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The relationship between peripheral arterial disease severity and allostatic load: A national health and nutrition examination survey study

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Major socioeconomic disparities persist in the management and outcomes of peripheral artery disease (PAD) globally. Allostatic load, which is described as a measure of physiologic adaptation to socio-environmental stress, has been reported to partially explain higher mortality rates in US Blacks. However, it is not clear if allostatic load is associated with PAD severity. The National Health and Nutrition Examination Survey (NHANES), 2003-2004 data was used to identify individuals with PAD based on the calculated Ankle-Brachial Index (ABI). After allostatic load was calculated for each individual, the cohort was stratified into tertiles of allostatic load and survey weights were used to generate nationally representative estimates. Factors associated with increased severity of PAD were evaluated using multivariate regression analyses. There were 5589 individuals included in the survey and 239 (5.9%) had PAD (ABI ≤ 0.9). Using survey weights, this corresponded to 5.9 million individuals. Individuals with PAD were more likely in the highest tertile of allostatic load (71%) compared to the middle (28%) or lowest (6%) tertiles. However, when severity of PAD was examined, the odds of moderate-to-severe PAD were not significantly different among individuals in the middle [adjusted Odds Ratio: 2.02 (0.52 - 7.80)] or highest [adjusted Odds Ratio: 2.53 (0.69 - 9.26)] tertiles compared to those in the lowest tertile. This study suggests that PAD severity is not associated with allostatic load. Increased efforts are necessary to identify factors that explain the socioeconomic disparities observed in the management and treatment of PAD.

Key words: Allostatic load, outcomes, peripheral arterial disease, severity, socioeconomic.

INTRODUCTION

Major disparities persist in the management of peripheral artery disease (PAD) around the world. While milder forms of PAD pose a relatively low risk of limb loss (less than 5% over 5 years), more severe PAD (referred to as

critical limb ischemia) poses a particularly high risk for major amputation (as high as 40% within 6 months) (Norgren et al., 2007). In order to prevent amputation, patients with critical limb ischemia require prompt restoration of blood flow to their legs (revascularization). Unfortunately, it is reported that Blacks presenting with PAD are more likely to undergo a major amputation as compared to Whites, sometimes as high as three to four times more likely (Feinglass et al., 2008, 2000; Guadagnoli et al., 1995; Huber et al., 1999). This disparity has persisted for decades. In one study, utilizing a statewide database, Huber et al. (1999) reported that Blacks and Whites in Florida did, in fact, receive treatment for PAD at the same rate as whites. Nonetheless, while Whites were more likely to receive limb-saving revascularization, Blacks were more likely to be treated with an amputation (Huber et al., 1999). While some have suggested that this disparity is largely explained by an increased burden of diabetes mellitus in the Black population (Brothers et al., 1997), it has been shown that this disparity exists and is even more pronounced among patients who do not have diabetes (Guadagnoli et al., 1995). In a study of Medicare beneficiaries, the authors concluded that there is "evidence for both segregation and discrimination: site of care was an important factor in a patient's likelihood of amputation, yet racial gaps persisted even after accounting for differences in the providers caring for Black and White patients" (Regenbogen et al., 2009). Despite the suggestion that a major cause of this disparity may be because Blacks tend to seek care at low-volume institutions with inadequate vascular surgical capabilities, our group and others have documented that these differences persist among patients seeking care at institutions with significant vascular surgical capability (Hughes et al., 2014; Regenbogen et al., 2009) Furthermore, data indicates that a high-volume practice while offering a decrease in the number of amputations for Whites does not confer the same advantage to Blacks. What rather makes a significant difference in the amputation-revascularization racial disparity is the diversity of the surgeon's practice (Stapleton et al., 2018). The higher the percentage of Black patients a surgeon sees, the more likely the surgeon is to perform a revascularization procedure rather than an amputation on a Black patient (Stapleton et al., 2018).

In a study utilizing the Area Resource File, Hayanga et al. (2009) to examine the association between access to surgical services and the proportion of minorities living in a particular US county, the authors identified that each percentage point increases in Blacks and/or Hispanics was associated with a significant decrease in surgeons, and surgical volume (Hayanga et al., 2009). Decreased access to health care by Blacks in the United States has long been reported (Nelson, 2002). This is particularly true for cardiovascular disease (Davis et al., 2007). More specifically, it has been well described that even when presenting with similar symptoms, Blacks are significantly less likely to receive cardiovascular interventions (Davis et al., 2007; Kressin et al., 2004). Consistent with the ongoing debate as to whether the amputation-revascularization racial disparity is largely sociologic or biological in etiology, some have postulated that PAD in Blacks may, in fact, be biologically different from, and more severe than, PAD in Whites (Sidawy et al., 1990) and that Black race is a strong and independent risk factor for PAD (Criqui et al., 2005). Indeed, using the Vascular Quality Initiative, a prospectively-maintained regional database, recently has been shown that Black patients present with more advanced vascular disease at the time of their initial major vascular operation (Soden et al., 2018). Presentation with more advanced disease at the time of initial major vascular operation may suggest that vascular disease in Blacks is potentially more complex and, perhaps, more difficult to treat successfully. What is not known is whether this "potentially more severe vascular disease" is a result of sociologic factors such as access to care, or if this is inherently biologic in nature.

Allostasis and allostatic load have been described as concepts proposed to explain the physiologic responses to environmental stressful stimuli (Carlson and Chamberlain, 2005; Logan and Barksdale, 2008). Allostasis is an extension of the concept of homeostasis, and represents successful physiologic adaptation to socio-environmental stress. It is postulated that repeated life stressors lead to a response pattern in which elements of the physiologic system, the immune system, the sympathetic nervous system and the hypothalamic–pituitary–adrenal axis, remain at heightened levels of activation. Thus, a high allostatic load would be proposed to result in this dysregulated physiologic profile. Allostatic load, which is calculated as a cumulative measure of several clinical/biologic factors including blood pressure, waist-hip ratio, glycated hemoglobin, cholesterol, albumin and CRP, has been reported to partially explain higher mortality rates in US Blacks (Duru et al., 2012). Allostatic load in the current study was calculated as previously described by Beckie (2012) using ten biologic indicators. Allostatic load has been associated with clinical outcomes of patients with cardiovascular and mental health diseases. Whether a greater allostatic load is associated with more severe PAD and a greater risk of amputation in Blacks is currently unknown. Therefore, this study was undertaken to evaluate if allostatic load is associated with PAD severity.

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Table 1. Allocation of Allostatic Load Points based on severity of risk factors.

Variable	Allostatic load point		
	0 Point	0.5 Point	1 Point
Systolic blood pressure (mmHg)	<120	120 - 149	≥150
Diastolic blood pressure (mmHg)	<80	80 - 89	≥90
Body mass index (kg/m^2)	<25	25 - 29	≥30
Glycohemoglobin (HbA1c)	≤5.6	5.7 - 6.4	≥6.5
C-reactive protein (mg/L)	<1	1 - 3	>3
Creatinine clearance (mL/min)	≥60	40 - 59	<40
HDL Cholesterol (mg/dL)	≥60	40 - 59	< 40
Total cholesterol (mg/dL)	<200	200 - 239	≥240
Total/HDL cholesterol ratio	<5	5 - <6	≥6
Albumin (mg/dL)	≥3.8	3 - <3.8	<3

METHODOLOGY

Data source and patient selection

The National Health and Nutrition Examination Survey (NHANES) is a nationally representative, stratified, population survey that employs interview data collected in subjects' homes as well as data from physical examination and blood samples. Beginning in 1999, NHANES uses a complex, multistage, probability sampling design to select study participants representative of the civilian, non-institutionalized US population (NCHS, 2003 - 2004). About 5000 participants are surveyed every year. Ankle-Brachial Indices (ABI's), the gold standard for diagnosing PAD, were calculated for all subjects participating in NHANES Wave for 2003 to 2004 (last year when ABI's were recorded).

PAD was diagnosed by calculating the ABI. An average of the two posterior tibial artery doppler occlusion pressures recorded for each participant in NHANES was divided by the higher of the two brachial artery doppler occlusion pressures to determine the ABI for each leg. Subjects with one or both ABI's ≤0.9 were diagnosed as having PAD. Subjects with an ABI >1.40, suggestive of calcified non-compressible vessels, were excluded. To eliminate atypical etiologies for PAD and given the extremely low prevalence of PAD among young patients, patients younger than 40 years old were excluded from analysis (Conte et al., 2015). Study subjects' demographic data including age, sex, educational background, Body Mass Index (BMI) and racial/ethnic self-identification were collected. Participants' comorbidities including a history of smoking, hypertension and diabetes mellitus were also recorded.

Determination of allostatic load

Allostatic load was calculated as previously described by Beckie (2012). Ten biologic indicators that measure cardiopulmonary function, parasympathetic function, cardiometabolic risk, glucose metabolism and inflammation will be examined. Parameters measured included systolic blood pressure, diastolic blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol, total/HDL cholesterol ratio, creatinine clearance, body mass index, glycohemoglobin, albumin and C-reactive protein. These ten biologic indicators which represent cardiometabolic risk, glucose metabolism, cardiopulmonary functioning, parasympathetic functioning, and inflammation have been used in past research using NHANES data (Beckie, 2012). Allostatic load was determined for each participant with each indicator defined as high-, moderate-, or low-risk categories using the following respective designations: systolic blood pressure: ≥150 mmHg, 120 to <150 mmHg, and <120 mmHg; diastolic blood pressure: ≥90 mmHg, 80 to <90 mmHg, and <80 mmHg; body mass index (BMI): ≥30 kg/m^3, 25 to <30 kg/m^3, and 18 to <25 kg/m^3; glycohemoglobin: ≥6.5%, 5.7% to <6.5%, and <5.7%; total cholesterol: ≥240 mg/dL, 200 to <240 mg/dL, and <200 mg/dL; HDL cholesterol: <40 mg/dL, 40 to <60 mg/dL, and ≥60 mg/dL; total/HDL cholesterol ratio: ≥6, 5 to <6, and <5; C-reactive protein: ≥3 mg/L, 1 to <3 mg/L, and <1 mg/L; albumin: <3.0 µg/mL, 3.0 to <3.8 µg/mL, and ≥3.8 µg/mL; and 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. Allostatic load was calculated by assigning one point for the high-risk category, a half point for moderate-risk, and zero points for low-risk. The details of this point allocation are shown in Table 1. Following previous research, a half point was added to the allostatic load score of participants who report taking medication for hypertension, diabetes, and/or cholesterol and who had a low-risk value for blood pressure, glycohemoglobin, or lipids, respectively. The maximum possible allostatic load score was 10 points (Rodriquez et al., 2018).

Outcome measures

The primary outcome measure was the severity of PAD as determined by the ABI (ABI < 0.4 severe PAD; ABI 0.4 – 0.79 moderate; and ABI 0.8 – 0.9 mild PAD). Effects of demographics including race/ethnicity and gender as well as insurance status were also evaluated. Subjects with missing variables pertaining to ABI were excluded from analysis.

Institutional Review Board (IRB)

Given that this study, utilized de-identified patient data, an IRB waiver was granted the following submission of an IRB application.

Statistical analyses

All participants in the survey were divided into three roughly equal parts (tertiles) based on their allostatic loads, because there are no widely accepted thresholds for high or low allostatic loads in the literature. Individuals with relatively low allostatic loads (1.5 - 3.5) were in the first tertile, those with moderate allostatic loads (4.0 - 4.5) were in the second tertile, while those with relatively higher allostatic loads (5.0 - 8.5) were in the third tertile.

Table 2. Demographic and Clinical Characteristics of All Survey Respondents by Level of Allostatic Load, NHANES 2003-2004.

Allostatic load tertile	Represented Population in Millions (%)			P-value
	1st Tertile [1.5 - 3.5]	2nd Tertile [4.0 - 4.5]	3rd Tertile [5.0 - 8.5]	
Sex				
Male	26.0 (46)	31.0 (50)	32.0 (50)	**0.111**
Female	31.0 (54)	31.0 (50)	32.0 (50)	
Age category				
<60	54.0 (95)	50.0 (81)	42.0 (66)	
60 - 69	1.6 (3)	5.5 (9)	10.0 (16)	**<0.001**
70 - 79	1.0 (2)	4.4 (7)	7.7 (12)	
≥80	0.5 (1)	1.7 (3)	3.4 (6)	
Race/ethnicity				
White	39.0 (68)	45.0 (74)	47.0 (75)	
Black	6.2 (11)	6.4 (10)	7.8 (12)	**<0.001**
Hispanic	9.3 (16)	7.3 (12)	6.0 (10)	
Others	2.5 (5)	2.7 (4)	2.1 (3)	
Body mass index				
Underweight	2.2 (4)	0.4 (1)	0.0 (0)	
Normal Weight	40.0 (71)	18.0 (29)	6.5 (10)	**<0.001**
Overweight	12.0 (21)	25.0 (41)	23.0 (36)	
Obese	2.4 (4)	18.0 (29)	34.0 (54)	
Level of highest education				
<High school	5.7 (15)	9.3 (16)	13.0 (21)	
High school	9.3 (24)	15.0 (27)	17.0 (27)	**<0.001**
Some college	13.0 (34)	17.0 (30)	20.0 (33)	
≥College	10.0 (27)	15.0 (27)	12.0 (19)	
Current smoking	16.0 (28)	19.0 (30)	20.0 (31)	0.384
Hypertension	4.6 (10)	13.0 (21)	32.0 (51)	<0.001
Diabetes Mellitus	0.3 (1)	2.5 (4)	10.0 (17)	<0.001

Using Pearson Chi-square tests, characteristics of individuals in the different levels of allostatic load were compared. The differences in the distribution of allostatic load between those with PAD and those without PAD were compared using Pearson Chi-square tests. Using similar methodology, differences in the severity of PAD (mild, moderate, or severe) across different tertiles of allostatic load were evaluated. The distribution of PAD severity across levels of each of the 10 stress biomarkers included in the allostatic load score were also evaluated.

Allostatic load was examined as a continuous variable and the association between this variable and ABI (0.1 - 0.9) was evaluated in a correlation plot. ABI was then used as the dependent variable in a multivariable linear regression analysis and factors associated with a 1 decimal point decrease in ABI (increased PAD severity) were examined. To further determine predictors of PAD severity, a multivariable logistic regression model was built and independent associations between individuals having moderate-severe PAD vs. mild PAD were determined. Lastly, to evaluate the independent association between allostatic load and the diagnosis of PAD, patients with PAD were compared to those without PAD in a multivariate logistic regression model.

All analyses were performed using NHANES survey weights in order to provide nationally representative estimates. Analyses were done using STATA Statistical software: 14.2 (College Station, TX: StataCorp LLC) and the level of significance was set at P <0.05.

RESULTS

The 2003 - 2004 NHANES wave identified 5589 individuals. Since there are no well-defined cut-offs for allostatic load burden, the NHANES subjects were divided up into three equal groups (tertiles) based on their allostatic load scores and three tertiles of allostatic load severity were created: 1.5 to 3.5, 4 - 4.5 and 5 - 8.5. Demographic and clinical characteristics of survey respondents by level of allostatic load tertile are shown in Table 2. The sample had an equal split of male to female proportions for allostatic load scores representing the second and third tercile. Females, however,

Table 3. Distribution of individuals with peripheral artery disease across tertiles of allostatic load.

Allostatic load tertile	PAD status, represented population in millions (%)		P-value
	PAD	No PAD	
1st Tertile	0.3 (6)	10.0 (14)	
2nd Tertile	1.4 (28)	28.0 (36)	0.001
3rd Tertile	3.3 (66)	39.0 (50)	

PAD, Peripheral Artery Disease.

Table 4. Association between Levels of Allostatic Load and Degree of Peripheral Artery Disease Severity.

Allostatic load tertile	Peripheral Artery Disease Severity, number in 10^5 (%)			P-value
	Mild (n = 26.0 × 10^5)	Moderate (n = 24.0 × 10^5)	Severe (n = 0.3 × 10^5)	
1st Tertile	1.9 (60)	1.3 (40)	0 (0)	
2nd Tertile	8.1 (58)	5.7 (41)	0.1 (1)	**<0.001**
3rd Tertile	16.0 (48)	17.0 (51)	0.2 (1)	

predominated (54% female and 46% male) in the first tercile of allostatic load (< 4). Of these NHANES subjects, 239 (5.9%) individuals were diagnosed as having PADthat is, an ABI ≤ 0.9. Using survey weights, this would correspond to 5.9 million individuals. The likelihood of a PAD diagnosis appeared to be related to the level of allostatic load: 6% of the PAD cohort was in the first allostatic load tertile, 28% was in the second tertile and 71% was in the 3rd tertile. Furthermore, amongst individuals with PAD two-thirds were in the highest tertile of allostatic load burden/severity compared to only half of the non-PAD individuals in this highest tertile of allostatic load burden (Table 3). In each allostatic load tertile, the overwhelming majority (99%) of PAD diagnosed was mild or moderate (Table 4). The distribution of allostatic load components across levels of PAD severity is illustrated in Table 5. Multivariate analysis of factors associated with severity of PAD as well as regression coefficient for 1 decimal point increase in ABI are depicted in Table 6. A statistically significant association between allostatic load and PAD severity was not identified. A scatter plot depicting allostatic load and PAD severity shows a slight downward slope with correlation coefficient of -0.135 suggestive of little to no correlation. A multivariate analysis of factors associated with a diagnosis of PAD is shown in Table 7, and a multivariate analysis of factors associated with allostatic load is represented in Table 8.

DISCUSSION

The current study was unable to identify an association between PAD severity and allostatic load. The study, however, suggests that individuals with PAD tend to have higher allostatic load scores. This latter finding is consistent with the study by Nelson et al. (2007) using an earlier NHANES wave that showed that individuals with PAD had higher allostatic load scores. Furthermore, this corroborates the previously reported finding associating a higher PAD prevalence in the setting of a higher allostatic load (Eraso et al., 2014; Nelson et al., 2007). It is possible that the inability to conclusively prove an association within the confidence intervals could be a result of Type II Error. The small sample size of individuals with PAD of 239 representing only 5.9% of this NHANES wave may have simply been too small to conclusively uncover an existing association.

Allostatic load is a concept that refers to the biologic response of environmental stressors (Carlson and Chamberlain, 2005; Logan and Barksdale, 2008). It represents the cumulative effect of chronic “wear and tear” leading to a failure of allostasis that result in permanent pathophysiologic changes. This concept would also explain the phenomenon referred to as “*The Biology of Poverty*” - how poverty “gets under the skin”. This is the observation that prolonged exposure to deprivation in early childhood predisposes to certain biological changes that persist throughout life (Lupien et al., 2001). Other investigators have long described this phenomenon of “weathering” in Blacks related to the long-term effect of perceived discrimination (Geronimus, 1992). While there are several potential “upstream” factors that may lead to the development of allostasis leading to more severe PAD and potential future amputation, it has been suggested that allostatic load could be a mechanism of sociodemographic health disparities (Szanton et al., 2005). It has been reported that Blacks have a higher allostatic load burden as compared to whites independent of SES, and that this may explain negative health outcomes and higher mortality among Blacks (Duru et al., 2012). This current study supports this hypothesis, and places allostatic load

Table 5. Distribution of Allostatic Load Components Across Levels of Peripheral Artery Disease Severity.

Variable	Peripheral Arterial Disease Severity, %		
	Mild (ABI 0.8 – 0.9)	Moderate (ABI 0.4 – 0.79)	Severe (ABI < 0.4)
Systolic Blood Pressure (mmHg)			
Lowest Risk (<120)	46.4	53.6	0
Moderate Risk (120 - 149)	57.3	42.3	0.4
Highest Risk (≥ 150)	48.9	47.7	3.4
Diastolic Blood Pressure (mmHg)			
Lowest Risk (<80)	49.9	48.5	1.6
Moderate Risk (80 - 89)	51.6	48.4	0
Highest Risk (≥ 90)	69.0	31.0	0
Body Mass Index (kg/m^2)			
Lowest Risk (< 25)	41.1	57.9	1.0
Moderate Risk (25 - 29)	57.3	40.0	2.7
Highest Risk (≥ 30)	55.1	44.9	0
Glycohemoglobin (HbA1c)			
Lowest Risk (≤ 5.6)	61.0	39.0	0
Moderate Risk (5.7 - 6.4)	44.5	53.2	2.3
Highest Risk (≥ 6.5)	41.0	55.7	3.3
C-reactive protein (mg/L)			
Lowest Risk (< 1)	52.1	47.3	0.6
Moderate Risk (1 - 3)	49.7	50.3	0
Highest Risk (> 3)	60.8	32.2	7.0
Creatinine clearance (mL/min)			
Lowest Risk (≥ 60)	49.5	49.8	0.7
Moderate Risk (40 - 59)	45.2	54.8	0
Highest Risk (< 40)	73.8	21.3	4.9
HDL Cholesterol (mg/dL)			
Lowest Risk (≥ 60)	62.1	37.5	0.4
Moderate Risk (40 - 59)	52.2	46.9	0.9
Highest Risk (< 40)	44.8	55.2	0
Total cholesterol (mg/dL)			
Lowest Risk (< 200)	55.4	44.0	0.6
Moderate Risk (200 - 239)	55.2	44.8	0
Highest Risk (≥ 240)	41.4	57.5	1.1
Total/HDL cholesterol ratio			
Lowest Risk (< 5)	49.3	50.3	0.4
Moderate Risk (5 - <6)	68.9	29.8	1.3
Highest Risk (≥ 6)	50.1	44.2	5.7
Albumin (mg/dL)			
Lowest Risk (≥ 3.8)	0	0	100
Moderate Risk (3 - < 3.8)	49.1	50.9	0
Highest Risk (< 3)	52.9	46.7	0.4

Table 6. Multivariate Analysis of Factors associated with Severity of Peripheral Artery Disease.

Characteristic	Adjusted odds of moderate-severe PAD vs. mild PAD (95% Confidence interval)	P-value	Regression coefficient for 1 decimal point decrease in ABI (95% Confidence Interval)	P-value
Level of allostatic load				
1st Tertile	Ref	-	Ref	-
2nd Tertile	2.02 (0.52 - 7.80)	0.310	0.02 (-0.07 - 0.11)	0.684
3rd Tertile	2.53 (0.69 - 9.26)	0.160	0.02 (-0.07 - 0.11)	0.631
Sex				
Male	Ref	-	Ref	-
Female	0.77 (0.40 - 1.49)	0.435	-0.01 (-0.05 - 0.04)	0.779
Age category				
< 60	Ref	-	Ref	-
60 - 69	1.08 (0.37 - 3.20)	0.890	0.02 (-0.06 - 0.09)	0.677
70 - 79	3.54 (1.12 - 11.23)	0.032	0.07 (-0.01 - 0.15)	0.074
≥ 80	3.71 (1.19 - 11.58)	0.024	0.09 (0.08 - 0.17)	0.032
Race/ethnicity				
White	Ref	-	Ref	-
Black	1.11 (0.46 - 2.67)	0.816	0.02 (-0.04 - 0.08)	0.559
Hispanic	1.79 (0.70 - 4.56)	0.225	0.05 (-0.01 - 0.11)	0.122
Others	0.34 (0.03 - 4.38)	0.408	-0.06 (-0.24 - 0.12)	0.515
Body mass index				
Underweight	-	-	-0.09 (-0.31 - 0.13)	0.420
Normal Weight	Ref	-	Ref	-
Overweight	0.97 (0.42 - 2.24)	0.948	0.00 (-0.05 - 0.06)	0.880
Obese	0.93 (0.37 - 2.36)	0.879	-0.01 (-0.08 - 0.05)	0.702
Level of highest education				
< High School	Ref	-	Ref	-
High School	2.12 (0.85 - 5.27)	0.106	0.02 (-0.05 - 0.08)	0.636
Some College	1.11 (0.47 - 2.61)	0.808	0.01 (-0.05 - 0.07)	0.817
≥ College	1.14 (0.33 - 3.93)	0.835	-0.01 (-0.09 - 0.08)	0.883
Current Smoker				
No	Ref	-	Ref	-
Yes	1.67 (0.78 - 3.58)	0.190	0.06 (0.01 - 0.12)	0.019
Hypertension				
No	Ref	-	Ref	-
Yes	0.64 (0.32 - 1.28)	0.209	0.01 (-0.04 - 0.05)	0.773
Diabetes				
No	Ref	-	Ref	-
Yes	1.96 (0.89 - 4.28)	0.094	0.04 (-0.01 - 0.09)	0.134

ABI, Ankle Branchial Index; PAD, Peripheral Artery Disease. Model is adjusted for all variables in the table

as a likely candidate in the pathway of sociodemographic PAD disparities.

Some have suggested that the disparity in amputation-revascularization is largely as a result of socioeconomic status. There is a strong link between low socioeconomic status (as defined by education and/or income) and PAD.

Table 7. Multivariate Analysis of Factors associated with a Diagnosis of Peripheral Artery Disease.

Characteristic	Adjusted Odds of having PAD (95% Confidence Interval)	P-value
Level of Allostatic Load		
1st Tertile	Ref	-
2nd Tertile	1.28 (0.66 - 2.50)	0.438
3rd Tertile	1.31 (0.60 - 2.86)	0.473
Sex		
Male	Ref	-
Female	1.29 (0.78 - 2.14)	0.297
Age Category		
<60	Ref	-
60 - 69	3.38 (1.60 - 7.16)	0.003
70 - 79	5.36 (3.32 - 8.66)	<0.001
≥80	19.28 (9.95 - 37.38)	<0.001
Race/Ethnicity		
White	Ref	-
Black	1.88 (0.96 - 3.66)	0.062
Hispanic	0.94 (0.45 - 1.95)	0.862
Others	0.56 (0.35 - 0.90)	0.020
Body Mass Index		
Underweight	4.84 (0.68 - 34.64)	0.109
Normal Weight	Ref	-
Overweight	1.47 (0.80 - 2.69)	0.196
Obese	2.00 (1.29 - 3.09)	0.004
Level of Highest Education		
<High School	Ref	-
High School	1.18 (0.73 - 1.90)	0.486
Some College	1.29 (0.81 - 2.06)	0.268
≥College	0.88 (0.35 - 2.25)	0.779
Current Smoker		
No	Ref	-
Yes	2.09 (1.31 - 3.33)	0.004
Hypertension		
No	Ref	-
Yes	1.58 (0.93 - 2.67)	0.085
Diabetes		
No	Ref	-
Yes	1.69 (0.71 - 4.02)	0.217

PAD, Peripheral Artery Disease. Model is adjusted for all variables in the table.

There is also a positive correlation between low socioeconomic status and Black race. This is true both for educational attainment as well as for family income (Pande and Creager, 2014). In fact, certain authors have proposed that race may simply be a surrogate for socioeconomic status. It is postulated that lower

Table 8. Multivariate Analysis of Factors associated with Allostatic Load.

Characteristic	Regression Coefficient for 1-point increase in Allostatic Load (95% Confidence Interval)	P-value
Sex		
Male	Ref	-
Female	-0.04 (-0.14 - 0.06)	0.353
Age Category		
<60	Ref	-
60 - 69	0.49 (0.38 - 0.60)	<0.001
70 - 79	0.53 (0.39 - 0.67)	<0.001
≥80	0.75 (0.62 - 0.88)	<0.001
Race/Ethnicity		
White	Ref	-
Black	0.01 (-0.10 - 0.13)	0.997
Hispanic	-0.16 (-0.29 - -0.04)	0.006
Others	0.07 (-0.15 - 0.29)	0.633
Body Mass Index		
Underweight	-0.09 (-0.49 - 0.30)	0.156
Normal Weight	Ref	-
Overweight	0.81 (0.71 - 0.90)	<0.001
Obese	1.45 (1.37 - 1.54)	<0.001
Level of Highest Education		
< High School	Ref	-
High School	-0.09 (-0.17 - -0.01)	0.013
Some College	-0.03 (-0.12 - 0.07)	0.355
≥ College	-0.12 (-0.20 - -0.03)	0.005
Current Smoker		
No	Ref	-
Yes	0.05 (-0.04 – 0.14)	0.171

Model is adjusted for all variables in the table.

socioeconomic status, which is more commonly seen in Blacks than Whites and is correlated with decreased access to care, leads to delayed presentation of PAD which, in turn, results in this apparent race-dependent treatment selection for PAD (Ho et al., 2005; Nguyen and Henry, 2010). This implies that by the time Blacks with PAD present to the physician/surgeon, it is too late to perform limb-saving revascularization procedures, leaving an amputation as the only available option for these patients. Some authors have submitted that it may not so much be individual SES that impacts negatively on one's health, but rather socioeconomic neighborhood stress associated with living in a deprived neighborhood (Do et al., 2008; Sundquist et al., 2012, 2004). While there are significant similarities between the PAD disparities emanating from low SES and Black ethnicity, data, however, suggest that low SES and race are independent, though perhaps synergistic, factors contributing to worse outcomes for PAD (Henry et al, 2011). This pathway of allostatic load may serve as a common denominator explaining both race-based and SES-based amputation-revascularization disparities.

Under-treatment of risk factors has also been blamed for the existence of these amputation-revascularization disparities. Blacks have a significantly higher prevalence of traditional cardiovascular risk factors such as diabetes, hypertension and dyslipidemia as compared to Whites (Wong et al., 2002). Unfortunately, there is also significant evidence demonstrating that these key cardiovascular risk factors are often undertreated in Blacks. Hypertension is under-treated and the glycemic indices for Blacks undergoing treatment for diabetes

mellitus are consistently higher than Whites (Malik et al., 2007). In addition, there is significant under-utilization of statins (Lipworth et al., 2014) in Blacks so that this population is not fully benefitting from the tremendous advantages of statins in combatting vascular disease. Furthermore, ever since Kevin Shulman's 1999 landmark New England Journal of Medicine article portraying the effect of physician racial and gender bias in referring patients for cardiac catheterization (Schulman et al., 1999), the role of physician bias has been increasingly recognized as playing a role in healthcare disparities.

One key limitation of this second (NHANES) study is that the NHANES wave used 2003 - 2004 is relatively dated. These data were used, however, as this is the most recent NHANES wave that includes Doppler occlusion pressures that allow for the calculation of ABI. These data are particularly pertinent because a limitation of other, similar studies is their reliance on surrogates for PAD (such as clinical symptoms) while this current study uses ABI, the gold standard for PAD diagnosis (Conte et al., 2019). There, nonetheless remains a potential negative impact to using this 15-year old data. Indeed, data suggests that while overall national amputation rates have decreased over the past two decades, amputation rates among Blacks have not decreased (Goodney et al., 2015). This suggests that this amputation-revascularization disparity is at least as bad today as it was during the 2003-2004 NHANES survey period.

This study may also be considered to highlight the need for continued collection of this clinical data. Our study is unable to establish allostatic load as a factor in the pathogenesis of this amputation-revascularization disparity. It is possible that the inability to conclusively prove this as a factor could be as a result of Type II Error relating to a sample size that was simply too small. In addition to continued study of allostatic load in better-powered studies, additional investigations regarding the molecular mechanisms by which this disparity operates still need to be studied. Current data point to the potential pathways of inflammation (Libby et al., 2002; Sullivan et al., 2000) and endothelial dysfunction. *In vitro* and *in vivo* racial differences in inflammation have been identified (Feairheller et al., 2011) and Blacks, with early life adversity, have been noted to have high concentrations of inflammatory biomarkers in mid-life (Slopen et al., 2010). There are studies that suggest race-specific differences in endothelial function and a propensity of Blacks towards endothelial dysfunction (Freedman et al., 2000; Grubbs et al., 2002; Mulukutla et al., 2010; Qureshi et al., 2007). The multi-factorial nature of this health disparity indicates a highly complex process that spans health policy, health economics and medical care as well as biologic and cellular processes. This current study was unable to identify a clear association between PAD severity and allostatic load. Therefore, we were unable to establish allostatic load as a probable down-stream factor in the amputation-revascularization disparities pathway.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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