. Regardless of ethnicity, individuals younger than 65 years with high AL had mortality rates that were more than twice as high as the rates for those with low AL. Thus, the relationship between AL and mortality depended jointly on race/ethnicity and age. These associations were weaker than results reported in the MacArthur cohort (Seeman, Crimmins, et al., 2004), plausibly because the NHANES cohort was younger and the operationalization of AL in the NHANES studies did not include primary mediators.

Women in NHANES who were older, Black, and U.S. born with lower SES demonstrated high AL scores (Chyu & Upchurch, 2011). Black women, as compared to women of other racial groups, accrued higher AL at younger ages. The persistent Black/White disparity in AL across women of all age groups implies that Black women were at a significant health disadvantage in early adulthood, and this pattern persisted over the life course, with particularly pronounced Black/White disparities by midlife (Chyu & Upchurch, 2011; Geronimus et al., 2006). Consistent with the findings of Peek et al. (2010), foreign-born MA women had lower AL across all age groups compared to MA women born in the United States, though this health advantage was attenuated with longer U.S. residency (Kaestner et al., 2009). Investigators found sex differentials in AL that indicated gradual decreases in the sex-based disparities beginning near age 60, supporting the notion that health advantages for women (i.e., related to estrogen) decrease postmenopause (Yang & Kozloski, 2011). Women had higher total AL and higher inflammatory, but lower metabolic, subscale scores than men, but these differences decreased with age. AL scores increased with age more for women than men, leading to a larger gap between the sexes in postmenopausal ages that persisted after adjustment for covariates ($p = .025$ for the Sex-by-Age interaction), with women having higher AL.

Taken together, the NHANES data documented age, SES, racial/ethnic, and sex gradients in AL, with older and disadvantaged groups exhibiting higher risk. Emerging evidence also points to the influence of NSES on AL. Although investigators found relationships between AL and mortality, the mediating effect of AL on the SES–mortality link merits further attention. Of public health concern are the cumulative negative health consequences of immigrants residing in the United States over time. The scoring algorithm used in these studies uniformly consisted of simply summing the number of AL parameters for which individuals had biomarker levels in the extreme quartile. The NHANES data lacked neuroendocrine system biomarkers and other primary mediators that might provide a more nuanced characterization of AL, particularly those reflecting the HPA axis.

AL Measurement in Studies of Middle-Aged and Older Americans

Collectively, the studies summarized in Table 4 embody an eclectic mix of American ethnic cohorts and use diverse analytic techniques for summarizing assorted operationalizations of AL. They explore the influence of diverse measures of perceived stress, social relationships, SES, health behaviors, personality traits, and psychosocial correlates of AL. Four studies used sex-specific high-risk AL cutoffs, which is important because there may be sex differences in biobehavioral responses to stress, with neuroendocrine modulators of risk for stress-related disorders (Taylor et al., 2000).

Three studies examined the relationships between various representations of SES and AL. In a subsample of the Wisconsin Longitudinal Study, low household income, both in adolescence and in middle age, was associated with higher AL measured with the original 10 biomarkers (Singer & Ryff, 1999). Increased AL was associated longitudinally with cumulative adversity over the life span, in terms of both economic circumstances and social relationships (parent–child interactions and quality of spousal ties). Interestingly, resilient individuals with economic disadvantage but compensating positive childhood and adulthood relationships had lower AL in late middle age. In the Normative Aging Study, low SES (education level) and greater hostility were related to higher AL (Kubzansky, Kawachi, & Sparrow, 1999). Hawkley, Lavelle, Berntson, and Cacioppo (2011) examined the pathways through which SES might contribute to AL in middle-aged adults. These researchers averaged continuous *z* scores of nine AL biomarkers to more accurately reflect the continuous nature of cumulative AL and found that sleep quality was a significant mediator between SES (sum of *z* scores for education and household income) and AL, with men having higher AL than women. Consistent with Kubzansky et al. (1999), Hawkley and colleagues (2011) found that hostility modestly mediated the association between SES and AL. Given the cross-sectional design of the study, however, reverse causation is plausible, such that hostility might perpetuate low SES (Matthews, Gallo, & Taylor, 2010). Controlling for sex and White race, Hawkley et al. (2011) found that SES and years of education were significantly associated with AL. Diverging from previous research (Karlamangla et al., 2002), this study showed that several individual AL biomarkers behaved as well as the continuously measured composite score in analyses of AL as an outcome. When investigators performed factor analysis, the CVS and obesity factors were as highly correlated with SES as the composite AL measure was (Hawkley et al., 2011). Correlations between SES and the SAM and lipid factors were small. Given that the NHANES studies demonstrated that AL increased up to the seventh decade of life (Crimmins et al., 2003), it is conceivable that this younger cohort might continue to accumulate multisystem dysregulation due to low SES over time.

Several studies examined the relationships between sex, ethnicity, acculturation, stressors, and age and diverse measures of AL. Consistent with NHANES data (Geronimus et al., 2006), Blacks in the Texas City Study demonstrated the highest AL and CVD and inflammatory subscale scores of all ethnic groups, whereas U.S.-born MAs had the highest metabolic scores (Peek et al., 2010). Foreign-born MAs and those with shorter U.S. residency had lower AL than those with longer residency or Whites. Thus, it appears that the longer immigrants reside in the United States, the more likely they are to adopt negative health behaviors, supporting the healthy immigrant hypothesis (Crimmins, Kim, Alley, Karlamangla, & Seeman, 2007). Mair, Cutchin, and Kristen Peek (2011) examined the relationships among stressors, sex, and AL (measured with *z* scores) in a subset of the Texas City Study. Although women had greater chronic stress exposure, men had higher total AL, CVS, and metabolic subscale scores. Women had higher immune subscale scores. Environmental stressors were stronger predictors of AL for women than for men and were linked to higher CVD risk for women only. In another study, investigators examining the relationships among age and sex and AL found that older American Samoan women at the highest risk of diabetes had higher AL than younger women or men and that older Samoan men experienced lower AL than younger Samoan men, while younger Samoan women had lower AL than did older women (Crews, 2007) .

Four empirical investigations examined pathophysiological states related to AL, including frailty, chronic diseases, self-rated health, and depression. Szanton, Allen, Seplaki, Bandeen-Roche, and Fried (2009) found that increased AL was associated with a 16% increased odds of frailty in a cross-sectional study of older women who had more varied functional status than those in the MacArthur cohort (Gruenewald et al., 2009). In Puerto Rican adults, increased AL was significantly associated with abdominal obesity, hypertension, diabetes, self-reported CVD, and arthritis but not with self-reported cancer (Mattei, Demissie, Falcon, Ordovas, & Tucker, 2010). In that study, total AL was a better predictor of chronic conditions than the MetS subscale except for diabetes and cancer. Men had higher AL than women, a finding that may have been influenced by the specific set of biomarkers used and the clinical conditions examined. More recently, researchers found no relationships between continuous measures of AL and 12 polymorphisms in the APOA1/C3/A4/A5 genetic cluster in the Puerto Rican cohort (Mattei, Demissie, Tucker, & Ordovas, 2011).

Juster, Marin, et al. (2011) examined the relationship between AL and depressive symptoms in a small sample of middle-aged Americans. The AL index score was associated with depressive symptoms at baseline, though attenuated by age and sex, and this association was reduced to a trend after 3 years, driven primarily by increasing age after 6 years. These results were generally consistent with the Taiwanese data demonstrating that AL was associated with acute and 3-year prospective depressive symptoms (Goldman, Turra, Glei, Lin, et al., 2006; Seplaki et al., 2004, 2006). Hampson, Goldberg, Vogt, Hillier, and Dubanoski (2009) examined the relationships among AL and self-rated health, depressive symptoms, and health behaviors of middle-aged adults using sex-specific

Table 4. Allostatic Load Measurement in Studies of Middle-Aged and Older Adults

		Sample			Allostatic Load Measures		
Author, Year	Purpose and Design	*N*	Age	Sex, Race/Ethnicity	Operationalization	Cutoff	Findings
Kubzansky et al., 1999	Examine relationships among SES (education), hostility & AL in Veterans Administration Boston in NAS 1987–1990. Cross-sectional	818	42–88 years, Mean = 60.8	M = 818, race/ethnicity NR	7 original + 1 other(fasting): Urine NE (ug/g cr) Urine EPI (ug/g cr) SBP & DBP (mm Hg) HDL-C (mg/dL) TC/HDL-C (mg/dL) WHR Other 2-hr gluc (mg%) Count in HR quartiles	Sample-based extreme quartile: ≥ 58 ≥ 9.1 ≥ 143/86 ≤ 387 ≥ 6.14 1.02 ≥ 134 Continuous variables & dichotomized ≥ 3 and < 3	AL biomarkers correlations: 0.01 (HDL, DBP) to 0.77 (TC/HDL ratio, HDL). ↑ AL = ↑ hostility. Hostility mediated effect of education on AL. Covariates: smoking, alcohol, physical activity, age
Singer & Ryff, 1999	Examine effects of SES (income) & social relationships on AL in midlife cohort in 35-year WLS. Cross-sectional	84	59 years	F = 39, M = 45, Race/ethnicity NR	10 original: same as Seeman et al., 1997, in Table 1	Same as Seeman et al., 1997	44% had AL ≥ 3. 50% ($n = 22$) with ↓ SES childhood & midlife had AL ≥ 3. ↑ AL = ↓ parental income and adult income and ↑ downward mobility, negative social relationships, childhood adversity & negative social relationships
Crews, 2007	Examine the associations of AL with age, gender, & diabetes in the Longitudinal Study (begun 1976) of the Samoans Study Project 1992. Cross-sectional	273	35–88, mean 55.5 ± 9.8	F = 148, M = 125. American Samoans on Tutuila Island	6 original + 8 others (fasting; measurement units NR): Count in HR quartile (0–15) SBP & DBP (mm Hg) HDL-C TC WHR Hb_{A1c} Others LDL-C Trig FG Fasting insulin BMI (kg/m^2) RFP index Triceps skinfolds Subsc skinfolds	Sex-specific extreme quartiles: M ≥ 154/64, F ≥ 156/62 M ≤ 21, F ≤ 25 M ≥ 212, F ≥ 222 M ≥ 0.98, F ≥ 0.87 M ≥ 10.2, F ≥ 10.6 M ≥ 154, F ≥ 163 M ≥ 200, F ≥ 137 M ≥ 211, F ≥ 179 M ≥ 169, F ≥ 214 M ≥ 31.2, F ≥ 33.1 M ≥ 0.53, F ≥ 0.50 M ≥ 32.2, F ≥ 55.3 M ≥ 57, F ≥ 60	AL score NR. 6 original biomarkers + skinfolds, BMI & relative fat pattern = highest AL (M 2.63 ± 1.95, F 3.56 ± 2.24). Age explained 3% of variance in AL. ↑ AL = ↑ age in F; ↑ AL = ↓ age in M. F had > AL than M. ↑ AL = ↑ diabetes in F
Szanton et al., 2009	Evaluate association between AL & frailty in older women at baseline in Baltimore (WHAS) I (1992–1995) & II (1994–1996). Cross-sectional	728	70–79 years, mean 74.2 ± 0.1	F = 728, W = 76%, B = 24%	5 original + 5 others (NF): DHEA-S (ug/dL) SBP & DBP (mm Hg) TC/HDL-C (mg/dL) Hb_{A1c} (%) Others BMI (kg/m^2) Cr cl (ml/min) Trig (mg/dL) IGF-1 (ng/ml) IL-6 (pg/mL) Count in HR quartiles	Extreme quartile: ≤ 0.24 ≥ 161/81 ≥ 5.39 ≥ 7.9 ≥ 30.5 ≥ 46.2 ≥ 205 ≥ 0.94 ≥ 3.95	AL range 0–8; AL 0–4 (91%). Nonfrail = 2.22 ± 0.09, prefrail = 2.59 ± 0.09, frail = 2.87 ± 0.17. AL not associated with race, education, pack years smoked. ↑ AL modestly related to ↑ frailty in 3 categories. OR for ↑ frailty for 1 increment ↑ AL = 1.16. Covariates: age, race, # chronic diseases, education, smoking

(continued)

Table 4. (continued)

		Sample			Allostatic Load Measures		
Author, Year	Purpose and Design	*N*	Age	Sex, Race/Ethnicity	Operationalization	Cutoff	Findings
Hampson et al., 2009	Examine the relationships between AL & self-reported health, depressive symptoms & health behaviors of 40- to 50-year follow-up of Longitudinal Hawaii Personality & Health Cohort. Cross-sectional	470	50 ± 2.0	F = 243, M = 227, JA = 198, NH = 80, EA = 56, O = 136	5 original + 6 others (measurement units NR): SBP (mm Hg) DBP (mm Hg) TC TC/HDL-C WHR Others BMI (kg/m^2) Urine protein FG Trig 1- & 2-tailed count (10/90, 25/75; 0–11) & continuous (folded z or linear z scores) AL scores	Sex-specific cutoffs, 25/75 cut point: M < 114/> 130, F < 110/> 132 M < 72/> 86, F < 68/> 80 M < 175/> 222, F < 177/> 227 M > 5.4, F > 5.4 M < 0.89/> 0.97, F < 0.77/ > 0.86 M < 25/> 32, F < 22/> 31.5 M > 2, F > 2 M < 93/> 105, F <86/> 100 M <73/>259, F < 61/> 225 Sample-based. + 1 point for medications	AL: M 10/90 = 1.92, 25/75 = 4.30, folded z = 0.62; linear z = 0.14; F 10/90 = 2.12, 25/75 = 4.31, folded z = 0.61, linear z = −0.13. M > F on 8/11 biomarkers. M AL > F AL using one-tailed count & linear z, but not two-tailed count or folded z scores. ↓ health = ↑ all AL measures but F 25/75 count. Depression not associated with AL except F linear z score. Controlling for education, ↑ smoking, ↑ alcohol, ↓ exercise = ↑ AL in M; of these, only education was associated with AL in F
Mattei et al., 2010	Examine associations of AL vs. MetS to self-reported chronic diseases (obesity, HTN, diabetes, CVD, arthritis & cancer) in Boston Puerto Rican Health Study. Baseline: 2004–2008. Cross-sectional	1,116	45–75 years, mean 57.4 ± 7.5	F = 804, M = 312, all Puerto Rican	9 original + 1 other (fasting): DHEA-S (ng/mL) Urine cort (ug/g cr) Urine NE (ug/g cr) Urine EPI (ug/g cr) SBP & DBP (mm Hg) HDL-C (mg/dL) TC (mg/dL) Hb_{A1c} (%) Other WC (cm) Count in HR quartile. AL: 0/1, 2, 3, 4, 5, ≥ 6. Created a MetS subscale: gluc, HDL-C, Trig, BP, WC	Sex-specific clinical or sample-based cutoffs: M < 589.5, F < 368.5 M ≥ 41.5, F ≥ 49.5 M ≥ 30.5, F ≥ 46.9 M ≥ 2.8, F ≥ 3.6 >140/90 <40 ≥240 >7 M > 102, F > 88 + 1 point for medications	AL: 3.8 ± 1.7 (M > F). F vs. M: ↑ TC, HDL-C, NE, CRP, WC. M vs. F: ↑ BP, DHEA-S. 74% had MetS. AL (≥ 6) stronger OR than MetS subscale (≥ 3) for CVD (4.15 vs. 2.39), HTN (5.24 vs. 4.98), obesity (5.53 vs. 3.52), arthritis (3.07 vs. 1.73), but not diabetes (4.19 vs. 5.22) & cancer (0.43 vs. 0.91). Covariates: age, sex, smoking, alcohol intake, physical activity, dietary fat intake, energy intake
Peek et al., 2010	Examine relationships between ethnicity, nativity, acculturation status, & AL in Texas City Stress & Health Study 2004–2006. Cross-sectional	1,410	25–90 years, mean 49 ± 16	F = 826, M = 584, W = 501, H = 733, B = 176	6 original + 6 others (NF): Plasma cort (ug/dL) SBP & DBP (mm Hg) HDL-C (mg/dL) TC/HDL-C Hb_{A1c} (%) Others Trig (mg/dL) BMI (kg/m^2) CRP (mg/L) IL-6 (pg/mL) IL-10 (pg/mL) TNF-α (ug/L)	Sum of sex-specific extreme quartiles (0–12). Cutoffs NR. CVS, metabolic, inflammatory & stress hormone (cort) subscales	AL: 2.9 ± 1.9 (range 0–11); W 2.87 ± 1.9; B 3.21 ± 1.83; MA-US 3.07 ± 1.94; MA-FB 2.55 ± 1.93. B had highest AL, followed by MA-US, W & MA-FB. B had > CVS & inflammatory subscales vs. W. Covariates: age, education, income, health insurance, physical inactivity, & smoking status

(continued)

Table 4. (continued)

Author, Year	Purpose and Design	Sample			Allostatic Load Measures		
		N	Age	Sex, Race/Ethnicity	Operationalization	Cutoff	Findings
Mair et al., 2011	Examine relationships among stressors, gender, & AL in Texas City Stress & Health Study 2004–2006. Cross-sectional	1,072	25–90 years, mean = 51.6	F = 627, M = 445, W = 426, B = 116, MA-US = 400, MA-FB = 130	5 original + 11 others (NF): SBP & DBP (mm Hg) HDL-C (mg/dL) TC/HDL-C Hb_{A1c} (%) Others Trig (mg/dL) BMI (kg/m^2) CRP (mg/L) IL-6 (pg/mL) IL-1 (pg/mL) IL-10 (pg/mL) TNF-α (ug/L) latent EBV-capsid antigen early antigen EBV nuclear antigen (EBNA) HSV-1	Cutoffs NR. AL = sum of 16 biomarkers. *Z* scores vs. dichotomous sum did not alter results. CVS, metabolic, inflammatory, immune subscales	M: > total, CVS, & metabolic AL vs. F. F > immune AL vs. M. B F vs. W F: ↑ CVS & immune subscales. Stressors (proximity to petrochemical plant, daily hassles, poor neighborhood perceptions) better predictor of AL in F than in M. Long-term residence in Texas City linked to ↑ CVD risk for F only. Covariates: marital status, social support, education, income, smoking, physical activity, # chronic health conditions, perceived stress, health insurance
Hawkley et al., 2011	Examined whether stress, coping, personality, psychosocial variables, social networks, or behaviors mediated SES–AL relationship in CHASRS 2003. Cross-sectional	208	51–69 years, mean = 58.4	F = 110, M = 98, W = 78, B = 72, MA = 58	8 original + 1 other (NF): Urine cort (ng/mg cr) Urine NE (ng/mg cr) Urine EPI (ng/mg cr) SBP & DBP (mm Hg) HDL-C (mg/dL) TC (mg/dL) Hb_{A1c} (%) Other WC (cm)	AL = averaged z scores. Factor analyzed AL biomarkers	FA = 4-factor structure: CVD (DBP, SBP), SAM (NE, EPI), lipid metabolism (TC, HDL-C), obesity (WC, Hb_{A1c}). Cortisol loaded on SAM & lipid factors. 4 factors correlated 0.04 to 0.4. ↑ AL = ↓ SES, ↑ perceived stress, ↑ hostility, poor sleep quality. Age was not associated with SES or AL. Race was not associated with AL. M AL > F AL. CVD & obesity AL factors as highly correlated with SES as AL
Juster, Marin et al., 2011	Examined association between AL & depression at BL, 3, & 6 years in Longitudinal Study of Aging (1994–2002). Cross-sectional & longitudinal	58	52–80 years, mean = 67.6	F = 26, M = 32, race/ethnicity NR	5 original + 2 others (fasting; units of measure NR): Plasma cort SBP & DBP (mm Hg) HDL-C TC Others Gluc Trig	Sample-based extreme quartiles. Cutoffs NR. AL range: 0–7. Medication not included in analyses.	AL: baseline = 2.21, 3 years = 2.19; 6 years = 2.02 (n = 32). Controlling for age & sex, ↑ AL = ↑ depressive symptoms acutely, but only a trend after 3 years & driven by ↑ age after 6 years

Note. 10 original = original operationalization of AL includes a composite score describing the levels of 10 markers of multisystem biological dysregulation: Primary mediators—DHEA-S (ng/dL), urine cort (ug/g cr), urine NE (ug/g cr), urine EPI (ug/g cr); Secondary outcomes—SBP & DBP (mm Hg), HDL-C (mg/dL), TC/HDL-C (mg/dL), Hb_{A1c} (%), WHR.

AL = allostatic load; B = Black; BL = baseline; BMI = body mass index; BP = blood pressure; DBP = diastolic blood pressure; CHASRS = Chicago Health, Aging and Social Relations Study; cort = cortisol; Cr cl = creatinine clearance; cr = creatinine; CRP = C-reactive protein; CVD = cardiovascular disease; CVS = cardiovascular; DHEA-S = dihydroepiandrosterone sulfate; EA = European American; EPI = epinephrine; EBV = Epstein-Barr virus; F = female; FA = factor analysis; FG = fasting glucose; Gluc = glucose; H = Hispanic; Hb_{A1c} = glycosylated hemoglobin; HDL-C = high-density lipoprotein cholesterol; HR = high risk; HSV = herpes simplex virus; HTN = hypertension; IGF-1 = insulin-like growth factor-1; IL-6 = interleukin 6; JA = Japanese; LDL-C = low-density lipoprotein cholesterol; M = male; MA = Mexican American; MA-FB = Mexican American-Foreign born; MA-US = Mexican American-United States born; MetS = metabolic syndrome; NAS = Normative Aging Study; NE = norepinephrine; NF = nonfasting; NH = native Hawaiian; NR = not reported; O = other; OR = odds ratio; RFP = relative fat pattern; SAM = sympathetic adrenomedullary; SBP = systolic blood pressure; SES = socioeconomic status; subsc = subscapular; TC = total cholesterol; TNF-α = tumor necrosis factor alpha; Trig = triglyceride; W = white; WC = waist circumference; WHAS = Women's Health and Aging Studies; WLS = Wisconsin Longitudinal Study; WHR = waist-hip ratio. Notations: ↑ = higher or increased, ↓ = lower or decreased.

high-risk cutoffs and numerous scoring algorithms summarized in Table 4. Compared to women, men demonstrated higher AL on the one-tailed and linear *z*-score measures indicating poorer CVS and metabolic health. Less education predicted high AL in women, whereas smoking, less alcohol consumption, and inactivity predicted high AL in men. Although AL predicted self-rated health in both sexes, it was associated with depressive symptoms only in women. The AL measures summing extreme scores at one tail of the biomarker distribution performed better than the ones summing extreme scores at both tails, and continuous measures performed better than count-based measures. Continuously measured AL biomarkers had the highest correlations with self-rated health and health behaviors. Hampson and colleagues coherently argued for using linear *z* scores that maximally use available variance and, in turn, increase statistical power. Even without measures of primary mediators, these authors also provided evidence for the advantages of sex-specific high-risk cutoffs.

Compared to the MacArthur and Taiwanese aging studies, which used internally consistent measures of AL in their respective cohorts, the findings of the studies presented in Table 4 are difficult to synthesize. Half of the studies had limited measures of neuroendocrine functioning, two lacked data on ethnicity, and two did not report high-risk cutoff criteria for AL measures. Although all studies used cross-sectional designs that prohibit determination of causal direction, they contribute to the literature regarding the inclusion of a broader range of allostatic challenges, exploration of sex-specific high-risk criteria and alternative scoring algorithms, and examination of the construct validity of AL with factor analytic techniques.

AL Measurement in Specific Clinical Populations

Of the nine AL studies summarized in Table 5, three focus on chronic fatigue syndrome (CFS), two deal with dementia caregivers (CGs), one each addressed hospitalized elders, mothers of childhood cancer survivors, and young adults in the Coronary Artery Risk Development in Young Adults Study (CARDIA), and one examined AL and health in Swedish diabetics. Most studies used cross-sectional designs with sample sizes of 28–782, and all but one used the count-based AL scoring algorithm.

Glover (2006) examined the relationship between increased distress and PTSD symptoms and AL in mothers of childhood cancer survivors. Using both ends of the cortisol continuum, the author found that increased AL (higher EPI and BMI and lower cortisol) was associated with an increasing number and severity of PTSD symptoms in a dose–response pattern. The predictive value of AL for differentiating between those with and without PTSD was not enhanced with the inclusion of cortisol or catecholamines in the AL measure.

Individuals with CFS also had significantly higher AL compared to controls (Maloney et al., 2006). The most discriminating AL biomarkers underlying the link between CFS and AL included high WHR and low levels of aldosterone and night-time urinary cortisol. Utilizing a different set of AL biomarkers, researchers found that CFS patients were nearly 3 times as likely as well controls to have high AL (Maloney, Boneva, Nater, & Reeves, 2009). CFS patients also displayed more depressive symptoms, higher insulin levels and, inexplicably, shorter duration of fatigue. High AL was unrelated to functioning or symptoms in the CFS group, contrary to previous findings that high AL was associated with increased pain, symptom frequency, and worse physical functioning in CFS patients (Goertzel et al., 2006). In the sole study in this review directly examining the association between genetic variance and AL, investigators genotyped CFS patients for polymorphisms related to HPA-axis activity and CVS and metabolic function (Smith, Maloney, Falkenberg, Dimulescu, & Rajeevan, 2009). The T allele of the angiotensin-1-converting enzyme (ACE) rs4968591 polymorphism was associated with higher AL in women (higher levels of IL-6 and CRP and lower levels of cortisol) after adjusting for covariates. The authors hypothesized that ACE might play a role in the communication between the CNS and immune system in response to stress, thus representing a diathesis–allostatic load effect.

In a study specifically designed to evaluate the plausible mechanisms by which stress and AL influenced the health of Australian dementia CGs, researchers found that higher levels of perceived stress were related to higher AL primary mediators in veteran CGs over 2 years compared to new or non-CGs (Clark, Bond, & Hecker, 2007). Although AL scores escalated over time, they did not differ between CG groups. Use of total AL was not superior to either the primary mediator or secondary outcome subscale scores in examining correlations between AL and stress. This finding challenges the literature documenting the benefit of the use of total AL indices over individual biomarkers but concurs with Rigney (2010), who, using the same full battery of original AL biomarkers, found that primary mediators, but not secondary outcomes or total AL scores, were associated with incident delirium in hospitalized elders.

American CGs had higher AL compared to non-CGs, with personal mastery but not depressive symptoms or role overload moderating the relationship between CG status and AL (Roepke et al., 2011). CG status accounted for 2.9% of the variance in AL when investigators controlled for sex. Contrary to predictions, CGs had higher AL compared to non-CGs when mastery was high but not when it was low. In this study, which was not specifically designed to measure AL, researchers used 6 of the 10 original AL, measured plasma catecholamine rather than urinary catecholamine, and used BMI as a proxy for WHR. In a study involving Swedish diabetics, investigators used five original AL biomarkers plus six others and found no relationship between total AL and a single-item self-rated health score (Carlsson, Nixon Andreasson, & Wandell, 2011).

Elegant analyses using structural equation modeling (SEM) recently supported a hypothesized overarching AL latent construct comprising physiological dysregulation across 6 correlated subconstructs and 18 metabolic, neuroendocrine, CVS, and inflammatory biomarkers (Seeman, Gruenewald, et al.,

Table 5. Allostatic Load Measurement in Specific Clinical Population Studies

		Sample			Allostatic Load Measures		
Author, Year	Purpose and Design	*N*	Age	Sex, Race/Ethnicity	Operationalization	Cutoff	Findings
Glover, 2006	Assess AL & PTSD in mothers of childhood cancer survivors compared to control mothers of healthy children. Cross-sectional	28	29–55 years	All F and W	9 original + 1 other (fasting): DHEA-S (ng/dL) Urine cort (ug/12 hr) Urine NE (ug/12 hr) Urine EPI (ug/12 hr) SBP & DBP (mm Hg) HDL-C (mg/dL) TC (mg/dL) Hb_{A1c} (%) Other BMI (kg/m^2) Count in HR quartile. Subscales: base AL (BP, HDL-C, TC, Hb_{A1c}, BMI); base + Cat AL (+ EPI & NE); total AL (+ cat & cort).	Extreme quartile: ≤ 1226 < 6.7 or > 23.7 ≥ 12.4 ≥ 2.0 ≥ 136/79 ≤ 46 ≥ 204 ≥ 5.6 ≥ 28.4	Base AL: PTSD = 2.6 ± 1.7, no PTSD = 1.8 ± 1.1, Con = 0.38±0.7. Base + Cat: PTSD = 3.3 ± 1.6, no PTSD = 1.9 ± 1.0, Con = 0.88 ± 1.0. Total AL: PTSD = 3.7 ± 1.5, no PTSD = 2.2 ± 1.1, Con = 1.0 ± 1.1. ↑ AL = ↑ PTSD, # symptoms, & severity of PTSD. PTSD group: 50% AL > 3. Covariate: age.
Maloney et al., 2006	Examine relationship between AL & CFS in Wichita CFS surveillance study. Cross-sectional	CFS: 43, Con: 60	27–69 years, mean 50.5 ± 8.7	F = 84, M = 19, W = 96, O = 7	7 original + 4 others: DHEA-S (ug/dL) Urine cort (ug/24 hr) Urine NE (pg/ml) Urine EPI (pg/ml) SBP & DBP (mm Hg) WHR Others CRP (mg/L) Alb (g/dL) Ald (ng/dL) IL-6 (upper quartile) Count in HR quartile. AL: ≤ 2, 3–4, & 5–7	Clinical cutoffs & sample-based: M ≤ 79.5, F ≤ 15.5 M < 26.5, F < 13.0 ≥433 ≥24 ≥140/90 M > 0.95, F > 0.87 ≥5 <3.6 ≤4.5 ≥82.2	Median AL: CFS = 3, Con = 2. AL was not associated with sex or age. CFS vs. Con: 2× more likely to have ↑ AL; attenuated by education. Most discriminating biomarkers: WHR, Cort & Ald. Coviates: age, sex, education
Clark et al., 2007	Examine associations among environmental & psychological stress and PMeds & SecO of AL in dementia caregivers. Cross-sectional & longitudinal (2 years)	*N:* Year 1 = 260, Year 2 = 242; NC *n:* Year 1 = 80, Year 2 = 57; VC *n*: Year 1 = 120, Year 2 = 88; Non-CG *n:* Year 1 = 60, Year 2 = 53	NC: 73.9 ± 7.1 years; VC: 74.2 ± 7.4 years; Non-CG: 71.9 ± 7.7 years	NC: F = 62.5%; VC: F = 65.8%; Non-CG: F = 68.3%. All Aust	10 original (fasting): DHEA-S (umol/L) Urine cort (ug/g cr) Urine NE (ug/g cr) Urine EPI (ug/g cr) SBP & DBP (mm Hg) HDL-C (mmol/L) TC/HDL-C Hb_{A1c} (%) WHR Count in HR quartile	Extreme quartile: M ≤ 2.0, F ≤ 1.4 ≥28.1 ≥47.5 ≥ 5.1 ≥145/76 ≤1.4 ≥4.8 5.8 M ≥ 0.98, F ≥ 0.87	Baseline AL was not associated with group: NC = 3.4 ± 1.6, VC = 3.3 ± 1.6, Non-CG = 3.2±1.7. AL ↑ in Year 2 due to ↑ PMed. > perceived stress in Years 1& 2 = ↑ PMed in Year 2. Perceived stress better predictor of AL than cumulative life events. No covariates

(continued)

Table 5. (continued)

		Sample			Allostatic Load Measures		
Author, Year	Purpose and Design	*N*	Age	Sex, Race/Ethnicity	Operationalization	Cutoff	Findings
Smith et al., 2009	Examined relationships between SNPs and AL in adults with/without CFS in the Wichita CFS study (1997–2000). Cross-sectional	$N = 182$; CFS $n = 50$, ISF $n = 68$, well $n = 62$, unknown = 2	26–69 years, mean 50.7 ± 8.7	F = 145, M = 37, W = 182	7 original + 4 others: Same as Maloney et al., 2006, except: Urine cort (ug/24 hr) IL-6 (pg/mL) Count in HR quartile. AL ≥ 3 & < 3.	Same as Maloney et al., 2006, except: M ≤ 25 or ≥ 72, F ≤ 8 or ≥ 37 ≥ 2.76	AL < 3: $n = 78$; AL ≥ 3: $n = 104$ (57%). ↑ AL = ↑ age, ↑ BMI. AL was not associated with sex or fatigue. ACE rs4968591 (TT) more common with ↑ AL (67.5%) than ↓ AL (49.3%) when controlling for age, sex, BMI, & fatigue. TT ACE SNP genotype = ↑ CRP, & IL-6 & ↓ cortisol in F
Maloney et al., 2009	Examine association between CFS & AL in Georgia 2004–2005. Cross-sectional	$N = 394$; CFS $n = 83$, ISF $n = 202$, well $n = 109$	19–59 years, mean 44.03 ± 9.9	F = 306, M = 88, W = 300, O = 94	6 original + 5 others: Sal cort (AUC) SBP & DBP (mm Hg) WHR TC (mg/dL) HDL-C (mg/dL) Others Heart rate (bpm) CRP (mg/L) Alb (g/dL) Gluc (mg/dL) Insulin (uU/ml) Count in HR quartile. AL ≥ 4 & < 4	Extreme quartiles & clinical cut-offs: ≤0.31, ≥0.95 ≥130/83 M > 0.94, F > 0.86 ≥206 < 38 ≥72 ≥3 <4 ≥96 ≥7.15	AL: CFS = 3.25, ISF = 2.91, well = 2.43. CFS: > CRP, WHR, TC & insulin vs. well Con. Dose–response pattern ↑ CFS with ↑ AL. ↑ AL = ↑ depressive symptoms. AL was not associated with functioning, fatigue, or symptoms in CFS. Covariates: age, race, sex, residential area, education, BMI
Seeman, Gruenewald, et al., 2010	Use SEM to test construct validity of AL & invariance across age & ethnicity in the CARDIA cohort in Year 15 examination (2000). Cross-sectional	782	32–49 years, mean 40 ± 3.6	F = 453, M = 329, W = 354, B = 428	7 original + 11 others: AM rise sal cort (nmol/L) PM decline sal cort (nmol/L) Urine NE (ug/g cr) Urine EPI (ug/g cr) SBP & DBP (mm Hg) HDL-C (mg/dL) Others LDL-C (mg/dL) FG (uU/mL) Fasting insulin (uU/mL) WC (cm) Fib (mg/dL) CRP (ug/L) IL-6 (pg/mL) Trig (mg/dL) Heart rate (bmp) Low-freq power (ms^2) High-freq power (ms^2) 6 constructs: HRV, BP, inflammation, metabolism, SNS, & HPA axis	Mean ± *SD*: 0.3 ± 0.6 −0.3 ± 0.03 3.4 ± 0.6 1.5 ± 0.6 114/75 ± 14.3/10.7 50.3 ± 13.7 114 ± 32.3 4.4 ± 0.2 2.5 ± 0.6 90 ± 15.7 339 ± 79.2 1.1 ± 0.8 0.9 ± 0.4 4.5 ± 0.6 73 ± 11.7 6.1 ± 1.1 5.9 ± 1.3	Subconstruct profiles reflecting poorer BP, inflammation, metabolic, & hormone function (flatter diurnal sal cort; ↑ SNS activity) loaded + on AL metaconstruct, & HRV factor (better HRV) loaded negatively on metaconstruct. Loadings similar in 4 sex/ethnic groups. W M: stronger loadings for trig, gluc & WC & weaker loading on inflammation factor. W M: ↓ values vs. others. W F: weaker loading on NE path on AL factor. ↓ AL in W F, followed by W M, B M & B F had the highest levels

(continued)

Table 5. (continued)

		Sample			Allostatic Load Measures		
Author, Year	Purpose and Design	*N*	Age	Sex, Race/Ethnicity	Operationalization	Cutoff	Findings
Rigney, 2010	Examine relationship between AL & delirium in hospitalized elders. Cross-sectional	44	66–93 years, mean 75.7 ± 6.4	F = 19, M = 25, W = 40, H = 3, AI = 1	10 original (NF). Count-based in HR quartile (0–10).	Sample-based extreme quartile. Cut-offs NR	AL: 2.36 ± 1.26. PMed: 0.95 ± 0.89. SecO: 1.39 ± 1.15. PMed, not SecO or total AL, predicted delirium. AL components were not associated with delirium
Roepke et al., 2011	Determine whether Alzheimer CG have >AL compared to non-CG at baseline. Cross-sectional	CG *n* = 87, Non-CG *n* = 43	CG: mean 74.3 ± 7.8 years; Non-CG: mean 74.9 ± 6.8 years	F = 88, M = 42, W = 121, O = 9	6 original + 1 other (NF): Plasma NE (pg/mL) Plasma EPI (pg/mL) SBP & DBP (mm Hg) HDL-C (mg/dL) TC/HDL-C (mg/dL) Other BMI (kg/m^2)	Extreme quartile. Cutoffs NR. Count-based in extreme quartile & summed (0–7)	AL: CG = 1.9 ± 1.3, non-CG = 1.4 ± 1.3. Personal mastery moderated CG status–AL relationship. ↑ mastery = ↑ AL. CG status accounted for 2.9% of variance in AL. M AL > F AL.
Carlsson et al., 2011	Examine the relationship between AL & self-rated health at baseline in diabetics. Cross-sectional	53	43–75 years	F = 25, M= 28, all Swedish	5 original + 6 others (fasting): Urine cort (nmol/24 h) Urine EPI SBP & DBP (mm Hg) Hb_{A1c} (%) Others WC (cm) Urine dopamine FG (mmol/L) Insulin (pmol/L) PP (mm Hg) Heart rate (bpm)	 <40 or >170 upper quartile >140/90 ≥7 F > 88, M > 102 Upper quartile ≥7 <18 or >173 ≥65 ≥75	AL range 2–8. Total AL NR. Most common AL biomarkers: ↑ WC (66%) & ↑ FG (77%). AL was not associated with age, self-rated health or any AL biomarkers

Note. 10 original = original operationalization of AL includes a composite score describing the levels of 10 markers of multisystem biological dysregulation: Primary mediators—DHEA-S (ng/dL), urine cort (ug/g cr), urine NE (ug/g cr), urine EPI (ug/g cr); Secondary outcomes—SBP & DBP (mm Hg), HDL-C (mg/dL), TC/HDL-C (mg/dL), Hb_{A1c} (%), WHR.

ACE = angiotensin converting enzyme; AI = American Indian; AL = allostatic load; Alb = albumin; Ald = aldosterone; AUC = area under the curve; Aust = Australian; B = Black; BMI = body mass index; BP = blood pressure; Cat = catecholamines; CARDIA = coronary artery risk development in young adults study; CFS = chronic fatigue syndrome; CG = caregivers; Con = controls; cort = cortisol; cr = creatinine; CRP = C-reactive protein; CVS = cardiovascular; DBP = diastolic blood pressure; DHEA-S = dihydroepiandrosterone sulfate; EPI = epinephrine; F = female; Fib = fibrinogen; FG = fasting glucose; Freq = frequency; Gluc = glucose; H = Hispanic; Hb_{A1c} = glycosylated hemoglobin; HDL-C = high-density lipoprotein cholesterol; HR = high risk; HRV = heart rate variability; ISF = insufficient symptoms of fatigue; LDL-C = low-density lipoprotein cholesterol; M = male; IL-6 = interleukin-6; NC = new caregivers; NE = norepinephrine; NF = nonfasting; Non-CG = noncaregivers; NR = not reported; O = other; PMed = primary mediators; PP = pulse pressure; PTSD = posttraumatic stress disorder; Sal = salivary; SAM = sympathetic adrenomedullary; SBP = systolic blood pressure; SecO = secondary outcomes; SEM = structural equation modeling; SNP = single nucleotide polymorphism; TC = total cholesterol; Trig = triglyceride; VC = veteran caregivers; W = white; WC = waist circumference; WHR = waist-hip-ratio. Notations: ↑ = higher or increased, ↓ = lower or decreased.

2010). Using data from the bi-ethnic CARDIA study, the SEM model identified that the core subconstructs of the AL metaconstruct, using continuously measured variables, were inflammation and metabolism followed by cardiovascular (BP) and neuroendocrine (cortisol). Due to an insignificant factor loading, the researchers eliminated EPI from the final model. Their findings support the hypothesized metaconstruct where individual biomarkers loaded on latent subconstructs, and the subconstructs loaded on an AL metaconstruct that reflected their shared variance. Blacks, particularly Black women, exhibited disadvantage in all AL factors except for heart rate variability and metabolism. These analyses provided the first test of the factorial invariance of these relationships across both gender and ethnicity.

Given the diversity of specific clinical conditions examined with largely cross-sectional designs and the heterogeneity of AL measures used in the studies presented in Table 5, it is difficult to draw firm conclusions regarding the relationships between CFS, PTSD, delirium, or self-rated health and AL. Whether measured in saliva or urine, hypocortisolemic patterns were evident in CFS (Maloney et al., 2009, 2006) and PTSD (Glover, 2006). Conflicting findings in the caregiver research highlights the need to evaluate multiple AL biomarkers in CGs to explicate the physical and mental toll exacted by altruistic care giving. Further efforts to evaluate the construct validity of AL using factor analytical and SEM techniques will also benefit the field.

AL Measurement in Studies of Working Adults

Numerous AL studies have focused on adverse working conditions and job insecurities, some of the most deleterious stressors adults can experience. Researchers have examined the adverse influence of stressful work environments on AL levels in cross-sectional studies in a variety of countries (Table 6). In a study of German industrial workers, increased job demands, but not social support or decision latitude, was associated with higher AL in men older than 45 years after researchers controlled for smoking status, sex, and age (Schnorpfeil et al., 2003). A subsequent study of German female schoolteachers revealed that greater effort–reward imbalance, vital exhaustion, and burnout symptoms were associated with modestly higher AL (Bellingrath, Weigl, & Kudielka, 2009). Using cluster analysis to create stress-recovery profiles in female Swedish workers, von Thiele, Lindfors, and Lundberg (2006) found that increased age, fatigue, and lack of recovery from work stress were associated with increased AL. Hasson, Von Thiele Schwarz, and Lindfors (2009) further found that poor self-rated health, older age, lower education, and working in the health care sector rather than in information technology were also associated with higher AL in these middle-aged women.

Increased age, male sex, and lower perceived job control were related to increased scores on secondary outcome biomarkers, or what authors referred to as glucolipid AL, in well-educated Chinese industrial workers (Li, Zhang, Sun, Dong, & Wang, 2007). Using a larger proportion of this cohort and a different set of AL biomarkers, researchers found that increased age, lower education, higher job demands, lower decision latitude, and type A personality traits were associated with higher AL (Sun, Wang, Zhang, & Li, 2007). Using clinical cutoffs as high-risk categories and only secondary outcomes, Langelaan, Bakker, Schaufeli, van Rhenen, and van Doornen (2007) found that AL was unrelated to burnout or exhaustion in male Dutch telecom managers. While the authors contended that the cohort may have been too young to manifest multisystem dysregulations, the use of clinical cutoffs rather than extreme sample quartiles may have represented an unrealistic threshold for the relatively healthy, educated group.

In American Latino day laborers, lower SES, higher daily discrimination, worse physical health, and greater tobacco and alcohol consumption were associated with higher AL (de Castro, Voss, Ruppin, Dominguez, & Seixas, 2010). Gallo, Jimenez, Shivpuri, Espinosa de los Monteros, and Mills (2011), using a 12-parameter AL index, found that chronic stresses related to work, finances, and caregiving in MA women were significantly associated with AL after adjusting for covariates. Lifestyle factors contributed little to the associations between the stressors and AL. In healthy, educated Canadian workers, increased AL was related to self-reported chronic stress, high frequency of burnout symptoms, and hypoactive morning cortisol profiles (Juster, Sindi, et al., 2011). As in all cross-sectional designs, the causal direction in this study was indeterminate: higher AL might lead to burnout symptoms, or, equally plausibly, job stress and burnout may contribute to higher AL. Such designs preclude recommendations regarding the utility of the AL index in predicting subsequent health outcomes. Examining explicit measures of stress as opposed to relying on inferences based on SES merits further attention. These studies of workplace stress highlight the importance of examining psychosocial antecedents of AL at younger ages, thus presenting an opportunity for early intervention.

Discussion

This systematic review represents the state of the science regarding the application of the AL model for advancing our knowledge of the myriad antecedents predisposing individuals to stress-related illnesses over the life span. The AL literature sheds light on both the influences of psychosocial, environmental, genetic, and sociodemographic stressors on AL indices that reflect multiple interrelated physiological regulatory systems and the consequences of AL for varied health outcomes. The impetus for heightened empirical research with the AL model is the inability of traditional models to bridge the fields of biomedical and psychosocial stress research to explain differential social and environmental risks for chronic disease outcomes or to account for ethnic, racial, and sex disparities in health. Empirical evidence supports the advantages of using multisystem physiological AL measures for predicting subclinical states of numerous health outcomes as opposed to the traditional biomedical approach of treating clinical manifestations

Table 6. Allostatic Load Measurement in Working Adults

		Sample			Allostatic Load Measures		
Author, Year	Purpose and Design	*N*	Age	Sex, Race/Ethnicity	Operationalization	Cutoff	Findings
Schnorpfeil et al., 2003	Evaluate relationships between AL & work characteristics of German airline manufacturing plant employees. Cross-sectional	324	21–60.5 years, mean 40.6 ± 9.3	F = 52, M = 272. All German.	10 original + 4 others (fasting): PMed	Extreme quartile:	Original AL = 2.44 ± 1.73 (0–8); 14-biomarker AL = 3.15 ± 2.2 (0–10). 14 biomarker AL: F (*n* = 44) = 2.4 ± 1.7, M (*n* = 277) 3.29 ± 2.28. ↑ AL = ↑ job demands × ↑ age, male sex, smoking status. AL was not associated with decision making or social support. ↓ social support = ↑ cortisol & CRP. Covariates: age, sex, smoking, work conditions
					DHEA-S (NR)	≤ 1770	
					Urine cort (ug/l)	≥ 60	
					Urine NE (nmol/l)	≥ 173	
					Urine EPI (nmol/l)	≥ 9.0	
					SecO		
					SBP & DBP (mm Hg)	≥139/85.7	
					HDL-C (mg/dL)	≤37	
					TC (mg/dL)	≥249	
					Hb_{A1c} (%)	≥5.4	
					WHR	≥0.97	
					Others		
					CRP (mg/l)	>2.30	
					TNF-α (ug/l)	≥2.2	
					BMI (kg/m^2)	≥28.4	
					Urine alb (mg/l)	≥4.3	
					Count in HR quartile (0–10; 0–14)		
Von Thiele et al., 2006	Examine the relationship between self-rated recovery from work stress & AL in female Swedish workers. Cross-sectional	241	45 ± 9.75 years	F = 241, Swedish	7 original + 6 others (fasting; measurement units NR.):	Sample-based extreme quartile:	AL range 0–11. Recovery profiles: recovered (*n* = 109) AL = 3.38 ± 2.51), nonrecovered (*n* = 51) AL = 2.84 ± 2.61, & fatigued (*n* = 82) AL = 3.88 ± 2.57. ↑ AL = ↑ lack of recovery + fatigue, ↑ age. No single biomarker related to fatigue profiles
					DHEA-S	≥2.5	
					SBP & DBP (mm Hg)	≥127/87.5	
					TC	≤5.8	
					HDL-C	≥1.54	
					Hb_{A1c} (%)	≤4.6	
					WHR	≤0.87	
					Others		
					Heart rate	≤69.3	
					Gluc	≤5.5	
					LDL-C	≤3.5	
					LDL/HDL	≤2.10	
					Trig	≤1.2	
					Prolactin	≤11	
					Count in HR quartile (0–11)		
Langelaan et al., 2007	Examine whether AL mediates relationship between burnout & physical health in male Dutch telecom managers. Cross-sectional	290	43 ± 8 years	M = 290, Dutch	5 original + 3 others (fasting):	Extreme quartile, clinical cutoffs:	AL: burned out (*n* = 33) = 2.03 ± 151, control (*n* = 257) = 1.72 ± 1.64, exhausted (*n* = 29) = 1.79 ± 1.57, nonexhausted (*n* = 45) = 1.91 ± 1.68. AL biomarkers were not associated with burnout. ↑ AL related to ↑ age but not to burnout or exhaustion. Covariates: smoking, physical activity
					SBP & DBP (mm Hg)	≥140/90	
					HDL-C (mmol/l)	≤0.8	
					TC (mmol/l)	≥6.5	
					Hb_{A1c} (%)	≥7.0	
					Others		
					BMI (kg/m^2)	≥30	
					Gluc (mmol/l)	≥6.9	
					CRP (mg/l)	≥6.0	
					AL = sum of *z* scores; count in HR quartile		

(continued)

Table 6. (continued)

		Sample			Allostatic Load Measures		
Author, Year	Purpose and Design	*N*	Age	Sex, Race/Ethnicity	Operationalization	Cutoff	Findings
Sun et al., 2007	Examine relationship between job strain & AL in Chinese industrial workers. Cross-sectional	1,219	23–58 years, mean 38.08 ± 9.17	F = 585, M = 634, Chinese	7 original + 6 others (fasting): Urine cort (ug/g cr) SBP & DBP (mm Hg) HDL-C (mmol/l) TC/HDL-C Hb_{A1c} (%) WHR Others Urine adnephrin (nmol/l) BMI (kg/m^2) Trig (mmol/l) Fib (g/l) CRP (ug/ml) IGR (mu/mmol). PMed (Fib, CRP, cort, adnephrin) & SecO (BMI, WHR, BP, Hb_{A1c}, IGR, TC/HDL, HDL & trig) subscales. AL (0–13).	Sample-based extreme quartile: ≥24.83 ≥131/80 ≤1.3 ≥3.53 ≥5.64 ≥0.87 ≥5.4 ≥25.2 ≥1.61 ≥4.69 ≥2.96 ≥1.76	↓ strain group AL (n = 1149) = 3.69 ± 2.11, ↑ strain group AL (n = 70): 4.54 ± 3.1. ↑ AL = ↑ job demands, ↑ age, ↑ type A personality, ↓ education, ↓ decision latitude. AL > in M vs. F. M SecO scores > F SecO scores; F PMed scores > M PMed scores. Covariates: age, sex, education, marital status, smoking, alcohol, physical activity, type A personality
Li et al., 2007	Examine relationship between job stress & glycolipid AL in Chinese industrial workers. Cross-sectional	504	37.94 ± 9.47 years	F = 252, M = 252, Chinese	4 original + 7 others (fasting): HDL-C (mmol/l) TC (mmol/l) Hb_{A1c} (%) WHR Others LDL-C (mmol/l) BMI (kg/m^2) Trig (mmol/l) HOMA (uU/mmol) HOMA β-cell function Adiponectin (ng/ml) Visfatin (ng/mL) Count in HR quartile (0–11)	Sample-based extreme quartile: ≤1.3 ≥5.17 ≥5.64 ≥0.87 ≥3.0 ≥25.2 ≥1.61 ≥2.05 ≤3.94 ≤5.79 ≥14.97	↑ BMI, ↑ WHR, ↑ TG, ↓ adiponectin, ↑ visfatin, & ↑ glycolipid AL in ↑ job stress (n = 39) vs. ↓ job stress (n = 465) group. ↑ AL = ↓ job control, ↑ age, & male sex. Covariates: age, smoking, alcohol, physical exercise, marital status, education
Hasson et al., 2009	Examine relationship between self-rated health & AL in female employees in HC & IT/media. Cross-sectional	N = 339, HC n = 241, IT n = 98	25–40 years, HC mean 46.5 ± 9.9, IT mean 41.2 ± 10.7	F = 339, Swedish	7 original + 5 others (fasting; measurement units NR): DHEA-S SBP & DBP (mm Hg) TC HDL-C Hb_{A1c} (%) WHR Others Heart rate LDL-C LDL/HDL ratio Trig Prolactin Count in HR quartile	Sample-based extreme quartile ≤2.8 ≥129/85 5.8 ≤1.43 ≥4.6 ≥0.94 ≥70 ≥3.5 ≥2.19 ≥1.3 ≥10	AL: 3.2 ± 2.37, range 0–10. HC AL: 3.09 ± 2.3; IT AL: 3.46 ± 2.4. HC vs IT: > HDL & WHR; IT/media vs. HC: > SBP, heart rate, Hb_{A1c}, trig & DHEA-S. AL was not associated with work sector. ↑ AL = ↓ self-rated health, ↑ age & ↓ education, controlling for age. Prolactin was not associated with AL; DHEA-S was not associated with AL in IT group

(continued)

Table 6. (continued)

		Sample			Allostatic Load Measures		
Author, Year	Purpose and Design	*N*	Age	Sex, Race/Ethnicity	Operationalization	Cutoff	Findings
Bellingrath et al., 2009	Examine relationship between work-related chronic stress & AL in female school teachers. Cross-sectional	104	25–61 years, mean 45 ± 9.75	F = 104, German	10 original + 7 others (fasting):		Both AL indices (10 vs. 17) related to age. ↑ AL related to ↑ effort/reward imbalance, ↑ vital exhaustion, ↑ emotional exhaustion, controlling for age. Single AL biomarkers were not associated with effort/reward imbalance or exhaustion. Expanded 17-biomarker AL resulted in minor ↑ in effect sizes
					PMed		
					DHEA-S (ug/ml)	< 1.33	
					Urine cort (ug/g cr)	> 25.6	
					Urine NE (ug/g cr)	>64.0	
					Urine EPI (nmol/l)	>5.55	
					SecO		
					SBP & DBP (mm Hg)	>134/89	
					HDL-C (mg/dL)	<76	
					TC/HDL-C	>3.58	
					Hb_{A1c} (%)	>5.4	
					WHR	>0.86	
					Others		
					Trig (mg/dL)	>120	
					FG (mg/dL)	>100	
					CRP (mg/l)	> 2.77	
					TNF-α (pg/ml)	> 1.44	
					Fib (g/l)	>3.63	
					D-dimer (ug/ml)	>0.38	
					% Body fat	>37.3	
					Count in HR quartile (0–10, 0–17)		
De Castro et al., 2010	Examine the relationships among social & economic stressors, perceived health, & AL in Latino day laborers. Cross-sectional	30	45.8 ± 13.2 years	M = 30, Latino	4 original + 2 others (NF):	Sample-based extreme quartile:	AL: 0 = 30%; 1 = 20%; 2 = 23%; 3 = 17%; 4 = 10%. ↑ AL = ↑ years working as day laborer, ↑ fear of work-related harm, ↑ smoking history, ↑ alcohol consumption, ↓ social status, ↓ ability to pay bills, ↓ self-rated physical, but not mental, health
					Sal cort (ng/ml)	>10.7	
					SBP & DBP (mm Hg)	>138/87.5	
					WHR	>0.9	
					Others		
					BMI (kg/m^2)	>28.5	
					CRP (mg/L)	>1.8	
					Count in HR quartiles. Low AL = 0–1. HIgh AL = 2–4 (range 0–6)		

(continued)

Table 6. (continued)

		Sample			Allostatic Load Measures		
Author, Year	Purpose and Design	*N*	Age	Sex, Race/Ethnicity	Operationalization	Cutoff	Findings
Juster et al., 2010	Examine associations between AL & self-reported chronic stress, hypoactive diurnal ACR & ↑ burnout symptoms in the absence of depressive symptoms in healthy Canadian workers. Cross-sectional	30	27–65 years, mean 45.4 ± 2.12	F = 19, M = 11, W = 27, O = 3	8 original + 7 others (fasting):	Extreme quartile, clinical cutoffs:	AL ≤ 2: 58.6%; AL ≥ 3: 41.3%. Mean AL = 2.69. ↑ AL = ↑ chronic stress, burnout symptoms (emotional exhaustion), ↓ morning cortisol. AL was not associated with depression
					DHEA-S (umol/L)	≤14.03	
					Sal cort (nmol/L)	≥662.5	
					SBP & DBP (mm Hg)	≥127.5/82.5	
					HDL-C (mmol/L)	≤1.18	
					TC (mmol/L)	≥4.6	
					Hb_{A1c} (%)	≥0.058	
					WHR	≥0.95	
					Others		
					CRP (mg/L)	≥6	
					Urine alb (g/L)	≥42	
					Cr (umol/L)	≥14.03	
					Pancreatic amylase (U/L)	≥46	
					Fib (g/L)	≥ 4.1	
					Trig (mmol/L)	≥ 1.45	
					Insulin (pmol)	≥75	
					Count in HR quartile (0–15). Low AL < 2; High AL ≥ 3		
Gallo et al., 2011	Examine relationships between chronic stressors (work, social, caregiving, financial) and AL in healthy Latino women in San Diego; evaluate mediating effects of lifestyle. Cross-sectional	301	49.8 ± 6.6 years	F = 301, MA	9 original + 3 others (fasting):	Sample-based extreme quartile:	AL: 3.04 ± 2.06. ↑ AL = ↑ stress in work, finances & caregiving. Lifestyle (↓ alcohol) explained 3.5% of variance in AL, controlling for covariates. Chronic stressors were not associated with lifestyle factors. Covariates: age, menopausal status, SES, employment status, marital status, health insurance, language of assessment
					Urine cort (ug/g cr)	<0.00 or ≥43.5	
					Urine NE (ug/g cr)	≥7.75	
					Urine EPI (ug/g cr)	≥3.66	
					SBP & DBP (mm Hg)	≥124.5/78	
					HDL-C (mg/dL)	≤45	
					TC/HDL-C	≥4.4	
					Hb_{A1c} (%)	≥5.8	
					WC (cm)	≥94.5	
					Others		
					CRP (ng/mL)	≥4.42	
					IL-6 (pg/mL)	≥0.94	
					TNF-α (pg/mL)	≥3.81	
					Count in HR quartile (0–12).		

Note. 10 original = original operationalization of AL includes a composite score describing the levels of 10 markers of multisystem biological dysregulation: Primary mediators—DHEA-S (ng/dL), urine cort (ug/g cr), urine NE (ug/g cr), urine EPI (ug/g cr); Secondary outcomes—SBP & DBP (mm Hg), HDL-C (mg/dL), TC/HDL-C (mg/dL), Hb_{A1c} (%), WHR.

ACR = awakening cortisol response; AL = allostatic load; Alb = albumin; BMI = body mass index; BP = blood pressure; cort = cortisol; cr = creatinine; CRP = C-reactive protein; DBP = diastolic blood pressure; DHEA-S = dihydroepiandrosterone sulfate; EPI = epinephrine; F = female; Fib = fibrinogen; gluc = glucose; Hb_{A1c} = glycoslated hemoglogin; HC = health care; HDL-C = high-density lipoprotein cholesterol; HOMA = homeostasis model assessment for insulin resistance; HR = high risk; IGR = insulin glucose ratio; IT = information technology; LDL-C = low-density lipoprotein cholesterol; M = male; IL-6 = interleukin-6; MA = Mexican American; NE = norepinephrine; NF = nonfasting; NR = not reported; O = other; PMed = primary mediators; Sal = salivary; SBP = systolic blood pressure; SecO = secondary outcomes; SES = socioeconomic status; TC = total cholesterol; TNF-α = tumor necrosis factor alpha; Trig = triglyceride; W = white; WC = waist circumference; WHR = waist–hip ratio. Notations: ↑ = higher or increased, ↓ = lower or decreased.

of pathology (for additional reviews, see Carlson & Chamberlain, 2005; Dowd, Simanek, & Aiello, 2009; Juster et al., 2010; Szanton, Gill, & Allen, 2005). Cumulative AL indices appear better able to capture the cumulative extent of the reciprocal and nonlinear regulatory influences among physiological systems that contribute to health outcomes than do individual biomarkers.

Allostasis is a fruitful organizing framework for nurse scientists, biologists, social scientists, epidemiologists, and health disparities researchers for examining the mechanisms of the mediating effect of multisystem dysregulated biology linking allostatic challenges, or stressors, to adverse health outcomes. The AL model offers a useful framework around which disciplines can unite. By targeting the antecedents of AL during key developmental periods and articulating areas of vulnerability and resilience, it will be possible to design interventions to improve health throughout the life span. Yet, this review of the empirical AL literature uncovered interpretative complexities involving the limitations of longitudinal inferences based on cross-sectional designs, variation in the operationalization of the AL construct, limited contemporaneous measures of psychosocial challenges, perceived stress, resiliency, or genetics, and finally, weaknesses inherent in self-reported or unadjudicated clinical outcomes in unrepresentative populations.

Most investigations reviewed herein used cross-sectional research designs with the attendant inability to examine causal relationships or temporal sequence to rule out reverse causation in which disease status would affect factors that increase stress and propagate AL. Cross-sectional data present selection issues in that with advancing age, only the healthiest remain in the population. Further, stress responses are not static and change over the life history of individuals (McEwen & Stellar, 1993).

Apart from design limitations, measurement issues continue to reign as the weakest link in the AL framework. The heterogeneity of AL measurement hampered direct comparisons across studies and yielded divergent antecedent and health outcome relationships. Consensus is yet to emerge on which indices of AL are necessary and sufficient for its measurement (McEwen & Wingfield, 2010), and how best to analyze AL biomarkers continues to challenge researchers. Controversies surrounding the measurement of AL include which biomarkers to include, how to measure, combine, and weight them, and what statistical analytic techniques are appropriate. The questions of whether to represent AL biomarkers as continuous, standardized, categorical, or dichotomous variables and whether risk-defining cutoffs should be sample based, sex-specific, or at one or both extremes of the distribution or whether clinical criteria are more appropriate remain unresolved. High-risk cutoffs might be unavailable for certain biomarkers (e.g., NE), and specifying thresholds is perhaps unhelpful, given the expectation that AL can provide early warning signs for future adverse health outcomes. Although the original 10 AL index is prevalent in the empirical literature, it was merely an initial attempt to operationalize AL and not intended to represent the gold standard for measuring the construct (Seeman, Epel, Gruenewald, Karlamangla, & McEwen, 2010). In fact, subsequent empirical work augmented the original 10 AL with additional biomarkers. While further investigations are warranted, it may be unrealistic to expect that a single set of biomarkers of multisystem dysregulation could be equally predictive of all health outcomes.

Beyond the original simple count-based index that likely produced conservative estimates of the size of the relationship between AL and its correlates, investigators have used alternative complex scoring methods to create AL indices, including recursive partitioning, canonical correlation analyses, and GOM (Gruenewald et al., 2006; Karlamangla et al., 2002; Seplaki et al., 2005, 2004, 2006). Such scoring systems were attempts to improve upon the simple count of equally weighted parameters measured beyond a certain threshold by incorporating continuous biological measures, permitting nonlinearity and unequal weighting of specific physiological parameters. The few studies comparing measures of AL have generally found that the choice of parameters included was less important than preserving the continuous properties of the measures for predicting a wider array of health outcomes (Gruenewald et al., 2006; Hampson et al., 2009; Karlamangla et al., 2002; Seeman, Epel, et al., 2010; Seplaki et al., 2005). However, evidence supporting the performance of the more complex scoring algorithms against the simpler count indices remains sparse.

Despite the centrality of neuroendocrine functioning to the conceptualization of AL, measures of neuroendocrine hormones were fraught with inconsistencies that preclude comparisons across the studies reviewed. Some of the inconsistency in the predictive ability of AL primary mediators stems from the methodological challenges in assessing HPA-axis functioning (Gustafsson et al., 2011). The circadian rhythmicity of cortisol is an example of one such challenge. In normal states, higher morning cortisol levels prepare an individual for daily activity, whereas lower evening levels permit critical immune system and tissue repair. Chronic stress can produce a loss of adaptive resiliency in the HPA axis, and reduced cortisol or a flattening of the cortisol awakening response (CAR) as well as lower diurnal cortisol levels are patterns that can reflect such loss (Taylor, Karlamangla, Friedman, & Seeman, 2011). Researchers have, in fact, linked lower morning cortisol and a dampened CAR to higher AL (Juster, Sindi, et al., 2011). However, there is not yet a standard for how best to distinguish between circadian changes in neuroendocrine parameters or changes that reflect a transient state and those that represent a long-term response to stress. Approaches to measuring cortisol, EPI, and NE have thus varied widely in both the studies reviewed here and others (Dowd, Simanek, & Aiello, 2009). Some researchers have assayed single-day measures of cortisol from saliva, plasma, or urine, while others have captured the diurnal pattern of cortisol or the CAR. Further, they have measured EPI and NE in 12- or 24-hr urine collections, both of which are labor-intensive, impractical, and potentially unreliable due to poor adherence.

Although dichotomous composite scores, such as the Framingham risk score (Wilson et al., 1998) and the MetS (Grundy et al., 2005), are common in clinical medicine, information is

generally lost when continuously measured variables are dichotomized and aggregated (Beckstead & Beckie, 2011). This loss of information is particularly noteworthy when specific AL biomarkers have small effects on clinical outcomes in relatively healthy cohorts. Using the simple count-based AL index provides a crude measure of cumulative biological risks because information is lost regarding specific levels of individual biomarkers and the potential variability in their contribution to overall risk (Seeman et al., 2008). Conversely, the more complex AL scoring algorithms, such as confirmatory factor analysis, present challenges for the AL framework to evolve from the research realm to translation for clinical utility. McEwen and colleagues acknowledge that no single accepted set of biomarkers for measuring AL exists, and they urge multidisciplinary researchers to pursue measures of community-level characteristics, including environmental and psychosocial challenges, that correlate with and accurately predict AL components (McEwen & Tucker, 2011; McEwen & Wingfield, 2010). Continued efforts to operationalize AL as a comprehensive index of physiological dysregulation across multiple regulatory systems will contribute to our understanding of the mechanisms by which allostatic challenges affect health over the life course.

Future Research Directions

Priorities for future research include conducting prospective longitudinal studies, examining a broad range of antecedent allostatic challenges, and collecting reliable measures of multisystem dysregulation explicitly designed to assess AL, at multiple time points, in large population-representative samples. Longitudinal data will facilitate the test of selection effects and allow for estimates of within-cohort age trajectories that represent true developmental changes with age, thus distinguishing aging and cohort effects (Yang & Kozloski, 2011). Studies that explore individual differences in resilience and vulnerability in person–environment interactions including genomics and psychopathology are needed. Further, a greater understanding of the interplay between stressor exposure and later outcomes in the context of development is imperative. Relatively unexplored and worthy of further study are the protective roles that resilience, connectedness, and spirituality play in the context of adverse environments, persistent stressors, and inherited genetic risks.

Allostasis involves the continuous adjustments of multiple regulatory systems to create new set points that maximize resources in response to demands (Juster, Bizik, et al., 2011). These dynamic regulatory mechanisms can result in biomarker parameters outside normal clinical ranges that are, nevertheless, appropriate at a particular point in time. Thus, the simultaneous measurement of multisystem biological dysregulation, antecedent correlates, and subsequent health outcomes is an important avenue for future research. To better understand the biological mechanisms underlying AL, future studies aimed at directly testing mediation and moderation hypotheses of the associations among antecedent challenges (see Figure 1), AL, and health outcomes in the same individuals are needed (Danese & McEwen, 2012). Understanding the moderating effects of stressors of different intensity, persistence, type, and developmental timing on AL and on long-term health is essential (Ganzel, Morris, & Wethington, 2010). It is unclear whether AL effects are attributable to stressors, themselves, to genetic vulnerabilities that phenotypically manifest in deprived environments, or to other influences. Genes involved in biological stress systems are reasonable candidates for studying the genetic sources of HPA-axis regulation and how they are modified by environmental contexts.

More comparative work is needed to evaluate existing clinical, subclinical, age-specific, and sex-specific high-risk thresholds that best predict health outcomes in diverse individuals. Further, the development and validatation of new techniques for collecting reliable, feasible, and cost-effective biological samples at both the individual and the community level is an important challenge for researchers. To disentangle the underlying dynamics of biological systems involved in AL, investigators must explore a broader spectrum of biomarkers of dysregulation, examine the temporal sequence between primary mediators and secondary outcomes, and investigate differential weighting and subscales of biomarkers in relation to the preclinical and overt clinical manifestations of specific health outcomes. High-quality data from longitudinal studies will facilitate the translation of research findings into evidence-based clinical practice for reducing health disparities.

The AL framework holds promise for identifying critical periods for intervention before AL manifests in tertiary outcomes and for evaluating the efficacy of therapeutic interventions at multiple levels. Empirical AL research findings are crucial for informing the implementation of early interventions to delay or prevent future chronic illness, to optimize health and quality-of-life outcomes, and to eliminate health disparities. Health disparities are defined as differences in the incidence, prevalence, mortality, and disease burden that exist among populations (National Institute on Minority Health and Health Disparities [NIMHD], www.nimhd.nih.gov). For example, while CVD is the leading cause of death worldwide, particular population groups are more affected than others (Roger et al., 2012) and have not benefited from the declining mortality trends (Institute of Medicine [IOM], 2011). Of particular concern is the disproportionately high burden of CVD in women and specific minority groups. Elimination of health disparities was among the highest priorities of the federal government in Healthy People 2010 (Satcher, 2010). Healthy People 2020 extended this target of achieving health equality (U.S. Department of Health and Human Services [DHHS], 2011). Innovative empirical substantiation of the AL framework is poised to make significant contributions to elucidating the patterning of health disparities, eliminating health differentials, and increasing our understanding of the burden and complexity of chronic illness.

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References

Beckstead, J. W., & Beckie, T. M. (2011). How much information can metabolic syndrome provide? An application of information theory. *Medical Decision Making*, *31*, 79–92.

Bellingrath, S., Weigl, T., & Kudielka, B. M. (2009). Chronic work stress and exhaustion is associated with higher allostastic load in female school teachers. *Stress*, *12*, 37–48.

Bird, C. E., Seeman, T., Escarce, J. J., Basurto-Davila, R., Finch, B. K., Dubowitz, T., … Lurie, N. (2010). Neighbourhood socioeconomic status and biological 'wear and tear' in a nationally representative sample of US adults. *Journal of Epidemiology and Community Health*, *64*, 860–865.

Borrell, L. N., Dallo, F. J., & Nguyen, N. (2010). Racial/ethnic disparities in all-cause mortality in U.S. adults: The effect of allostatic load. *Public Health Reports*, *125*, 810–816.

Carlson, E. D., & Chamberlain, R. M. (2005). Allostatic load and health disparities: A theoretical orientation. *Research in Nursing and Health*, *28*, 306–315.

Carlsson, A. C., Nixon Andreasson, A., & Wandell, P. E. (2011). Poor self-rated health is not associated with a high total allostatic load in type 2 diabetic patients—But high blood pressure is. *Diabetes and Metabolism*, *37*, 446–451.

Chyu, L., & Upchurch, D. M. (2011). Racial and ethnic patterns of allostatic load among adult women in the United States: Findings from the National Health and Nutrition Examination Survey 1999–2004. *Journal of Women's Health*, *20*, 575–583.

Clark, M. S., Bond, M. J., & Hecker, J. R. (2007). Environmental stress, psychological stress and allostatic load. *Psychology, Health & Medicine*, *12*, 18–30.

Cohen, S., Janicki-Deverts, D., & Miller, G. E. (2007). Psychological stress and disease. *Journal of the American Medical Association*, *298*, 1685–1687.

Crews, D. E. (2007). Composite estimates of physiological stress, age, and diabetes in American Samoans. *American Journal of Physical Anthropology*, *133*, 1028–1034.

Crimmins, E. M., Johnston, M., Hayward, M., & Seeman, T. (2003). Age differences in allostatic load: An index of physiological dysregulation. *Experimental Gerontology*, *38*, 731–734.

Crimmins, E. M., Kim, J. K., Alley, D. E., Karlamangla, A., & Seeman, T. (2007). Hispanic paradox in biological risk profiles. *American Journal of Public Health*, *97*, 1305–1310.

Crimmins, E. M., Kim, J. K., & Seeman, T. E. (2009). Poverty and biological risk: The earlier "aging" of the poor. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *64*, 286–292.

Danese, A., & McEwen, B. S. (2012). Adverse childhood experiences, allostasis, allostatic load, and age-related disease. *Physiology and Behavior*, *106*, 29–39.

de Castro, A. B., Voss, J. G., Ruppin, A., Dominguez, C. F., & Seixas, N. S. (2010). Stressors among Latino day laborers. A pilot study examining allostatic load. *American Association of Occupational Health Nurses Journal*, *58*, 185–196.

Dowd, J. B., & Goldman, N. (2006). Do biomarkers of stress mediate the relation between socioeconomic status and health? *Journal of Epidemiology and Community Health*, *60*, 633–639.

Dowd, J. B., Simanek, A. M., & Aiello, A. E. (2009). Socio-economic status, cortisol and allostatic load: A review of the literature. *International Journal of Epidemiology*, *38*, 1297–1309.

Gallo, L. C., Jimenez, J. A., Shivpuri, S., Espinosa de los Monteros, K., & Mills, P. J. (2011). Domains of chronic stress, lifestyle factors, and allostatic load in middle-aged Mexican-American women. *Annals of Behavioral Medicine*, *41*, 21–31.

Ganzel, B. L., Morris, P. A., & Wethington, E. (2010). Allostasis and the human brain: Integrating models of stress from the social and life sciences. *Psychological Review*, *117*, 134–174.

Geronimus, A. T., Hicken, M., Keene, D., & Bound, J. (2006). "Weathering" and age patterns of allostatic load scores among Blacks and Whites in the United States. *American Journal of Public Health*, *96*, 826–833.

Glei, D. A., Goldman, N., Chuang, Y. L., & Weinstein, M. (2007). Do chronic stressors lead to physiological dysregulation? Testing the theory of allostatic load. *Psychosomatic Medicine*, *69*, 769–776.

Glover, D. A. (2006). Allostatic load in women with and without PTSD symptoms. *Annals of the New York Academy of Sciences*, *1071*, 442–447.

Goertzel, B. N., Pennachin, C., de Souza Coelho, L., Maloney, E. M., Jones, J. F., & Gurbaxani, B. (2006). Allostatic load is associated with symptoms in chronic fatigue syndrome patients. *Pharmacogenomics*, *7*, 485–494.

Goldman, N., Turra, C. M., Glei, D. A., Lin, Y. H., & Weinstein, M. (2006). Physiological dysregulation and changes in health in an older population. *Experimental Gerontology*, *41*, 862–870.

Goldman, N., Turra, C. M., Glei, D. A., Seplaki, C. L., Lin, Y. H., & Weinstein, M. (2006). Predicting mortality from clinical and nonclinical biomarkers. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *61*, 1070–1074.

Groer, M., Beckie, T., Breiter, D., Burns, C., Canty-Mitchell, J., Crowell, S., … Webb, M. (2010). Allostasis: A model for women's health. In K. Kendall-Tackett (Ed.), *The psychoneuroimmunology of chronic disease: Exploring the links between inflammation, stress, and illness* (pp. 183–218). Washington, DC: American Psychological Association.

Groer, M., Meagher, M., & Kendall-Tackett, K. (2010). An overview of stress and immunity. In K. Kendall-Tackett (Ed.), *The psychoneuroimmunology of chronic disease: Exploring the link between inflammation, stress and illness* (pp. 9–22). Washington, DC: American Psychological Association.

Gruenewald, T. L., Seeman, T. E., Karlamangla, A. S., & Sarkisian, C. A. (2009). Allostatic load and frailty in older adults. *Journal of the American Geriatrics Society*, *57*, 1525–1531.

Gruenewald, T. L., Seeman, T. E., Ryff, C. D., Karlamangla, A. S., & Singer, B. H. (2006). Combinations of biomarkers predictive of later life mortality. *Proceedings of the National Academy of Sciences of the United States of America*, *103*, 14158–14163.

Grundy, S. M., Cleeman, J. I., Daniels, S. R., Donato, K. A., Eckel, R. H., Franklin, B. A., ... Costa, F. (2005). Diagnosis and management of the metabolic syndrome: An American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation*, *112*, 2735–2752.

Gustafsson, P. E., Janlert, U., Theorell, T., Westerlund, H., & Hammarstrom, A. (2011). Socioeconomic status over the life course and allostatic load in adulthood: Results from the Northern Swedish Cohort. *Journal of Epidemiology and Community Health*, *65*, 986–992.

Gustafsson, P. E., Janlert, U., Theorell, T., Westerlund, H., & Hammarstrom, A. (2012). Social and material adversity from adolescence to adulthood and allostatic load in middle-aged women and men: Results from the Northern Swedish Cohort. *Annals of Behavioral Medicine*, *43*, 117–128.

Hampson, S. E., Goldberg, L. R., Vogt, T. M., Hillier, T. A., & Dubanoski, J. P. (2009). Using physiological dysregulation to assess global health status: Associations with self-rated health and health behaviors. *Journal of Health Psychology*, *14*, 232–241.

Hasson, D., Von Thiele Schwarz, U., & Lindfors, P. (2009). Self-rated health and allostatic load in women working in two occupational sectors. *Journal of Health Psychology*, *14*, 568–577.

Hawkley, L. C., Lavelle, L. A., Berntson, G. G., & Cacioppo, J. T. (2011). Mediators of the relationship between socioeconomic status and allostatic load in the Chicago Health, Aging, and Social Relations Study (CHASRS). *Psychophysiology*, *48*, 1134–1145.

Hu, P., Wagle, N., Goldman, N., Weinstein, M., & Seeman, T. E. (2007). The associations between socioeconomic status, allostatic load and measures of health in older Taiwanese persons: Taiwan social environment and biomarkers of aging study. *Journal of Biosocial Science*, *39*, 545–556.

Institute of Medicine. (2011). *A nationwide framework for surveillance of cardiovascular and chronic lung diseases*. Washington, DC: National Academies Press.

Juster, R. P., Bizik, G., Picard, M., Arsenault-Lapierre, G., Sindi, S., Trepanier, L., & Lupien, S. (2011). A transdisciplinary perspective of chronic stress in relation to psychopathology throughout life span development. *Development and Psychopathology*, *23*, 725–776.

Juster, R. P., Marin, M. F., Sindi, S., Nair, N. P., Ng, Y. K., Pruessner, J. C., & Lupien, S. J. (2011). Allostatic load associations to acute, 3-year and 6-year prospective depressive symptoms in healthy older adults. *Physiology and Behavior*, *104*, 360–364.

Juster, R. P., McEwen, B. S., & Lupien, S. J. (2010). Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neuroscience and Biobehavioral Reviews*, *35*, 2–16.

Juster, R. P., Sindi, S., Marin, M. F., Perna, A., Hashemi, A., Pruessner, J. C., ... Lupien, S. J. (2011). A clinical allostatic load index is associated with burnout symptoms and hypocortisolemic profiles in healthy workers. *Psychoneuroendocrinology*, *36*, 797–805.

Kaestner, R., Pearson, J. A., Keene, D., & Geronimus, A. T. (2009). Stress, allostatic load and health of Mexican immigrants. *Social Science Quarterly*, *90*, 1089–1111.

Karatsoreos, I. N., & McEwen, B. S. (2011). Psychobiological allostasis: Resistance, resilience and vulnerability. *Trends in Cognitive Sciences*, *15*, 576–584.

Karlamangla, A. S., Singer, B. H., McEwen, B. S., Rowe, J. W., & Seeman, T. E. (2002). Allostatic load as a predictor of functional decline. MacArthur studies of successful aging. *Journal of Clinical Epidemiology*, *55*, 696–710.

Kubzansky, L. D., Kawachi, I., & Sparrow, D. (1999). Socioeconomic status, hostility, and risk factor clustering in the Normative Aging Study: Any help from the concept of allostatic load? *Annals of Behavioral Medicine*, *21*, 330–338.

Langelaan, S., Bakker, A. B., Schaufeli, W. B., van Rhenen, W., & van Doornen, L. J. (2007). Is burnout related to allostatic load? *International Journal of Behavioral Medicine*, *14*, 213–221.

Li, W., Zhang, J., Sun, J., Dong, Z., & Wang, S. (2007). Job stress related to glyco-lipid allostatic load, adiponectin and visfatin. *Stress and Health*, *23*, 257–266.

Mair, C. A., Cutchin, M. P., & Kristen Peek, M. (2011). Allostatic load in an environmental riskscape: The role of stressors and gender. *Health Place*, *17*, 978–987.

Maloney, E. M., Boneva, R., Nater, U. M., & Reeves, W. C. (2009). Chronic fatigue syndrome and high allostatic load: Results from a population-based case-control study in Georgia. *Psychosomatic Medicine*, *71*, 549–556.

Maloney, E. M., Gurbaxani, B. M., Jones, J. F., de Souza Coelho, L., Pennachin, C., & Goertzel, B. N. (2006). Chronic fatigue syndrome and high allostatic load. *Pharmacogenomics*, *7*, 467–473.

Mattei, J., Demissie, S., Falcon, L. M., Ordovas, J. M., & Tucker, K. (2010). Allostatic load is associated with chronic conditions in the Boston Puerto Rican Health Study. *Social Science and Medicine*, *70*, 1988–1996.

Mattei, J., Demissie, S., Tucker, K. L., & Ordovas, J. M. (2011). The APOA1/C3/A4/A5 cluster and markers of allostatic load in the Boston Puerto Rican Health Study. *Nutrition, Metabolism and Cardiovascular Disease*, *21*, 862–870.

Matthews, K. A., Gallo, L. C., & Taylor, S. E. (2010). Are psychosocial factors mediators of socioeconomic status and health connections? A progress report and blueprint for the future. *Annals of the New York Academy of Sciences*, *1186*, 146–173.

McEwen, B. S. (1998a). Protective and damaging effects of stress mediators. *New England Journal of Medicine*, *338*, 171–179.

McEwen, B. S. (1998b). Stress, adaptation, and disease. Allostasis and allostatic load. *Annals of the New York Academy of Sciences*, *840*, 33–44.

McEwen, B. S. (2003). Interacting mediators of allostasis and allostatic load: Towards an understanding of resilience in aging. *Metabolism: Clinical and Experimental*, *52*, 10–16.

McEwen, B. S. (2004). Protection and damage from acute and chronic stress: Allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. *Annals of the New York Academy of Sciences*, *1032*, 1–7.

McEwen, B. S. (2006a). Protective and damaging effects of stress mediators: Central role of the brain. *Dialogues in Clinical Neuroscience*, *8*, 367–381.

McEwen, B. S. (2006b). Sleep deprivation as a neurobiologic and physiologic stressor: Allostasis and allostatic load. *Metabolism: Clinical and Experimental*, *55*, S20–S23.

McEwen, B. S., Eiland, L., Hunter, R. G., & Miller, M. M. (2012). Stress and anxiety: Structural plasticity and epigenetic

regulation as a consequence of stress. *Neuropharmacology*, *62*, 3–12.

McEwen, B. S., & Gianaros, P. J. (2010). Central role of the brain in stress and adaptation: Links to socioeconomic status, health, and disease. *Annals of the New York Academy of Sciences*, *1186*, 190–222.

McEwen, B. S., & Gianaros, P. J. (2011). Stress- and allostasis-induced brain plasticity. *Annual Review of Medicine*, *62*, 431–445.

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

McEwen, B. S., & Stellar, E. (1993). Stress and the individual. Mechanisms leading to disease. *Archives of Internal Medicine*, *153*, 2093–2101.

McEwen, B. S., & Tucker, P. (2011). Critical biological pathways for chronic psychosocial stress and research opportunities to advance the consideration of stress in chemical risk assessment. *American Journal of Public Health*, *101*, S131–S139.

McEwen, B. S., & Wingfield, J. C. (2003). The concept of allostasis in biology and biomedicine. *Hormones and Behavior*, *43*, 2–15.

McEwen, B. S., & Wingfield, J. C. (2010). What is in a name? Integrating homeostasis, allostasis and stress. *Hormones and Behavior*, *57*, 105–111.

Merkin, S. S., Basurto-Davila, R., Karlamangla, A., Bird, C. E., Lurie, N., Escarce, J., & Seeman, T. E. (2009). Neighborhoods and cumulative biological risk profiles by race/ethnicity in a national sample of U.S. adults: NHANES III. *Annals of Epidemiology*, *19*, 194–201.

Nelson, K. M., Reiber, G., Kohler, T., & Boyko, E. J. (2007). Peripheral arterial disease in a multiethnic national sample: The role of conventional risk factors and allostatic load. *Ethnicity and Disease*, *17*, 669–675.

Peek, M. K., Cutchin, M. P., Salinas, J. J., Sheffield, K. M., Eschbach, K., Stowe, R. P., & Goodwin, J. S. (2010). Allostatic load among non-Hispanic Whites, non-Hispanic Blacks, and people of Mexican origin: Effects of ethnicity, nativity, and acculturation. *American Journal of Public Health*, *100*, 940–946.

Rigney, T. (2010). Allostatic load and delirium in the hospitalized older adult. *Nursing Research*, *59*, 322–330.

Roepke, S. K., Mausbach, B. T., Patterson, T. L., Von Kanel, R., Ancoli-Israel, S., Harmell, A. L., … Grant, I. (2011). Effects of Alzheimer caregiving on allostatic load. *Journal of Health Psychology*, *16*, 58–69.

Roger, V. L., Go, A. S., Lloyd-Jones, D. M., Benjamin, E. J., Berry, J. D., Borden, W. B., … Turner, M. B. (2012). Heart disease and stroke statistics–2012 update: A report from the American Heart Association. *Circulation*, *125*, e2–e220.

Satcher, D. (2010). Include a social determinants of health approach to reduce health inequities. *Public Health Reports*, *125*, 6–7.

Schnorpfeil, P., Noll, A., Schulze, R., Ehlert, U., Frey, K., & Fischer, J. E. (2003). Allostatic load and work conditions. *Social Science and Medicine*, *57*, 647–656.

Seeman, T., Epel, E., Gruenewald, T., Karlamangla, A., & McEwen, B. S. (2010). Socio-economic differentials in peripheral biology: Cumulative allostatic load. *Annals of the New York Academy of Sciences*, *1186*, 223–239.

Seeman, T., Glei, D., Goldman, N., Weinstein, M., Singer, B., & Lin, Y. H. (2004). Social relationships and allostatic load in Taiwanese elderly and near elderly. *Social Science and Medicine*, *59*, 2245–2257.

Seeman, T., Gruenewald, T., Karlamangla, A., Sidney, S., Liu, K., McEwen, B., & Schwartz, J. (2010). Modeling multisystem biological risk in young adults: The Coronary Artery Risk Development in Young Adults Study. *American Journal of Human Biology*, *22*, 463–472.

Seeman, T., Merkin, S. S., Crimmins, E., Koretz, B., Charette, S., & Karlamangla, A. (2008). Education, income and ethnic differences in cumulative biological risk profiles in a national sample of US adults: NHANES III (1988–1994). *Social Science and Medicine*, *66*, 72–87.

Seeman, T. E., Crimmins, E., Huang, M. H., Singer, B., Bucur, A., Gruenewald, T., … Reuben, D. B. (2004). Cumulative biological risk and socio-economic differences in mortality: MacArthur studies of successful aging. *Social Science and Medicine*, *58*, 1985–1997.

Seeman, T. E., McEwen, B. S., Rowe, J. W., & Singer, B. H. (2001). Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. *Proceedings of the National Academy of Sciences of the United States of America*, *98*, 4770–4775.

Seeman, T. E., Singer, B. H., Rowe, J. W., Horwitz, R. I., & McEwen, B. S. (1997). Price of adaptation—allostatic load and its health consequences. MacArthur studies of successful aging. *Archives of Internal Medicine*, *157*, 2259–2268.

Seeman, T. E., Singer, B. H., Ryff, C. D., Dienberg Love, G., & Levy-Storms, L. (2002). Social relationships, gender, and allostatic load across two age cohorts. *Psychosomatic Medicine*, *64*, 395–406.

Seplaki, C. L., Goldman, N., Glei, D., & Weinstein, M. (2005). A comparative analysis of measurement approaches for physiological dysregulation in an older population. *Experimental Gerontology*, *40*, 438–449.

Seplaki, C. L., Goldman, N., Weinstein, M., & Lin, Y. H. (2004). How are biomarkers related to physical and mental well-being? *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *59*, 201–217.

Seplaki, C. L., Goldman, N., Weinstein, M., & Lin, Y. H. (2006). Measurement of cumulative physiological dysregulation in an older population. *Demography*, *43*, 165–183.

Singer, B., & Ryff, C. D. (1999). Hierarchies of life histories and associated health risks. *Annals of the New York Academy of Sciences*, *896*, 96–115.

Smith, A. K., Maloney, E. M., Falkenberg, V. R., Dimulescu, I., & Rajeevan, M. S. (2009). An angiotensin-1 converting enzyme polymorphism is associated with allostatic load mediated by C-reactive protein, interleukin-6 and cortisol. *Psychoneuroendocrinology*, *34*, 597–606.

Sterling, P., & Eyer, J. (1988). Allostasis: A new paradigm to explain arousal pathology. In S. Fisher & J. Reason (Eds.), *Handbook of life stress, cognition, and health* (pp. 629–649). New York, NY: Wiley.

Sun, J., Wang, S., Zhang, J., & Li, W. (2007). Assessing the cumulative effects of stress: The association between job stress and allostatic load in a large sample of Chinese employees. *Work & Stress*, *21*, 333–347.

Szanton, S. L., Allen, J. K., Seplaki, C. L., Bandeen-Roche, K., & Fried, L. P. (2009). Allostatic load and frailty in the Women's Health and Aging Studies. *Bioogical Research for Nursing*, *10*, 248–256.

Szanton, S. L., Gill, J. M., & Allen, J. K. (2005). Allostatic load: A mechanism of socioeconomic health disparities? *Biological Research for Nursing*, *7*, 7–15.

Taylor, S. E., Karlamangla, A. S., Friedman, E. M., & Seeman, T. E. (2011). Early environment affects neuroendocrine regulation in adulthood. *Social Cognitive and Affective Neuroscience*, *6*, 244–251.

Taylor, S. E., Klein, L. C., Lewis, B. P., Gruenewald, T. L., Gurung, R. A., & Updegraff, J. A. (2000). Biobehavioral responses to stress in females: Tend-and-befriend, not fight-or-flight. *Psychological Review*, *107*, 411–429.

U.S. Department of Health and Human Services. Office of Disease Prevention and Health Promotion. (2011). *Healthy people 2020*. Washington, DC: Author. Retrieved June 27, 2012, from http://www.healthypeople.gov/2020/about/default.aspx

von Thiele, U., Lindfors, P., & Lundberg, U. (2006). Self-rated recovery from work stress and allostatic load in women. *Journal of Psychosomatic Research*, *61*, 237–242.

Weinstein, M., Goldman, N., Hedley, A., Yu-Hsuan, L., & Seeman, T. (2003). Social linkages to biological markers of health among the elderly. *Journal of Biosocial Science*, *35*, 433–453.

Wilson, P. W., D'Agostino, R. B., Levy, D., Belanger, A. M., Silbershatz, H., & Kannel, W. B. (1998). Prediction of coronary heart disease using risk factor categories. *Circulation*, *97*, 1837–1847.

Yang, Y., & Kozloski, M. (2011). Sex differences in age trajectories of physiological dysregulation: Inflammation, metabolic syndrome, and allostatic load. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *66*, 493–500.