Using NHANES Data to Characterize the Magnitude of Allostatic Load in Vulnerable Communities: Impact to Existing Risk Assessment Uncertainty and Variability Factors

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Background

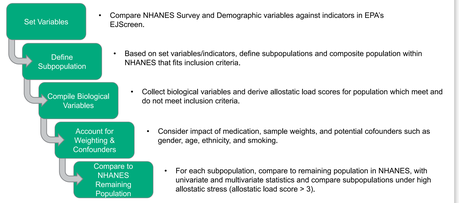
- Characterization of the degree of susceptibility among vulnerable communities is an emerging need in health-based risk assessments, with particular interest in the impact of non-chemical stressors.
- Recent agency and academic investigations have highlighted that historically disadvantaged communities are likely disproportionately affected by non-chemical stressors. The development of geographical tools such as the US Environmental Protection Agency's (USEPA's) EJScreen to locate such communities attempted to further define the nature of disadvantaged communities.
- Publications have suggested that basal stress levels, or allostatic loads, are elevated among vulnerable populations compared to the general population, which may influence their sensitivity to chemical stressors (Varshavsky et al., 2023; McHale et al., 2018).
- Allostatic load is a metric of chronic stress levels and has been classified by assignment of an "allostatic load score," which ranges from 0 to 9 (Moore et al., 2021). This score can be determined by a percentile ranking of indicators: serum albumin, body mass index, serum c-reactive protein, serum creatinine, diastolic blood pressure, glycated hemoglobin, systolic blood pressure, total cholesterol, and serum triglycerides.
- The publicly available National Health and Nutrition Examination Survey (NHANES) datasets contain all nine biometric indicators of human health required to estimate allostatic load for the general population and for defined subpopulations as well as the necessary demographic and survey information to allocate into potentially vulnerable populations.

Objective

Characterize the degree of chronic stress (i.e., allostatic load) within subpopulations defined by the presence of non-chemical stressors and the implications for disproportionately affected subpopulations within a cumulative impact assessment.

Methods

Figure 1. Workflow of Approach



- U.S. EPA's EJScreen and variables in the 2015–2016 and 2017–2018 NHANES datasets were compared to determine identifiers for possible subpopulations (**Figure 1**). The NHANES variables used to determine subpopulations is presented in **Table 1**.
- Selected subpopulation variables from NHANES were refined further based on survey completeness.
- These final subpopulations from NHANES were defined as pertaining to:
  - Income Level
  - Food Security
  - Attained Education
  - Healthcare Access
  - Composite Subpopulation (meets inclusion criteria for all responses in **Table 1**).

Table 1. NHANES Identifiers used in defining subpopulations and inclusion criteria

Subpopulation	NHANES Code	Variable Description	Inclusion Values	Inclusion Criteria Description
Income Level	INDFMMPC	Family Monthly Poverty Level Category	1	Poverty Level Index ≤ 1.3
Food Security	FSQ012	Receipt of SNAP Benefit (last 12 months)	1	Response = 'Yes'
	FSDHH	Household Food Security Category	3,4	Low or very low food security
Attained Education	DMDEDUC2	Education Level	1,2,3	Corresponds with GED or less
Healthcare Access	HUQ030	Health Insurance Coverage	2	Not covered by health insurance
	HUQ071	Location for Routine Health Care	2	No routine location for healthcare

Determining Allostatic Load Scores

- NHANES data from 2015–2016 and 2017–2018 were combined, and survey weights were adjusted. Variables pertaining to sex, race, smoking status, disease state, and medication were collected, in addition to allostatic load biomarkers and potentially vulnerable population identifiers.
- Allostatic load scores from 0 to 9 were calculated in accordance with Moore et al., 2021 (**Table 2**). For each biomarker, a score of 1 or 0 is assigned, as determined by the assignment percentile threshold in the criteria below. Note that, for serum albumin and serum creatinine, a score of 1 is assigned if the levels are below the 25th percentile.

An allostatic load score of 3 or higher indicates potentially being under chronic allostatic stress, as proposed by Moore et al., 2021.

Table 2. Allostatic load biomarkers and NHANES data locations

Biomarker	Score Assignment Threshold	Datafile*	NHANES Code	NHANES Description
Body mass index	>75th percentile	BMX	BMXBMI	BMI
C-reactive protein	>75th percentile	HSCRP	LBXHSCRP	C-reactive protein (mg/dL)
Diastolic blood pressure	>75th percentile	BPX	BPXDI	Blood pressure diastolic (mm Hg)
Systolic blood pressure	>75th percentile	BPX	BPXSY	Blood pressure systolic (mm Hg)
Glycated hemoglobin	>75th percentile	GHB	LBXGH	Glycated hemoglobin (%)
Total cholesterol	>75th percentile	TCHOL	LBXTC	Total cholesterol (mg/dL)
Serum triglycerides	>75th percentile	BIOPRO	LBDSTRSI	Triglycerides (mmol/L)
Serum albumin	<25th percentile	BIOPRO	LBDSALSI	Serum albumin (g/L)
Serum creatinine	<25th percentile	BIOPRO	LBDSCRSI	Serum creatinine (µmol/L)

* Datafile _I or _J depending on NHANES cycle (I = 2015–2016, J = 2017–2018)

Adjustment for Medication and Disease State

- Medication use may mitigate health outcomes of basal stress and mask stress across populations. Therefore, a complete list of the medications used and declared disease states were analyzed and annotated for adjustment as follows:
  - If treatment of a declared disease state *mitigates* a health outcome (e.g., medication for *declared* hypercholesterolemia), assigned total cholesterol scores were increased to a 1 (if not a 1 already), because the declared disease state and subsequent medication intervention may have been masking the underlying biomarker.
  - Adjustments made for medication are made dependent on the declared disease state. Scenarios in which medications may cause negative health outcomes (side effects) were not considered.

Sensitivity Analysis

- A sensitivity analysis was implemented using the entire NHANES dataset, in which the medication-adjusted dataset, which was used in this analysis, is compared to the counts of original allostatic load score assignments without accounting for medication.
- The objective is to quantify the impact of the adjustment for medication on our data by presenting the magnitude of shifts across each biomarker and total allostatic load score (0-9).

Analysis and Survey T-tests

- Survey weighted t-tests were performed for each subpopulation, comparing the respondents within the subpopulations to other respondents who did not meet inclusion criteria within NHANES. For this reason, the "other" comparator changes with each analysis (cite the population breakdown/summary table).
- Multivariate t-tests were also conducted to account for sex, ethnicity, and age.
- An additional multivariate t-test that accounted for smoking was also evaluated.

Results

- White respondents were the largest demographic group within each subpopulation.
- Observable changes in demographic breakdown were observed within the subpopulations, with a notable increase in Mexican-Americans in the Composite Subpopulation (**Figure 2**).

Figure 2. Weighted demographic information in each NHANES subpopulation

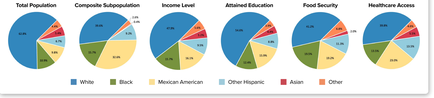


Table 3. Weighted Population information for the NHANES dataset and subpopulations based on non-chemical indicators.

		Subpopulation	Remaining Population
Total Population* (n = 18,248)	# of Respondents	18,248	--
	Avg. Age (yrs) [SD]	38.2 [22.6]	--
	Sex (% Female)	51.2%	--
Composite Subpopulation (n = 3,798)	# of Respondents	79	3,719
	Avg. Age (yrs) [SD]	35.5 [11.8]	45.4 [16.0]
	Sex (% Female)	38.2%	56.0%
Income Level (n = 10,895)	# of Respondents	5,483	5,412
	Avg. Age (yrs) [SD]	40.9 [19.4]	46.5 [18.7]
	Sex (% Female)	53.62%	50.1%
Food Security (n = 4,887)	# of Respondents	1,398	3,489
	Avg. Age (yrs) [SD]	38.5 [17.4]	41.5 [18.4]
	Sex (% Female)	55.6%	54.0%
Attained Education (n = 9,550)	# of Respondents	4,229	5,321
	Avg. Age (yrs) [SD]	48.8 [17.9]	48.0 [16.6]
	Sex (% Female)	48.7%	53.3%
Healthcare Access (n = 11,518)	# of Respondents	743	10,775
	Avg. Age (yrs) [SD]	36.2 [13.0]	45.1 [19.4]
	Sex (% Female)	31.7%	52.4%

* Total population for which health data was recorded.

Of the 18,248 respondents in the NHANES dataset to consider, a total 11,518 participants were available that had information related to all the biological endpoints to be considered in this analysis. The composite subpopulation is 10 years younger and overwhelmingly male (38.2% female) compared to the remaining population in that analysis, and is small (n = 79) given the subpopulation meets criteria for inclusion in all other subpopulations (**Table 3**). Moreover, in each comparison except attained education, the age of the subpopulation of interest is lower.

- In **Figure 3**, binned weighted distributions of allostatic load scores show the shift between the subpopulations and respondents who did not meet criteria for inclusion (remaining population).
- The composite subpopulation (i.e., meeting all inclusion criteria) has 46% of respondents under chronic allostatic stress, compared to 55% in the remaining population. However, this observation has a relatively low sample size (n=79) (**Figure 3**).
- 36% of the subpopulation with limited access to healthcare are under chronic allostatic stress, compared to 49% of the remaining population. Notably, this subpopulation is 9 years younger than the remaining population and 68.3% male (**Figure 3**).
- The subpopulation with lower attained education level showed an increase in chronic allostatic stress score compared to the remaining general population (58% compared to 50%). Both medians in the attained education subpopulation and the remaining population are 3 (**Figure 3**).
- The largest difference was between the limited healthcare access subpopulation and the remaining population, in which the number of respondents with elevated diastolic blood pressure shifted from 9.4% in the subpopulation to 12.9% in the remaining population (**Figure 4**).
- The largest two shifts in which the allostatic score in the subpopulation exceeded the value in the remaining population are in the composite comparison, where the percent of persons in the subpopulation having elevated BMI and elevated serum triglycerides increased to 16.8% and 11.8% from 13.4% and 8.5%, respectively, in the remaining population (**Figure 4**).
- Statistically significant increases in allostatic score were observed between the education subpopulation and the remaining population in the univariate and multivariate tests (**Figure 4**).
- Statistically significant decreases in allostatic score were observed between healthcare access and the remaining population in all three tests when compared to the remaining population (**Figure 4**).

Figure 3. Distributions of Allostatic Load Scores for Subsets in NHANES

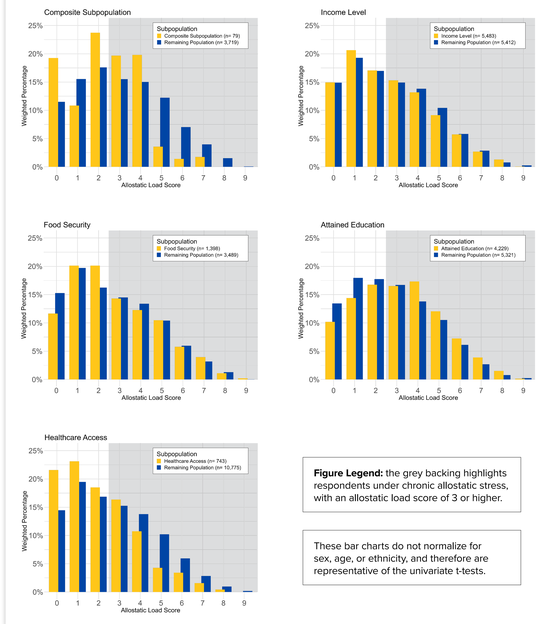


Figure Legend: the grey backing highlights respondents under chronic allostatic stress, with an allostatic load score of 3 or higher.

These bar charts do not normalize for sex, age, or ethnicity, and therefore are representative of the univariate t-tests.

Table 4. Statistical Results

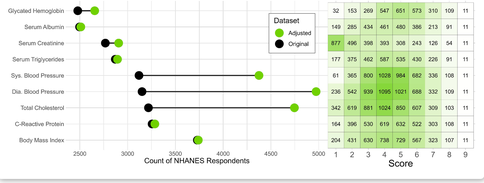
	Median Allostatic Score		Univariate		Multivariate**		Multivariate with Smoking	
Subpopulation	Selected Subpopulation	Remaining Population	beta-value*	p-value	beta-value*	p-value	beta-value*	p-value
Composite Subpopulation	2	3	-0.665	0.043	-0.162	0.437	-0.146	0.462
Income Level	2	2	-0.058	0.325	0.119	0.037	0.098	0.086
Food Security	2	2	0.077	0.190	0.187	0.069	0.191	0.069
Attained Education	3	3	0.358	<0.001	0.261	<0.001	0.236	<0.001
Healthcare Access	2	2	-0.616	<0.001	-0.225	0.023	-0.267	0.007

*beta-value direction indicates correlation (positive = positive correlation, negative = negative correlation) **Multivariate considers gender, age and ethnicity confounders.

Figure 4. Biomarker Composition Across Subpopulation Allostatic Load Score

Discussion

Figure 5. Sensitivity Analysis of Medication Adjustment Shift in NHANES Population



- The heatmap on the right in **Figure 5** shows the adjusted contributions across scores—that is, the counts of each biomarker in each score bin, with the green shade representing the highest contribution.
- Elevated systolic blood pressure, diastolic blood pressure, and total cholesterol are all drivers of the allostatic load score range. Additionally, the biggest shifts occur in blood pressure and cholesterol—which are more widely medicated than other indicators such as BMI.
- Low serum creatinine is most common when it is the only biomarker, suggesting a different health profile for respondents with scores in this stress indicator.
- The median allostatic load score prior to the medication shift was 2, rising to 3. The mean of 2.35 [SD = 1.74] rose to 2.78 [SD = 2.01].

Limitations

- A limited number of NHANES respondents provided complete demographic information pertaining to the selected categories of income level, education attainment, food security, and healthcare access which define potentially disadvantaged subpopulations.
- The locations of these respondents are unknown and presumed to not be in the same community. Therefore, key information used to define potentially vulnerable communities within existing tools was not publicly available in NHANES.
- While this effort may show differences in allostatic load scores for certain subpopulations, as defined by EJScreen indicators, the extent to which these differences may exacerbate chemical dose response is known.
- That said, the conservative nature of current risk assessments (conservatism added at multiple points) may already be addressing this potentially increased susceptibility; although, additional work is needed.
- The subpopulations considered within this evaluation are survey-based approximations of potentially vulnerable communities. Importantly, a number of indicators considered within the EJScreen tool were not evaluated here.

Conclusion

- Modern risk and cumulative impact assessments requires understanding the potential health impacts of non-chemical stressors.
- This effort demonstrates a quantitative method using NHANES data to compare allostatic load among populations that are subject to non-chemical stressors at varying levels.
- Preliminary evidence based on limited data suggests significant increases between the education attainment subset and allostatic load, as well as a decrease between the limited healthcare access subset and allostatic load.
- A more robust dataset may help evaluate the effectiveness of allostatic load scoring as a tool to distinguish the health impact of non-chemical stressors in a disadvantaged subpopulation from those in the general population. Our preliminary results indicate the possibility of significant overlap in allostatic load score distributions for a disadvantaged subpopulation (based on a limited number of EJScreen indicators) and a non-disadvantaged population.
- The causal associations between potentially vulnerable subpopulation indicators and allostatic load factors are poorly understood and further investigation intrapopulation variability in risk assessments is required.

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