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Variation in the Calculation of Allostatic Load Score: Twenty-One Examples from NHANES

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Abstract

After decades of resistance there is now a genuine consensus that disease cannot be prevented or even successfully treated unless the role of stress is addressed alongside traditionally recognized factors such as genes and the environment. Measurement of allostatic load, which is quantified by the allostatic load score (ALS), is one of the most frequently used methods to assess the physiologic response to stress. Even though there is universal agreement that in the calculation of ALS, biomarkers from three categories should be included (cardiovascular, metabolic and immune), enormous variation exists in how ALS is calculated. Specifically, there is no consensus on which biomarkers to include or the method which should be used to determine whether the value of a biomarker represents high risk. In this Perspective, we outline the approach taken in 21 different NHANES studies.

Keywords

Allostatic Load Score; Stress; Biomarkers; Blood Pressure; A1C; C-Reactive Protein

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Conflict of Interest Statement

Author Michelle T. Duong declares she has no conflict of interest.
Author Brianna A. Bingham declares she has no conflict of interest.
Author Paola C. Aldana declares she has no conflict of interest.
Author Stephanie T. Chung declares she has no conflict of interest.
Author Anne E. Sumner declare that they have no conflict of interest.

Ethical Responsibilities of Authors

This manuscript has not been submitted to more than one journal for simultaneous consideration and has not been published previously. No data have been fabricated or manipulated to support our conclusions. No data, text, or theories by others are presented as if they were the author's own.

Consent to submit has been received explicitly from all co-authors. Authors whose names appear on the submission have contributed sufficiently to the scientific work and therefore share collective responsibility and accountability for the results.

PERSPECTIVE

Chronic psychosocial stress activates both the hypothalamic-pituitary-adrenal axis (HPA) and the sympathetic-adrenal-medullary (SAM) system. The downstream result is the release of hormones and cytokines which exacerbate or promote cardiovascular, metabolic and immune disease (Figure) [1,2]. Measurement of allostatic load, which is quantified by the allostatic load score (ALS), is one of the most frequently used methods to assess the physiologic response to stress[1,2].

This perspective on the calculation of ALS was written because we needed to evaluate the influence of stress on the metabolic health of African immigrants and rapidly recognized that guidelines on the calculation of ALS had not yet been established. In the absence of any consensus, and no previous publications on the calculation of ALS in African immigrants, we focused on publications which measured ALS using National Health and Nutrition and Examination Survey (NHANES) data. NHANES is a population-based, multiethnic cross-sectional survey conducted by the National Center for Health Statistics. We identified 13 publications. To determine whether these 13 publications were representative of how ALS was calculated using NHANES data, we did a PUBMED literature search on January 12, 2016 using the term “Allostatic Load Score and NHANES”. Twelve publications appeared. Of these 12 references, three did not use NHANES data and one was included in our original search. Therefore, this review on the calculation of ALS is based on 21 studies which used NHANES data in surveys of various lengths of time between 1988 and 2010[3–23].

Biomarkers included in the Allostatic Load Score

The 21 studies calculated ALS in 18 different ways using 26 different biomarkers (Tables 1 and 2). The number of biomarkers per ALS equation varied between 7 and 14 with at least one biomarker from three categories: cardiovascular, metabolic and immune. In the cardiovascular category, systolic and diastolic blood pressures were included in every equation except for one in which blood pressure was used as an outcome measure (Table 1) [23]. In the metabolic category, risk for diabetes was the primary focus and 16 of the 18 equations used A1C to assess glycemic status. Of the two equations that did not use A1C, one equation used fasting glucose and the other did not include any measure of hyperglycemia[7,18]. In the immune category 17 out of the 18 equations used C-reactive protein (CRP) and one equation used WBC[12].

Calculation of Allostatic Load Score

Across all 21 publications, ALS was calculated by turning each biomarker into a dichotomous variable with 1 point given if the biomarker was in the high risk range and 0 if not; the higher the score the greater the impact of stress on physiologic dysregulation. Of the 26 variables used in the 18 equations, 24 variables were continuous and two were categorical. The two categorical variables were asthma, present or absent and antibodies to herpes simplex virus I or II, present or absent[9,21]. Depending on the number of variables included in the ALS equation, scores ranged between 0 and 14.

To determine if a biomarker was in the high risk range, the continuous variables had to be converted to dichotomous variables. In the 18 equations described in this Perspective, five different methods were used to convert continuous variables into dichotomous variables. Table 2 presents each equation according to the method chosen to convert continuous variables into their dichotomous counterparts. In Section A (Equations 1 through 5), thresholds were determined by study-specific clinical guidelines. In Section B (Equations 6 through 13), the population was divided into quartiles and high risk was defined as greater than the 75th percentile for all variables except for albumin, high density lipoprotein (HDL) and estimated glomerular filtration rate (eGFR). For these three variables, high risk was defined as a value less than the 25th percentile. In Section C (Equation 14), the population was divided into quintiles. Then the procedure described for Equations 6–13 was followed. In Section D (Equations 15 through 17), a combined approach was used. For some variables, high risk was based on study-specific clinical guidelines and for other variables, a quartile analysis was performed. In Section E (Equation 18), all variables were based on study-specific clinical guidelines except for blood pressure for which cut-offs were based on 90th percentile values.

With the exception of Chyu et al. [6], the general practice was to assign the high risk category for a variable if treatment was provided (i.e. anti-hypertensive, hypolipidemic or glucose lowering medication). Only one study made specific reference to sex-specific cut-offs[23].

Overview

After decades of resistance there is now a genuine consensus that disease cannot be prevented or even successfully treated unless the role of stress is addressed alongside traditionally recognized factors such as genes and the environment. Our goal was to illuminate the variety of approaches that have been taken within the context of NHANES data to calculate ALS.

Until a consensus on how to measure ALS is developed, each investigator will have to use a previously published ALS equation or develop a new one tailored to a specific research question. In calculating the score, we think it is preferable to decide on thresholds of risk for each biomarker by dividing the population into quartiles or quintiles rather than relying on clinical guidelines. We have made this judgment for two reasons. First, there are no nationally accepted clinical guidelines for the variables used to calculate ALS. Second, clinical guidelines are rarely population-specific. For example, six of the twenty-six biomarkers used in the calculation of ALS, vary by ethnicity[24–26]. These variables are: HDL, triglyceride (TG), body mass index (BMI), waist to hip ratio (WHR), waist circumference (WC) and eGFR. Standard clinical guidelines rarely take into account how differences by ethnicity in these variables affect cardiometabolic risk[25,26].

For our analyses of the physiologic response to stress in African immigrants, we decided to use the ALS equation proposed by Geronimus et al. and subsequently by Kaestner et al. [10,11]. Both of these studies were designed to address the effect of socioeconomic status, racism, ethnic identity and immigration on ALS[10,11].

Clearly, the role of stress in the development and treatment of disease needs to be considered at every level of health care, from the formulation of public policy to the design of initiatives to improve health care delivery at the community and individual level. Going forward, great benefit could accrue from the convening of an expert panel to work on developing a consensus statement on how to measure allostatic load.

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Figure 1. The Path from Psychosocial Stress to Disease

HPA is an abbreviation for the hypothalamic-pituitary axis. SAM is the abbreviation for the sympathetic-adrenal medullary system.

Table 1

Frequency of 26 Biomarkers used in 18 Different Allostatic Load Score Equations

Biomarkers	Frequency
Cardiovascular	
Systolic Blood Pressure	17
Diastolic Blood Pressure	17
Cholesterol	15
HDL	15
Triglycerides	10
Pulse	7
Homocysteine	3
Peak menstrual flow volume	1
Metabolic	
A1C	16
Albumin	16
Body Mass Index	8
eGFR	7
Waist to Hip Ratio	7
Waist Circumference	4
Creatinine	3
Fasting glucose	2
Alkaline phosphatase	1
Blood urea nitrogen	1
Cytomegalovirus optical density	1
Forced expiratory volume	1
HOMA-IR	1
Immune	
C-reactive protein	17
Asthma diagnosis	1
Fibrinogen	1
Herpes I & II antibodies	1
White blood cell count	1

Table 2

Eighteen ALS Equations from 21 NHANES Studies

Equation Number	Number of Bio-markers	Biomarkers ^a	Authors	Survey Period (years)	N	Age	% Male	Race	Main Finding
A. High Risk for Each Biomarker Determined by Clinical Guidelines									
1	14	CV: SBP, DBP, HDL, pulse, total cholesterol, TG Metabolic: albumin, WHR, A1C, BMI, creatinine Immune: CRP, herpes simplex virus I & II	Frei et al. ^b Reference 9	1988–1994	4620	20y	49%	White: 43% Black: 26% Mexican: 27% Other: 4%	Even after adjustment for biological, socioeconomic, lifestyle and health variables, low vitamin D concentrations are associated with high ALS.
2	9	CV: SBP, DBP, HDL, pulse, total cholesterol Metabolic: Albumin, WHR, A1C Immune: CRP	Frei et al. ^b Reference 9	1988–1994	14213	20y	47%	White: 43% Black: 26% Mexican: 27% Other: 4%	Even after adjustment for biological, socioeconomic, lifestyle and health variables, low vitamin D concentrations are associated with high ALS.
3	9	CV: SBP, DBP, HDL, pulse, total cholesterol Metabolic: Albumin, WHR, A1C Immune: CRP	Borrrell et al. Reference 4	1988–1994	13715	25y	48%	Distribution by Race/Ethnicity not provided	High ALS is associated with as increased risk of all-cause mortality.
			Merkin et al. Reference 14	1988–1994	13199	20y	N/A	White: 40% Black: 30% Mexican: 30%	Blacks living in low socioeconomic neighborhoods are consistently found to have high ALS and adverse biological risk profiles.
			Rosenberg et al. Reference 17	1988–1994	3387	45–64y	48%	Distribution by Race/Ethnicity not provided	Low serum β -carotene concentrations are associated with high ALS.
			Seeman et al. Reference 19	1988–1994	15578	20y	49%	White: 77% Black: 10% Mexican: 5% Other: 8%	Low education and income are associated with high ALS.
4	9	CV: SBP, DBP, HDL, pulse, total cholesterol Metabolic: BMI, A1C, Albumin Immune: CRP	Chen et al. Reference 5	2005–2008	3330	18y	53%	White: 48% Black: 21% Mexican: 19% Other: 12%	High ALS is associated with sleep apnea, insomnia, short sleep duration, and sleep disorders.
			Parente et al. Reference 15	1999–2008	4875	35–85y	0%	White: 75% Black: 25%	Even after adjusting for demographic, behavioral and co-morbidities, breast cancer increases ALS in black women but not white women.
5	7	CV: SBP + DBP, HDL, TG Metabolic: WC, fasting glucose Immune: CRP, fibrinogen	Sabbah et al. Reference 18	1988–1994	6847	17y	N/A	Distribution by Race/Ethnicity not provided	Higher allostatic load is associated with ischemic heart disease and periodontal disease.
B. High Risk for Each Biomarker by Quartile Analyses:									

Equation Number	Number of Bio-markers	Biomarkers ^a	Authors	Survey Period (years)	N	Age	% Male	Race	Main Finding
(75 th percentile for all variables except albumin, HDL and eGFR 25 th percentile)									
6	14	CV: SBP, DBP, HDL, pulse, total cholesterol, TG Metabolic: albumin, WHR, A1C, BMI, creatinine Immune: CRP, herpes simplex virus I & II	Frei et al. ^b Reference 9	1988–1994	4620	20y	49%	White: 43% Black: 26% Mexican: 27% Other: 4%	Even after adjustment for biological, socioeconomic, lifestyle and health variables, low vitamin D concentrations are associated with high ALS.
7	11	CV: SBP, DBP, HDL, TG, total cholesterol, peak menstrual flow Metabolic: A1C, BMI, eGFR, albumin Immune: CRP	Allsworth et al ^c Reference 3	1988–1994	2470	17–30y	0%	White: 28% Black: 33% Mexican: 35% Other: 4%	Menarche at the age of 10 or younger is associated with higher ALS in young adult women.
8	10	CV: SBP, DBP, HDL, pulse, total cholesterol, homocysteine Metabolic: BMI, A1C, Albumin Immune: CRP	Chyu et al. Reference 6	1999–2004	5765	18y	0%	White: 81% Black: 12% Mexican: 7%	Compared to other racial/ethnic groups, black women have the highest ALS. Mexican women not born in the US have lower ALS than their US-born counterparts.
9	10	CV: SBP, DBP, TG, total cholesterol, homocysteine Metabolic: BMI, A1C, albumin, eGFR Immune: CRP	Upchurch et al. Reference 22	1999–2004	1680	40–59y	0%	White: 82% Black: 12% Mexican: 6%	Higher levels of physical activity and higher SES are associated with lower ALS. Black and Mexican American women have higher ALS than white women.
9	10	CV: SBP, DBP, TG, total cholesterol, homocysteine Metabolic: BMI, A1C, albumin, eGFR Immune: CRP	Gerominus et al. Reference 10	1999–2002	6586	18–64y	51%	White: 43% Black: 20% Other 37%	Independent of income and throughout the life span, blacks have higher ALS than whites.
10	10	CV: SBP, DBP, TG, total cholesterol, homocysteine Metabolic: A1C, eGFR, albumin, WHR Immune: CRP	Kaestner et al. Reference 11	1988–1994	6161	30–60y	N/A	White: 41% Black: 31% Mexican: 28%	For Mexican immigrants, increased duration of stay in the United States is associated with higher ALS.
10	10	CV: SBP, DBP, TG, total cholesterol, homocysteine Metabolic: A1C, eGFR, albumin, WHR Immune: CRP	Slade et al. Reference 20	1999–2004	14184	18y	47%	White: 50% Black: 20% Hispanic: 27% Other: 3%	Greater pain prevalence amongst low income groups is not explained by greater allostatic load.
10	10	CV: SBP, DBP, HDL, pulse, total cholesterol, homocysteine Metabolic: A1C, eGFR, albumin, WHR Immune: CRP	Duru et al. Reference 8	1988–1994	4515	35–64y	46%	White: 58% Black: 42%	Blacks have higher ALS than whites and this higher ALS in blacks explains, in part, the higher mortality rate experienced by blacks.
11	9	CV: SBP, DBP, HDL, pulse, total cholesterol Metabolic: Albumin, WHR, A1C Immune: CRP	Frei et al. ^b Reference 9	1988–1994	14213	20y	47%	White: 43% Black: 26% Mexican: 27% Other: 4%	Even after adjustment for biological, socioeconomic, lifestyle and health variables, low vitamin D concentrations are associated with high ALS.
12	9	CV: SBP, DBP, HDL, total cholesterol	Rainisch et al. Reference 16	1999–2008	8052	12–19y	52%	White: 71% Black: 16%	Among adolescents, higher ALS is associated with older age and lower SES.

Equation Number	Number of Bio-markers	Biomarkers ^a	Authors	Survey Period (years)	N	Age	% Male	Race	Main Finding
13	8	Metabolic: BMI, A1C, WC, albumin Immune: CRP CV: SBP, DBP, HDL, pulse, total cholesterol Metabolic: eGFR, albumin Immune: CRP	Doamekpor et al. Reference 7	2001–2010	2897	20y	48%	Mexican: 13% Black: 100% (US-born: 95%; Foreign-born: 5%)	Mexican American adolescents born in the United States have higher ALS than Mexican Americans born in Mexico. Foreign-born blacks have lower ALS than American born blacks.
C. High Risk for Each Biomarker by Quintile Analyses: (80th percentile for all variables except albumin and eGFR 20th percentile)									
14	7	CV: HDL, TG Metabolic: eGFR, albumin, A1C, WC Immune: CRP	Zota et al. Reference 23	1999–2008	8194	40–65y	49%	White: 76% Black: 10% Hispanic: 10% Other: 4%	Higher ALS appears to enhance the ability of lead to increase blood pressure
D. Combination of Clinical Guidelines and Quartiles									
15	14	CV: SBP, DBP, HDL, pulse, total cholesterol Metabolic: A1C, WHR, albumin, creatinine, cytomegalovirus optical density, alkaline phosphatase, BUN, forced expiratory volume Immune: CRP	Levine et al. Reference 13	1988–1994	9942	30y	47%	White: 83% Black: 9% Hispanic: 8%	The model known as Biological Age is more highly associated with all-cause mortality and cancer mortality than either the Framingham Risk Score or ALS.
16	11	CV: SBP, DBP, HDL, TG, total cholesterol, peak menstrual flow Metabolic: A1C, BMI, eGFR, albumin Immune: CRP	Allsworth et al. ^c Reference 3	1988–1994	2470	17–30y	0%	White: 28% Black: 33% Mexican: 35% Other: 4%	Menarche at the age of 10 or younger is associated with higher ALS in young adult women.
17	10	CV: SBP, DBP, total cholesterol, TG, pulse Metabolic: WHR, A1C, albumin, eGFR Immune: WBC	Kobrosly et al. Reference 12	1988–1994	4511	20–59y	46%	White: 36% Black: 30% Mexican: 30% Other: 4%	Higher allostatic load which is referred to as physiologic dysfunction may be associated with a decline in working memory.
E. Combination of Clinical Guidelines and 90th percentile for BP									
18	10	CV: SBP + DBP, HDL, LDL, TG Metabolic: WC, fasting glucose, HOMA-IR, A1C Immune: CRP, asthma	Theall et al. Reference 21	1999–2006	11866	12–20y	50%	White: 62% Black: 14% Hispanic: 17% Other: 7%	Adolescents who live in high-risk neighborhoods have higher ALS than their counterparts in low-risk neighborhoods.

^aEach biomarker is turned into a dichotomous variable with 1 point assigned if the biomarker is in the high risk range and 0 if the biomarker is not in the low risk range. Score can be 0 to 14 depending on the number of biomarkers in each equation.

^bFrei et al. used 4 different ALS formulations: (1) 14 variables with thresholds based on clinical guidelines (Equation 1), (2) 14 variables with thresholds based on quartiles (Equation 6), (3) 9 variables with thresholds based on clinical guidelines (Equation 2), (4) 9 variables with thresholds based on quartiles (Equation 11).

Allsworth et al. used 2 different ALS formulation: (1) 11 variables with all thresholds determined from high risk quartiles (Equation 7), (2) 11 variables with thresholds determined from a combination of clinical guidelines and high risk quartiles (Equation 16).

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