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Allostatic Load: Importance, Markers, and Score Determination in Minority and Disparity Populations

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Abstract Allostatic load is a physiological measure of the cumulative burden of stress on the body assessed by markers of physiological dysregulation. It is a multisystem construct that quantifies biological risk which leads to poor health and maladaptive trajectories. In this overview, which is based on a presentation made at the Flip the Script: Understanding African American Women's Resilience in the Face of Allostatic Load meeting at Ohio State University in August 2018, we build upon previous reviews by discussing four key aspects of allostatic load, specifically its: (1) importance, (2) operationalization, (3) use in minority health and health disparities research, and (4) value in such research. Operationalized in various ways, allostatic load is composed of 10 original markers and additional markers deriving from research among minority and disparity populations. The markers represent four biological systems: (1) cardiovascular, (2) metabolic, (3) inflammatory, and (4) neuroendocrine. System-specific racial/ethnic and sex-based differences have been observed. An overall score can be determined using sample-generated or empirically derived clinically relevant cut points. In summary, allostatic load provides an overall and a body system-specific mechanistic link between exposures to stressors and health outcomes that may help explain health disparities among minority populations.

Keywords Allostasis · Stress · African Americans · Hispanic Americans · Epidemiologic measurements

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Allostatic load is a measure of physiological dysregulation due to the cumulative burden of chronic stress on the body. This dysregulation is caused by the excess secretion of hormones such as catecholamines and glucocorticoids in response to chronic stressors. The term arises from the concept of allostasis, which is a dynamic regulatory process where homeostasis is maintained through adaptation in the presence of physical and behavioral stressors [1]. The measure is a multisystem construct that quantifies stress-induced biological risk, which may explain mechanisms of poor health and maladaptive health trajectories [2, 3]. In the context of allostasis, allostatic load provides an in-depth look at

how the adaptations of the body's physiological systems to stress affect health and may lead to disparities.

Two reviews, one being systematic, were conducted that capture the varied formulations and applications of allostatic load in health research and the factors related to it [4, 5]. Based on a presentation made at the Flip the Script: Understanding African American Women's Resilience in the Face of Allostatic Load meeting at the Ohio State University in August 2018, this overview builds upon that work by providing a perspective on the measurement of allostatic load with emphasis on its uses and relevance in minority health and health disparities research. We discuss four key aspects of allostatic load: (1) why is allostatic load important? (2) how has allostatic load been operationalized? (3) what markers have been used to represent allostatic load in minority health and health disparities research? and (4) why allostatic load may be a valuable measure to assess in minority health and health disparities research?

Why Is Allostatic Load Important?

The accumulation of allostatic load occurs in two ways: short-term, or sudden, shifts and long-term, or chronic, elevations. To understand the effects of these stressors on the body, allostatic load measures physiological responses to sudden shifts which result in bodily wear and tear as well as responses to chronic conditions which may lead to outcomes such as diabetes or hypercholesterolemia [6]. In the presence of these stressors, allostatic load assesses the adaptation of physiological systems as they become overused [7]. The measure itself has been associated with mental and physical well-being, functioning, and all-cause and cause-specific mortality [8, 9].

How Has Allostatic Load Been Operationalized?

Purpose and Markers

In considering how to operationalize allostatic load, there was a need for a multifactorial approach to quantify the physiological burden of stress which would describe and predict an individual's health [10]. Allostatic load was created by integrating biological markers, including those influenced by the social and physical environment, life course experiences, and genetics, into a single measure for this purpose [10]. Traditionally, allostatic load has been calculated using the "original 10" markers that were first published in 1997 by Seeman and colleagues and studied in a predominately White older adult sample [6]. The markers can be divided into two defined categories: primary mediators and secondary outcomes (Table 1). Primary mediators are the chemical messengers that are released as part of allostasis [11]. Secondary outcomes are integrated processes that reflect the cumulative effects in a specific tissue or organ in response to the primary mediator [11]. Among the primary mediators are (1) dehydroepiandrosterone sulfate, (2) cortisol, (3) epinephrine, and (4) norepinephrine. The remaining six secondary outcomes include (5) systolic blood pressure, (6) diastolic blood pressure, (7) waist–hip ratio, (8) high-density lipoprotein cholesterol, (9) total cholesterol, and (10) glycated hemoglobin. All of these markers serve distinct functional purposes in the calculation of allostatic load as a measurement for the burden of stress on the body (Table 1).

Aside from the "original 10," early research in a non-White population tested the measurement of allostatic load and built upon these markers. Research among Taiwanese older adults supported the validity of the construct of allostatic load, for this population identified sex-specific high-risk cut points, and utilized an additional six markers including dopamine, insulin-like growth factor-1, fasting glucose, and triglycerides [12, 13]. Other international researches have included markers not used previously such as apolipoprotein A1, apolipoprotein B, body mass index, C-reactive protein, and waist circumference [14, 15].

Methodologic Considerations

As more markers were added to measurements of allostatic load, several biological systems and pathways were represented in the overall measure: (1) cardiovascular, (2) metabolic, (3) inflammatory, and (4) neuroendocrine. Examples of markers in the cardiovascular system include systolic and diastolic blood pressure and lipid levels. The metabolic system includes markers such as glycated hemoglobin, waist–hip ratio, and body mass index. Later markers such as C-reactive protein, interleukin-6, fibrinogen, and insulin-like growth factor-1 represented the inflammatory pathway. The neuroendocrine system relies on measures reflecting the hypothalamic–pituitary–adrenal axis such as cortisol,

Table 1 The "original 10" markers of allostatic load and their functional purpose[a]

Category	Marker	Functional purpose
Primary mediators	Dehydroepiandrosterone sulfate, serum	Functional hypothalamic–pituitary–adrenal axis antagonist and indicator of adrenal gland functioning
	Cortisol, urinary	Integrated measure of 12-hour hypothalamic–pituitary–adrenal axis activity
	Epinephrine, urinary Norepinephrine, urinary	Integrated indices of 12-hour sympathetic nervous system activity
Secondary outcomes	Systolic blood pressure Diastolic blood pressure	Indices of cardiovascular activity and major risk factor for vascular disease
	Waist–hip ratio	Index of long-term levels of metabolism and adipose tissue deposition
	High-density lipoprotein cholesterol	Index of atherosclerotic risk protection
	Total cholesterol	Index of long-term atherosclerotic risk
	Glycated hemoglobin	Integrated measure of glycemia over 2–3 months

[a] Based on research by Seeman TE et al. in Archives of Internal Medicine in 1997

epinephrine, norepinephrine, and dehydroepiandrosterone sulfate.

There are some methodologic issues to consider when assessing system-specific or individual markers. Some researches have observed income and education gradients among racial/ethnic minorities for some system-specific measures [16]. Stronger gradients have been observed among African Americans and Whites for the cardiovascular and metabolic system markers, while among Mexican Americans, a stronger gradient has been observed for the inflammatory system markers. Leading experts have also noted that it is important to distinguish between primary mediators and effects and secondary and tertiary outcomes [11, 17]. Individual mediators and effects are not independent of each other as they can influence each other as well as have effects on multiple secondary outcomes. This may present some statistical issue where strongly correlated variables are included in the same measure. For example, systolic and diastolic blood pressure, lipid measures, body mass index, and waist–hip ratio are usually strongly correlated. Lastly, research linking allostatic load and mortality has differed based on the composition of the allostatic load measure [18]. Including primary mediators in predictive models may attenuate statistical relationships. Therefore, including markers that are not relevant to the research question would increase measurement error [4]. Importantly, measures should suggest pathophysiological pathways that lead to specific diseases [11].

Sex-based differences may also exist. Among men, clustering of markers with levels deemed as high-risk have been observed for C-reactive protein, epinephrine, fibrinogen, interleukin-6, and norepinephrine [19]. Among women, high-risk clustering includes C-reactive protein, interleukin-6, glycated hemoglobin, and systolic blood pressure [19]. Women may have a sex-based advantage until about age 60, after which mean allostatic load score is dramatically higher compared to that of men [20]. Differences by sex may also exist for certain system subscales where women have higher inflammatory scores and lower metabolic scores compared to men [20]. Of note, these observed differences may be the result of survival or cohort effects.

Determining a Score

The traditional, and most common, method for determining an allostatic load score has been to use quartiles to identify a high-risk category for each marker [5]. This method was first used in research conducted using data from the MacArthur Studies of Successful Aging and subsequently using data from the National Health and Nutrition Examination Survey [6, 16]. For most markers, the highest quartile is identified as the high-risk category except for a few markers where the lowest quartile is the high-risk category (e.g., high-density lipoprotein cholesterol, the ratio of forced expiratory volume in 1 second to forced vital capacity, and heart rate variability). Markers with values in the high-risk category are assigned one point and a summary score is calculated to represent overall allostatic load. This approach assumes that each marker contributes equally to allostatic load, which has not been evaluated. Research among Taiwanese and other international participants have used deciles with grade of membership-based scores. Other research has averaged continuous z scores of multiple markers, which may more

accurately reflect the continuous nature of allostatic load and greater predictive value for the outcomes of interest [21]. However, using this method may obscure the impact of system-specific contributions. Despite the specific method used in studies, previous research has used sex-specific high-risk cut points for three individual markers: high-density lipoprotein cholesterol, waist circumference, and waist–hip ratio.

Clinically Relevant Scoring

Another method for determining scores for allostatic load involves the use of empirically derived clinically relevant cut points. The cut points are determined by pre-established values in clinical medicine and generate three categories: high-risk (1 point), moderate-risk (0.5 point), and low-risk (0 points) [22]. Table 2 contains risk categories used in an NHANES analysis focused on minority health and health disparities research. For markers not routinely used in clinical practice, tertiles have been used to establish cut points for the three risk categories.

For individuals with low-risk levels of blood pressure, glycated hemoglobin, or cholesterol because they are taking medication, it has been suggested that an additional point should be added to the overall allostatic load score [23]. The assumption is that despite lowering an individual's risk, damage may have already been done to the individual's health and not be fully reversible by treatment [23]. Others argue that medication reduces actual physiological values, leads to a reversal of abnormalities, and subsequently lowers an individual's risk of chronic disease [18]. Therefore, further adjustment to the overall score is unnecessary. As a compromise, we suggest the use of half-point scoring to recognize that some bodily damage may exist, but that the risk for chronic disease has decreased [22].

Important Knowledge Gaps

A central tenet of allostatic load is that biological risks are cumulative over time. However, from life course epidemiology, we know that critical, sensitive, induction, and latency periods, context effects, and resilience and vulnerability processes can occur over the life course [24]. Such periods may increase biological risk and lead to subsequent presentation in specific markers, or a group of markers, of allostatic load. Further, there is a need to create testable theoretical models that include the life course epidemiology concepts of mediating and moderating factors. Testing of the effects of lifestyle factors, such as smoking, excessive or binge alcohol drinking, and unhealthy eating, in well-characterized cohort studies have been limited. Research in these areas is needed to elucidate the extent to which life course processes exist when determining allostatic load.

Another challenge of allostatic load is from which biological specimens are markers being assessed. The feasibility of obtaining markers from specimens collected through invasive modalities, such as by

Table 2 Clinically relevant cut points for high-, moderate-, and low-risk categories of specific biomarkers

System	Marker	High-, moderate-, and low-risk categorization
Cardiovascular	Systolic blood pressure	≥ 150 mmHg, 120 to 149 mmHg, and < 120 mmHg
	Diastolic blood pressure	≥ 90 mmHg, 80 to 89 mmHg, and < 80 mmHg
	Total cholesterol	≥ 240 mg/dL, 200 to 239 mg/dL, and < 200 mg/dL
	HDL cholesterol	< 40 mg/dL, 40 to 59 mg/dL, and > 60 mg/dL
	Total/HDL cholesterol ratio	≥ 6, 5 to < 6, and < 5
Metabolic	Glycated hemoglobin	≥ 6.5%, 5.7 to < 6.5%, and < 5.7%
	Waist–hip ratio (women)	≥ 0.85, > 0.80 to < 0.85, and ≤ 0.80
	Waist–hip ratio (men)	≥ 1.0, > 0.95 to < 1.0, and ≤ 0.95
	Body mass index	≥ 30 kg/m^2, 25 to < 30 kg/m^2, and 18 to < 25 kg/m^2
	Albumin	< 3%, 3 to < 3.8%, and ≥ 3.8%
	Creatinine clearance	< 30 mL/min/1.73 m^2, 30 to < 60 mL/min/1.73 m^2, and ≥ 60 mL/min/1.73 m^2
Inflammatory	C-reactive protein	> 3 mg/L, 1 to 3 mg/L, and < 1 mg/L

HDL high-density lipoprotein

venipuncture, may limit the extent to which research using allostatic load can be conducted in community-based settings with minority and disparity populations. There is a need to compare the validity and reliability of using invasive compared to non-invasive modalities when constructing allostatic load. Given our knowledge of minority and disparity population research interest in specimen collection and past efforts to address existing barriers [25], such analyses would help researchers identify the right balance between feasibility and validity and reliability.

What Markers Have Been Used to Represent Allostatic Load in Minority Health and Health Disparities Research?

For this overview, we conducted an informal review of minority health and health disparities literature published in the past 10 years that included African Americans and US Latinos to identify the most frequently used markers of each of the four biological systems (Table 3) [20, 21, 26–59]. In minority health and health disparities research, markers of allostatic load have generally been limited by the availability of specific markers in the dataset used to conduct these analyses. The datasets have been high-quality, representatives of defined populations and cross-sectional or longitudinal, but often investigators were not able to collect all of the original 10 indicators due to the large study populations included. However, the size of these datasets has allowed researchers to include several other markers.

In research among African Americans, additional markers have included albumin, body mass index, C-reactive protein, creatinine clearance, heart rate, homocysteine, and waist circumference (Table 4). Some investigators have suggested that for African Americans, triglyceride levels should not be included as a measure of allostatic load [60, 61]. The utility of a triglycerides measure for African Americans has been questioned because despite their higher prevalence of obesity and insulin resistance, triglyceride levels seem to be lower in African Americans compared to Whites [62, 63]. The largest study of Latinos from diverse national backgrounds, the multisite Hispanic Community Health Study/Study of Latinos, has expanded the list of possible markers [40]. These markers include some common, as well as rarely, used measures: C-reactive protein, the ratio of forced expiratory volume in 1 second to forced vital capacity, resting heart rate, heart rate variability, homeostatic model assessment of insulin resistance, interleukin-6, resting pulse pressure, waist circumference, and white blood cell count (Table 4).

Sex-based differences have also been observed among minorities. For African American women,

Table 3 Relative frequency of additional markers of allostatic load by system

Frequency	Cardiovascular system	Metabolic system	Inflammatory system	Neuroendocrine system
Most frequent	Systolic blood pressure	Glycated hemoglobin	C-reactive protein	Cortisol, urinary
	Diastolic blood pressure	Waist–hip ratio	Interleukin-6	Epinephrine, urinary
	Total cholesterol	Body mass index	Fibrinogen	Norepinephrine, urinary
Moderately frequent	HDL cholesterol	Albumin	Insulin-like growth factor-1	DHEA-S
	Triglycerides[a]	Fasting glucose, plasma	Tumor necrosis factor alpha	Dopamine
	Heart rate	Waist circumference	Interleukin-10	Aldosterone
	Homocysteine	Estimated GFR	Herpes simplex	Adnephrin
Least frequent	FEV_1/FVC[b]	2-hour glucose	Interleukin-1	Epinephrine, plasma
	Pulse pressure	LDL cholesterol		Norepinephrine, plasma
		HOMA-IR		
		Apolipoprotein A1		
		Apolipoprotein B		

DHEA-S dehydroepiandrosterone sulfate, *FEV_1/FVC* ratio of forced expiratory volume in 1 second to forced vital capacity, *GFR* glomerular filtration rate, *HDL* high-density lipoprotein, *HOMA-IR* homeostatic model assessment of insulin resistance, *LDL* low-density lipoprotein

[a] Triglycerides have been suggested to not be routinely included in the measurement of allostatic load in African Americans

[b] FEV_1/FVC is included in the cardiovascular system because of its use as a marker of cardiopulmonary function

Table 4 Additional markers of allostatic load among minority groups by system

Minority group	Cardiovascular system	Metabolic system	Inflammatory system	Parasympathetic system
African Americans	Heart rate	Albumin	C-reactive protein	
		Body mass index		
		Creatinine clearance		
		Homocysteine		
		Triglycerides[a]		
Latinos[b]	Heart rate	HOMA-IR	C-reactive protein	Heart rate variability
	FEV_1/FVC[c]	Waist circumference	Interleukin-6	
	Pulse pressure		White blood cell count	

FEV_1/FVC ratio of forced expiratory volume in 1 second to forced vital capacity, *HOMA-IR* homeostatic model assessment of insulin resistance

[a] Triglycerides have been suggested to not be routinely included in the measurement of allostatic load in African Americans

[b] Most research on allostatic load in Latinos has been conducted among Mexicans

[c] FEV_1/FVC is included in the cardiovascular system because of its use as a marker of cardiopulmonary function

research in the Coronary Artery Risk Development in Young Adults (CARDIA) study found higher mean scores of overall allostatic load and the inflammation system subscale compared to African American men or White women or men [37]. Analyses of the National Health and Nutrition Examination Survey (NHANES) data reported higher overall allostatic load in African American women than Mexican or White women in the early decades of adulthood [32]. In a more recent NHANES analysis, African Americans and Latinos had significantly higher allostatic load scores compared to Whites [22]. In general, African American men have higher allostatic load scores across age groups compared to White men [23]. Among African American men in the CARDIA study, higher mean levels have been observed in the individual markers of cortisol and blood pressure [37].

Why Is Allostatic Load a Valuable Measure to Assess in Minority Health and Health Disparities Research?

Racial/ethnic minority groups experience greater chronic stress than Whites due to the effects of discrimination leading to social disadvantage across the socioeconomic spectrum. Furthermore, less privileged socioeconomic groups experience greater chronic stress than higher socioeconomic groups. Allostatic load has been used to discover relationships between allostasis, or the lack thereof, and social determinants [4]. By assessing allostatic load in minority and disparity populations, researchers can investigate relationships between factors such as socioeconomic status and other social determinants and the consequences of chronic and acute stress on the body.

Allostatic load captures the intermediate physiological dysregulation that could contribute to health disparities in downstream outcomes (e.g., incidence and mortality) [3]. It is an important measure because it can be used to identify racial/ethnic variations in biological responses to stressors and their associations with adverse health outcomes (e.g., variations in pathophysiological mechanisms of health disparities). Since minorities, specifically African Americans, have some of the highest allostatic load scores, more research is key to mitigating the effects of health disparities. Additional markers beyond the "original 10" can also uncover new relationships between social determinants and allostatic load. These associations may differ among minority and disparity populations due to adaptive biological responses to stressors over time.

In conclusion, differences in allostatic load may reflect disparities in the exposure to stressors and provide a mechanistic link which contributes to health disparities. Allostatic load is anticipated to make vital contributions to the field of minority health and health disparities. More research is needed towards the further development of measures of allostatic load and ways in which resilience can be built to prevent damage to physiological systems. Such research would have implications for understanding biological processes related to stress as well as for the development of tailored interventions to reduce the effects of stress among minority and disparity populations.

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