ABSTRACT

Title of Dissertation: RACIAL/ETHNIC DISPARITIES IN AMPUTATION AND REVASCULARIZATION: THE ROLES OF SOCIOECONOMIC NEIGHBORHOOD STRESS AND ALLOSTATIC LOAD

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Blacks are several times more likely to undergo a leg amputation as compared to Whites. This is because while peripheral artery disease (PAD), the most common cause of amputation, is more likely to be treated by revascularization (restoration of blood flow) in Whites, PAD is more likely to be treated by amputation in Blacks. Whereas an ongoing debate argues as to whether this disparity is primarily a sociologic versus a biologic phenomenon, I proposed that there are socioeconomic neighborhood stressors that create more severe PAD and renders individuals less likely to undergo successful revascularization and more likely to undergo amputation. Three specific aims are addressed in this dissertation resulting in three manuscripts.

In **Study 1**, utilizing the Nationwide Inpatient Sample Database (NIS) in a retrospective study design, I determined that among patients admitted to the hospital

for severe PAD, low socioeconomic status (SES) correlates positively with the likelihood of amputation, but paradoxically correlates negatively with the severity of PAD. In **Study 2**, I used the National Health and Nutrition Examination Survey, in a cross-sectional study design, to evaluate if there was a relationship between PAD severity, as determined by the ankle-brachial index (ABI) and the level of allostatic load. I did not identify an association. In **Study 3**, I employed the Nationwide Readmission Databases to show that low SES positively correlates with readmission for amputation following surgical revascularization.

Findings from these three papers indicate that there is a positive correlation between low SES and the likelihood of amputation both upon initial admission as well as during subsequent follow up after surgical revascularization. I was unable to establish a clear relationship between PAD severity and allostatic load. The paradoxical finding that low SES individuals present with less severe manifestation of PAD signifies that there are yet-to-be-established factors involved in this complex disparity.

This dissertation underscores the dominant role of social determinants of health and submits that in order to adequately address this amputation-revascularization disparity and avoid unnecessary amputations, major investments need to be made not only in healthcare, but also in America's social infrastructure.

RACIAL/ETHNIC DISPARITIES IN AMPUTATION AND REVASCULARIZATION: THE ROLES OF SOCIOECONOMIC NEIGHBORHOOD STRESS AND ALLOSTATIC LOAD

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List of Abbreviations

ABI	Ankle-Brachial Index
BMI	Body Mass Index
CLI	Critical Limb Ischemia
MHI	Median Household Income
NIS	Nationwide Inpatient Sample
NHANES	National Health and Nutrition Examination Survey
NRD	National Readmission Databases
PAD	Peripheral Artery Disease
SES	Socioeconomic Status

Chapter 1: Introduction and Literature Review

Introduction

Significant disparities exist in the management and outcomes of peripheral artery disease (PAD) in the United States. PAD is a disease that involves obstruction of the arterial circulation of the lower extremities. The risk factors are similar to the traditional risk factors for cardiovascular disease and include smoking, diabetes mellitus, hypertension and hypercholesterolemia. 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 lower extremity amputation (as high as 40% within 6 months).[1] These patients require prompt revascularization (restoration of blood flow) in order to save their legs. Building on my previous work where I briefly surveyed some of the mechanisms underlying this disparity,[2] I now undertake a more comprehensive exploration of the factors underlying the amputation-revascularization racial disparities.

Racial/Ethnic Disparities

Blacks presenting with PAD are reported to be more likely to undergo a major amputation as compared to Whites – sometimes as high as three to four times more likely.[3-6] This disparity has persisted for decades. In one study, utilizing a statewide database, Huber, et al. 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.[6] Although the adverse effect of racial segregation on high-quality health care[7] and on the availability of surgical services for Blacks and Hispanics[8] has been reported, some have suggested that this disparity is largely explained by an increased burden of diabetes mellitus in the Black population.[9] It has, however, been shown that this disparity exists and is even more pronounced among patients who do not have diabetes. In a study that examined 86,865 Medicare beneficiaries, Regenbogen, et al. 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."[10] Moreover, while it is often suggested that this disparity may be because Blacks tend to seek care at low-performing institutions with inadequate vascular surgical capabilities, it has been documented that these differences persist among patients seeking care at institutions with significant vascular surgical capability.[10] Consistent with the ongoing debate as to whether the PAD-amputation 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,[11] and that Black race is a strong and independent risk factor for PAD.[12] Some support for this premise is that even when Blacks undergo revascularization procedures, they are less likely to have successful outcomes including when the procedures are performed at centers with excellent outcomes.[10] Data indicate that Blacks not only have a reduced likelihood of undergoing limb-saving revascularization but are also more likely to undergo a major amputation even if revascularization is undertaken.[10] Indeed, using the Vascular Quality Initiative, a

prospectively-maintained regional database, we have recently shown that Black patients present with more advanced vascular disease at the time of their initial major vascular operation.[13] 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 disease" is a result of socio-ecologic factors such as access to care, or if this is inherently biologic in nature.

Lack of Access to Care

In a study utilizing the Area Resource File, Hayanga, et al., after categorizing each county in the US into most, moderately or least segregated, performed multivariate linear regression analysis to examine the association between access to surgical services and the proportion of minorities living in a particular county. These authors identified that each percentage point increase in Blacks and/or Hispanics was associated with a significant decrease in surgeons, and surgical volume.[8] Decreased access to health care by Blacks in the United States has long been reported.[14] This is particularly true for cardiovascular disease.[15] More specifically, it has been well described that even when presenting with similar symptoms, Blacks are significantly less likely to receive cardiovascular interventions.[15, 16] This decreased access to care may also be reflected in the observation that Blacks are more likely to seek care at and lower volume institutions with inferior vascular capabilities.[17] While some ascribe this as a potential reason for this disparity, Stapleton, et al. have recently shown that this disparity is actually more pronounced in high-volume surgeons.[18] It, therefore, remains

unknown if Black race predisposes individuals towards more severe PAD and a higher propensity towards amputation independent of access to care.

Socioeconomic Status and Insurance Type

There is a strong link between low socioeconomic status (as defined by education and/or income) and PAD. There is also a positive correlation between low socioeconomic status (SES) and Black race. This is true both for educational attainment as well as for family income.[19] In fact, some have suggested that race may simply be a surrogate for socioeconomic status. It is postulated that lower 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.[20, 21] 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. While there are significant similarities between the PAD disparities emanating from low SES and Black ethnicity, some data, however, suggest that low SES and ethnicity are independent, though perhaps synergistic, factors contributing to worse outcomes for PAD.[17] In a recent nationwide study, I reported that patients of low income are more likely to undergo an amputation versus revascularization, and that this disparity occurs in a highly linear fashion.[22] After stratifying patients who presented with severe PAD into four income quartiles based on ZIP codes, I showed that the likelihood of amputation increased in a step-wise fashion as one moved from one ZIP code income quartile to a lower one. In this same

study, I also demonstrated that Medicaid insurance and uninsured status were associated with a higher likelihood of amputation while private insurance was associated with a lower likelihood of amputation and a higher likelihood of revascularization. Clearly, lower income also affects access to care given that poor patients are less likely to have private insurance and more likely to have no insurance or Medicaid (which is not universally accepted by clinicians). The report that diabetics in lower income neighborhoods of California are ten times more likely to undergo an amputation as compared to diabetics from more affluent areas in the state unequivocally underscores this disparity.[23] What is not clear from the literature is if it is individual low income that actually affects the severity of PAD and the likelihood of an amputation or if it is living in a lower income ZIP code that leads to more severe PAD. Furthermore, it is not known by what mechanism living in a lower income ZIP code may lead to more severe PAD and a greater likelihood of undergoing an amputation.

Prevalence and Under-Treatment of Risk Factors

Blacks have a significantly higher prevalence of traditional cardiovascular risk factors such as diabetes, hypertension and dyslipidemia as compared to Whites.[24] 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.[25] Furthermore, there is significant under-utilization of statins[26] in Blacks so that this population is not fully benefitting from the

tremendous advantages of statins in combatting vascular disease. Under-treatment of these risk factors, alone, would be expected to lead to a greater prevalence of vascular disease in Blacks as well as worse outcomes when vascular disease is treated invasively.[20] Whether the absence of these traditional cardiovascular risk factors or their adequate treatment in the Black population will lead to an elimination of this amputation – revascularization disparity, is currently unknown at this time.

Socioeconomic Neighborhood Stress

Distressed neighborhoods have been associated with a range of negative health outcomes in general and cardiovascular health outcomes in particular.[27] It is believed that this may be due to the stress of high unemployment rates, high crime as well as limited opportunities for exercise and purchasing healthy food in these neighborhoods.[28] Neighborhood socioeconomic deprivation has been described as a marker of the prevalent contextual characteristics that affect one's health. Deprived neighborhoods have, therefore, been associated with increased risk of cardiovascular disease[29] and death.[27] More specifically, Stevens, et al. reported that diabetics in low-income neighborhoods in California were ten times more likely than diabetics from wealthier neighborhoods to undergo an amputation.[30] While little specific work has been done to determine a relationship between PAD and neighborhood stress, the impact that neighborhood stress has on overall cardiovascular disease would suggest that there may be some correlation between neighborhood stress and PAD. Unfortunately, specific mechanisms by which neighborhood stress may impact PAD have not been systematically examined.

Perceived Discrimination

Increasingly, racism and perceived discrimination have been described as determinants of health in general, and of cardiovascular events in particular.[31, 32] This form of chronic stress, common in Blacks, is often measured by lifetime discrimination.[33] The Multi-Ethnic Study of Atherosclerosis reported that, while controlling for chronic stress and depression, perceived discrimination was associated with an increased incidence of cardiovascular events.[34] It has been suggested that this may be the reason why Blacks in West Africa and the Caribbean have a lower prevalence of certain cardiovascular diseases, such as hypertension, as compared to African Americans.[35] The literature, however, is not clear as to whether PAD is more prevalent and more severe in African-Americans as compared to native Africans and/or Afro-Caribbeans.[36] It is also unknown whether there is a difference in PAD severity and/or amputation risk between African-Americans and Africans in America.[37]

Physician Bias and Patient Trust

Kevin Shulman's 1999 landmark New England Journal of Medicine article clearly portrayed the effect of physician racial and gender bias in referring patients for cardiac catheterization.[38] There is some evidence that physician bias may also play an important role in the amputation-revascularization disparity. While it has generally been suggested that referral to high volume vascular surgeons practicing in high volume hospitals may be one way to ameliorate this amputation-revascularization disparity,[17] data suggests that this is likely not the case.[10] What rather makes a significant difference is the diversity of the surgeon's practice.[18] The higher the

percentage of Black patient a surgeon sees, the more likely the surgeon is to perform a revascularization procedure rather than an amputation on a Black patient.[18] The complex roles that physician bias and attendant patient trust play in this disparity has not yet been fully explored.

Allostasis and Allostatic Load

Allostasis and allostatic load have been described as concepts proposed to explain the physiologic responses to socio-environmental stressful stimuli.[39, 40] Allostasis is an extension of the concept of homeostasis, and represents successful physiologic adaptation to socio-environmental stress. While the notion of allostasis is comparable to homeostasis, homeostasis aims at reducing variability while allostasis places specific emphasis on the capacity to adapt to stressful stimuli.[3] 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. It represents the cumulative effect of chronic "wear and tear" leading to a failure of allostasis that results 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.[41] Other investigators have long described this phenomenon of "weathering" in Blacks related to the long-term effect of perceived discrimination.[42]

Allostatic load burden has been reported to partially explain higher mortality rates in US Blacks, independent of SES and health behaviors.[43] Allostatic load is calculated as a cumulative measure of several clinical/biologic factors including blood pressure, waist-hip ratio, glycated hemoglobin, cholesterol, albumin and C-reactive protein. Whether a greater allostatic load is associated with more severe PAD and a greater risk of amputation in Blacks is currently a significant gap in the literature that awaits an answer.

Inflammation

The central role of inflammation in the pathogenesis of vascular disease is well established.[44, 45] Moreover, a specific relationship between PAD and inflammation has been recognized.[46, 47] Most commonly, inflammation is determined by measurement of bio-inflammatory markers, often IL-6, CRP and fibrinogen.[47] In vitro and in vivo racial differences in inflammation have been identified,[48] and Blacks, with early life adversity, have been noted to have high concentrations of inflammatory biomarkers in mid-life.[49] While it is plausible that inflammation may mediate a relationship between Black race/low SES and a more severe PAD leading to a greater likelihood for amputation, this mechanism has not yet been studied.

Endothelial Dysfunction

Endothelial dysfunction develops when insults to, and intrusion into, the vascular matrix result in increased blood vessel stiffness and resistance and is increasingly recognized to be a critical phase of cardiovascular pathogenesis.

Endothelial dysfunction is measurable as early as childhood and adolescence.[50] Vascular distensibility provides a validated marker of endothelial dysfunction and can be measured non-invasively as pulse wave velocity (PWV). Biochemical mediators of endothelial dysfunction have also been identified including immune activating cytokines, circulating adhesion molecules that facilitate lymphocytic infiltration of the vasculature, and vasoconstrictive peptides. Blood levels of these molecules have been linked to cardiovascular disease risk,[51] and endothelial dysfunction is specifically implicated in the pathogenesis of PAD.[52] Furthermore, there are several studies that suggest race-specific differences in endothelial function and a propensity of Blacks towards endothelial dysfunction,[53-56] This potentially credible mechanism of endothelial dysfunction mediating a relationship between race and PAD and leading to a greater likelihood for amputation also remains to be elucidated.

Hypothesis

Biologic response patterns to stress are increasingly recognized as major contributors to health outcomes, particularly for cardiovascular disease including ischemic heart disease and stroke.[57] The stressful environment created by neighborhood socioeconomic deprivation has been associated with adverse health outcomes.[58] It is postulated that this relationship may be mediated through ***allostatic load***, Figure 1. Studies have identified an association between PAD prevalence and higher allostatic load as well as higher allostatic load in Blacks.[59, 60]

It is well known that in the United States, Blacks are significantly more likely to live in socioeconomically deprived neighborhoods as compared to Whites.[61]

Previous reports have indicated that ***neighborhood socioeconomic deprivation*** – judged by median household income – is associated with a higher prevalence of, and worse outcomes for, cardiovascular disease.[62, 63] This is true even after adjusting for individual-level risk factors.[64] Whether ***median household income*** is specifically associated with more severe PAD in Blacks, however, has not been adequately studied. I have recently shown, on a national level, that lower median household income closely correlates with a greater risk of amputation, and a lesser likelihood of revascularization.[22] What is not known is if this correlation occurs because a lower median household income specifically correlates with more severe PAD.

Based on this evidence, I was persuaded that a lower median household income is associated with a higher allostatic load and a greater severity of PAD leading to a higher risk for amputation in Blacks. My overarching hypothesis was that ***low socioeconomic status, as demonstrated by lower median household income, creates a more severe PAD and a greater risk for amputation. I further posited that this increased PAD severity is associated with a higher allostatic load, Figure 1. My specific aims, therefore, were:***

1. **To evaluate if a lower median household income is associated with more severe PAD.** In a retrospective study, I tested the hypothesis that among hospitalized patients in the *Nationwide Inpatient Sample (NIS) Database*, a lower median household income correlates with more severe PAD.

2. **To evaluate if allostatic load is associated with PAD severity.** In a cross-sectional study design, I tested the hypothesis that, among patients participating in the *National Health and Nutrition Examination Survey (NHANES)*, the severity of PAD, as determined by the ankle-brachial index (ABI), is associated with the level of allostatic load.

3. **To determine if median household income influences outcomes following surgical revascularization.** In a retrospective study, I tested the hypothesis that among patients undergoing surgical revascularization in the *Nationwide Readmission Databases (NRD)*, median household income will affect surgical outcomes.

In proving my hypotheses from these studies, I sought to clarify the relationship between socioeconomic stress as defined by median household income and PAD and answer the question regarding the role of allostatic load in the amputation-revascularization disparity. By so doing, I hoped to help answer the question as to if biologic response patterns to stress play a defining role in this racial/ethnic amputation-revascularization disparity.

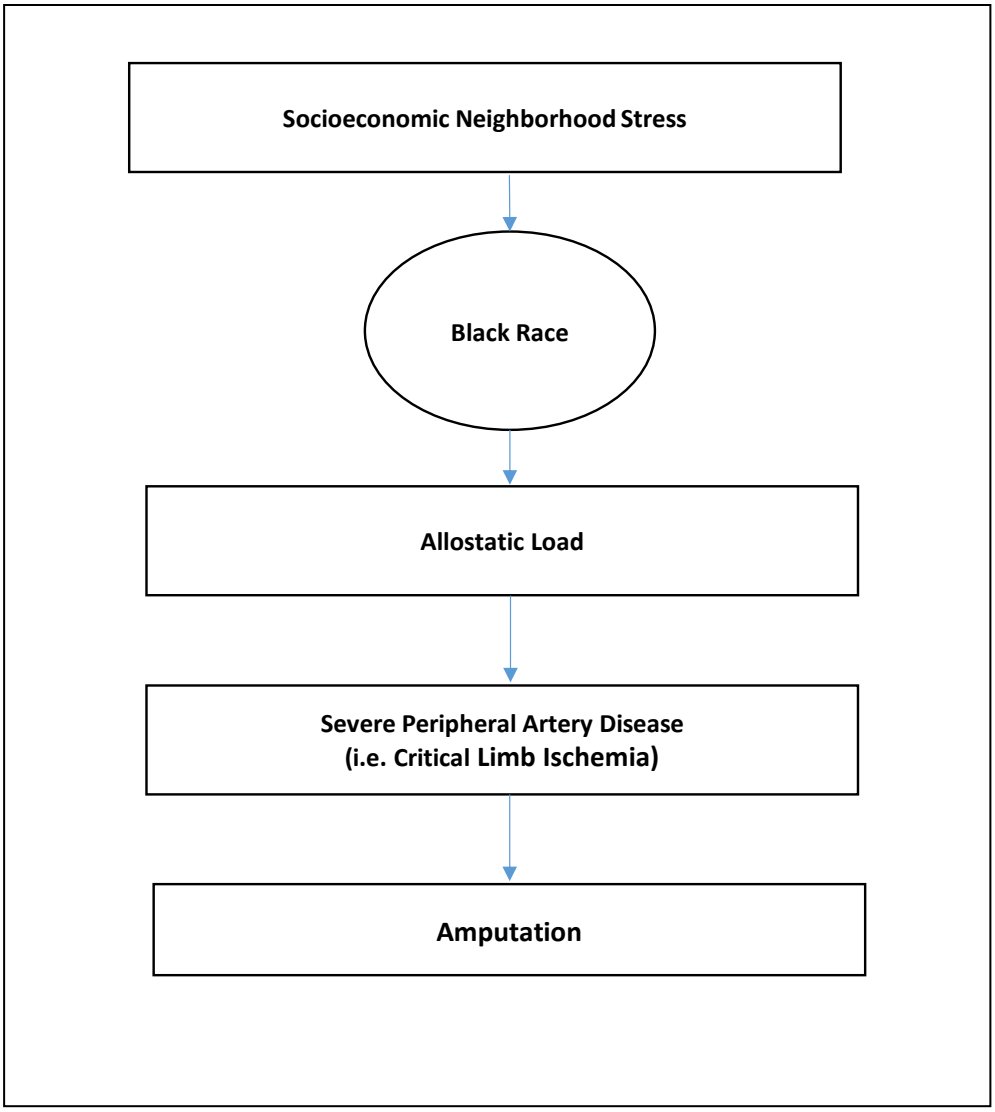


Figure 1: The Effect of Neighborhood Stress on PAD Severity

Chapter 2: PAPER 1 – NIS STUDY

The Relationship Between PAD Severity and Socioeconomic Status: A Nationwide Inpatient Sample Study

Introduction

The vascular literature continues to report considerable racial/ethnic disparities in the management and outcomes of peripheral artery disease (PAD) in the United States. This is particularly true for patients with severe PAD - referred to as critical limb ischemia. These patients are at the highest risk for limb loss with some data estimating the risk to be as high as 40% within six months.[1] Aggressive efforts at blood flow restoration -revascularization - are imperative in order to salvage the legs for these patients who have severe PAD, also known as critical limb ischemia. Unfortunately, Black race as well as low socioeconomic status (SES) have been associated with a lesser likelihood of undergoing limb-saving revascularization and a greater likelihood of undergoing a major amputation.[17, 22, 65-67] While a commonly postulated explanation given for this disparity is decreased access to care, there is also some allusion that Blacks may present with more severe vascular disease.[11, 13] This might explain some data that suggests that Blacks may have less success following lower extremity arterial reconstruction.[10] Even though this could be a likely consequence of Blacks presenting with more severe vascular disease at the time of intervention,[13] the specific role that race plays in the severity of vascular disease remains unclear.[20, 67]

Biologic response patterns to stress are increasingly recognized as major contributors to cardiovascular disease including ischemic heart disease and stroke.[57]

Specifically, data suggest that poorer neighborhoods are associated with both a higher prevalence of, as well as worse outcomes for, cardiovascular disease.[62, 63] A higher prevalence of PAD has also been reported for individuals with lower SES.[19] Whether household income is directly associated with more severe PAD, however, is not clear. I have recently shown, on a national level, that lower median household income closely correlates with a greater risk of amputation, and a lesser likelihood of revascularization.[22] In another statewide study, Stevens, et al. reported that diabetics in low-income neighborhoods in California are ten times more likely than diabetics from wealthier neighborhoods to undergo an amputation.[30] What is not known is if this correlation occurs because a lower household income specifically correlates with more severe PAD. In an effort to clarify the relationship between PAD severity and socioeconomic status, I undertook this study to evaluate if a lower median household income (MHI) is associated with more severe PAD.

Methods

Data Source and Patient Selection: Data was obtained from the Agency for Healthcare Research and Quality's (AHRQ) Healthcare Cost and Utilization and Project (HCUP) National Inpatient Sample (NIS) Database from 2005 - 2014. The NIS is the largest repository of all-payer inpatient admissions across the US containing about 7 million hospitalizations annually.[68] It is a 20% stratified sample of hospitalizations across the country making it a powerful source of data regarding patients across the country.

Patients with severe PAD – i.e., critical limb ischemia (CLI) - were identified using International Classification of Diseases, 9th Edition (ICD-9) diagnosis codes of

440.22, 440.23, and 440.24. Using the same codes, these patients were further stratified as presenting with ischemic rest pain or with tissue loss (ulceration or gangrene). To restrict the cohort to patients who underwent interventions for critical limb ischemia, patients with revascularization procedures (ICD-9 procedure codes 39.25, 39.29, 39.50 and 39.90) and those with major lower extremity amputations (ICD-9 procedure codes 84.15 and 84.17) were identified. Those patients presenting with limb ischemia who also underwent either a revascularization procedure or a major amputation (above- or below-knee amputation) constituted the study sample.

The median household income (MHI) quartile for each patient's ZIP code was provided in the database as a measure of the patient's socioeconomic status in relation to other individuals in that geographical location. Because the MHI quartile was the major explanatory variable in this study, the analyses were restricted only to patients who had information on MHI quartile (98% of the cohort). To eliminate atypical etiologies for PAD and given the extremely low prevalence of PAD among young patients, patients younger than 40 years were excluded from analysis.

Patient Characteristics: Demographic data including sex, insurance type (Private, Medicare, Medicaid, Self-pay, Other), and age were extracted from the database. Race/ethnicity was categorized as White, Black, Hispanic, Other (i.e., Asian, Pacific Islander, Native American etc.). Because a sizable proportion of the cohort was missing information on race/ethnicity and it was not clear if the data was missing at random, a separate category of "Unknown" race/ethnicity was also created.

Using ICD-9 diagnosis codes, patients with cardiac co-morbidities were defined as those with congestive heart failure or coronary artery disease or history of previous coronary revascularization. Patients with Chronic Obstructive Pulmonary Disease, those with end-stage renal failure and those with Type I or Type II diabetes mellitus were also identified. Overall co-morbid burden was measured with the Charlson Co-morbidity Index (CCI), which uses an aggregate measure based on 19 chronic conditions to predict long-term outcomes in longitudinal data.[69, 70] The CHARLSON module in Stata was used in calculating the CCI from ICD-9 diagnosis codes and then CCI was classified as 0-1, 2-3, >3.[71] The type of admission to the hospital (elective vs. non-elective) was characterized. Hospital location/teaching status were classified by the database as Rural, Urban Non-Teaching, and Urban Teaching.

Outcome Measures: The primary outcome measure was PAD severity as determined by Rutherford's Classification, Table 1. This was further classified into ischemic rest pain (Rutherford IV) or tissue loss (Rutherford V and VI), with tissue loss being worse. Other outcomes were hospital mortality, major amputation, and post-operative complications. The variable created for post-operative complications was a composite of post-operative shock, hemorrhage/hematoma, wound breakdown, wound infection, vascular graft defect, vascular graft infection, neurological complications, cardiovascular complications, respiratory complications and urinary complications. Effect of demographics including race/ethnicity as well as insurance status were also evaluated.

Statistical Analysis: All analyses were performed using weights provided by the NIS in order to derive nationally representative estimates. Because the sampling strategy of the NIS changed from year 2012 onwards, the Trend Weights were used for all years for consistency of comparisons.[72] Patient demographics, co-morbidity and hospital characteristics were compared across MHI quartiles using Pearson chi-square tests. Similar analyses were performed comparing the severity of presentation of PAD across MHI quartiles. The distribution of the outcomes of interest across MHI quartiles and across levels of PAD severity were also evaluated. To assess the differences in characteristics between patients who underwent amputations and those who did not, comparisons were made with Pearson chi-square tests.

Bivariate logistic regression models were built to assess the association between severity of presentation and each characteristic. A *P*-value of 0.1 was decided *a priori* as the cut-off for inclusion of each variable in a multivariable model. Using multivariate logistic regression models, the independent association between MHI quartile and severity of PAD presentation was assessed. Because the unmeasured clinical characteristics may be different between patients with elective admissions and those with non-elective admissions, sensitivity analyses were performed stratifying patients by their admission type. All analyses were performed using STATA Statistical Software: Release 14.2 (College Station, TX: StataCorp LLC) and the significance level was set as $P < 0.05$.

Institutional Review Board (IRB): Given that this study, utilized de-identified patient data, an IRB waiver was granted following submission of an IRB application (Appendix A).

Results

There were 765, 175 patients identified as the study sample (number adjusted using survey weights). This was a primarily male population (58%). Individuals from a lower MHI quartile MHI were more likely to present at a younger age (38% in the 40 – 64-year range for the 1st Quartile; vs 25% in the 40 – 64-year range for the 4th Quartile) while a greater percentage of individuals from the highest MHI constituted the oldest group (17% of 4th MHI Quartile patients were $\geq$ 85 vs 10% of 1st MHI Quartile patients). Blacks and Hispanics were more likely to come from poorer neighborhoods while Whites were more likely to come from wealthier neighborhoods, Table 2. Medicare was the dominant insurance used across all four income quartiles. There was a significant comorbidity profile amongst this group of PAD patients, Table 2. In each group, most patients (over 75%) presented with tissue loss (i.e., non-healing ulcer and/or gangrene), Table 3. Those living in wealthier ZIP codes were more likely to undergo revascularization versus amputation (66% Revascularization vs 34% amputation in 1st MHI compared to 75% Revascularization vs 25% Amputation in 4th MHI. Whites were more likely to be revascularized vs amputated as compared to Blacks (75% Revascularization vs 25% Amputated for Whites; compared to 58% Revascularized vs 42% Amputated for Blacks), Table 4.

Upon multivariate analysis, male sex, increasing age, non-White ethnicity, non-private insurance and an increased comorbidity index were all associated with greater

odds of severe PAD (i.e., tissue loss vs ischemic rest pain) Table 6. Increasing income, however, was also positively associated with PAD severity i.e., individuals living in wealthier neighborhoods were more likely to have more severe PAD clinical presentation. Table 6.

Discussion

Socioeconomic status is increasingly recognized as playing a significant role in health disparities in general[58, 64, 73-75] and cardiovascular health disparities in particular.[76] Several studies have indicated that low SES individuals with PAD have a greater likelihood of undergoing amputation and a lesser likelihood of undergoing limb-preserving revascularization.[17, 22, 23] Further data implies that it may not only be individual socioeconomic characteristics that impact on health but, perhaps more important, one's neighborhood characteristics.[77-79] Poverty has been described as "getting under the skin" and changing the biology and health outcomes of the poor.[28, 41] Stevens, et al. reported that diabetics in low-income neighborhoods in California are ten times more likely than diabetics from wealthier neighborhoods to undergo an amputation.[30]

My current study indicates that while individuals living in ZIP codes with a lower MHI are more likely to present with less clinically severe PAD, they are also less likely to undergo limb-saving revascularization and more likely to undergo amputation. The increased likelihood to undergo an amputation with decreasing income is identical to what I have previously reported in a closely related study using the same database.[80] This current study, however, indicates that this increased likelihood to undergo

amputation for the lower SES is paradoxically associated with less severe PAD according to Rutherford's Classification.[81] This surprising finding, therefore, challenges the philosophy held by many that the primary reason certain populations are more likely to undergo amputation is because they present too late with disease that is too advanced.[67] Instead, it raises the question as to what role physicians' attitudes may play in this healthcare disparity.[82] In an era where there is increased reporting of procedural outcomes data, often to the lay public, there is the possibility that concern regarding their published outcomes could discourage surgeons from taking on patients they deem to be high risk. Evidence suggests that this already happens in cardiac surgery where scrutiny appears to be at its highest. In one survey of UK cardiac surgeons, over a third acknowledged that they had turned down high-risk patients because of this concern.[83] Unfortunately, it appears that procedural outcomes transparency which is meant to benefit the population could ironically pose a peril for some of the most vulnerable patients. Yet, these are the very individuals who often need the procedures the most. Whether such a bias, in fact, exists in US Vascular Surgery practice is unknown at this time. There is, however, some evidence that physician bias may potentially play an important role in the amputation-revascularization racial disparity. Whereas it has generally been suggested that referral to high volume vascular surgeons practicing in high volume hospitals may be one way to ameliorate the amputation-revascularization racial disparity,[17] data suggests that this is likely not the case.[10] What has been shown to make a significant difference in the amputation-revascularization racial disparity is the diversity of the surgeon's practice.[18] 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.[18] Analogously, whether a surgeon seeing a higher percentage of lower SES patients would likewise result in a lower amputation rate for this population, however, has not yet been studied.

Notwithstanding, It is important to note that current evidence indicates that PAD, specifically severe PAD or critical limb ischemia, does not necessarily progress along the Rutherford Classification Scale from claudication through ischemic rest pain to nonhealing ulcer and then gangrene.[84] Therefore, while gangrene is considered a more severe presentation of PAD as compared to ischemic rest pain, the progression of PAD itself is not necessarily linear. It is possible – perhaps, even likely - that wealthier individuals with better primary medical care were admitted and revascularized much sooner as compared to individuals in a lower SES stratum. Given that a diagnosis of PAD typically lags behind a diagnosis of coronary artery disease,[1] individuals in a higher SES stratum may likely already have been under good primary and cardiovascular care and be enjoying the benefits of this care long before their admission with critical limb ischemia. Evidence to support this theory is the fact that the beneficial effect of statin use in PAD is well documented.[85] So is the reality that individuals of lower SES are less likely to benefit from this medication.[86]

There are several limitations associated with this study. First, utilizing ZIP codes to capture neighborhood socioeconomic stress - i.e., MHI - assumes that all individuals living in a particular ZIP code necessarily belong to that "ZIP code's socioeconomic deprivation bracket". While this may, indeed, be customary, this assumption is not likely to be universally accurate. A further limitation in using ZIP-

code based MHI is the question as to whether these disparities may simply be reflective of local practice patterns. Studies indicate that amputation and revascularization rates vary nationwide not only according to income and race, but also according to according to the hospital referral region.[87] Unfortunately, by using ZIP-code based MHI, it is not possible to determine how much of this disparity was simply related to local practice patterns of that hospital referral region as opposed to low SES-mediated health disparities. Notwithstanding these limitations, there is good data that indicates that the ZIP-code based MHI specifically is an excellent indicator of SES and is useful for monitoring health disparities. Moreover, ZIP-code based MHI is generally noted to be less likely to have missing data as compared to other parameters such as block group and census tract.[88] Still another limitation is that given that the NIS is an exclusively inpatient database, I am unable to comment on any potential outpatient revascularization efforts that may have been undertaken. In an effort to limit this inadequacy, I excluded limb ischemia patients who did not undergo any procedures during their admission so that presumably only those who required a relatively prompt procedure were included. This approach in itself could have introduced bias one way or another. Other limitations include the ubiquitous drawbacks of large database studies including potential errors in coding and sampling.[89]

Despite these limitations, one distinct advantage of the study design is the very large sample size available. I believe that this large sample size and the multivariate logistic regression methods used sufficiently mitigated many of these limitations and produced some very meaningful results. A second major advantage of my study design

is that the NIS database represents real-life management of the effect of neighborhood stress on the severity of PAD and the likelihood of amputation on a national level.

In conclusion, while individuals living in lower income neighborhoods are more likely to undergo amputation rather than limb-saving revascularization following an admission for severe PAD, these lower income individuals also, paradoxically, typically present with less severe PAD.

Tables

Table 1: Rutherford Classification of Peripheral Arterial Disease[1]

Category	History
0	Asymptomatic
1	Mild claudication
2	Moderate claudication
3	Severe claudication
4	Ischemic rest pain
5	Tissue ulceration (minor)
6	Tissue loss/gangrene

Table 2: Demographic and Clinical Characteristics of Patients managed for Critical Limb Ischemia by Household Income Quartiles

Characteristic	Median Household Income Quartile for Patient ZIP Code, n (%)			
	1st Quartile (n = 257,639)	2nd Quartile (n = 205,252)	3rd Quartile (n = 167,846)	4th Quartile (n = 134,438)
Sex				
Male	143,621 (56.0)	119,700 (58.0)	97,566 (58.0)	77,901 (58.0)
Female	113,992 (41.0)	85,542 (42.0)	70,265 (42.0)	56,571 (42.0)
Age Category				
40 – 64	96,687 (38.0)	69,855 (34.0)	51,817 (31.0)	33,659 (25.0)
65 – 84	134,674 (52.0)	111,549 (54.0)	93,199 (56.0)	77,783 (58.0)
≥ 85	26,278 (10.0)	23,848 (12.0)	23,830 (14.0)	23,046 (17.0)
Race/Ethnicity				
White	109,328 (42.0)	119,411 (58.0)	103,547 (62.0)	93,443 (69.4)
Black	73,937 (29.0)	29,729 (14.5)	20,540 (11.6)	13,248 (9.9)
Hispanic	29,249 (11.0)	14,645 (7.2)	12,215 (7.3)	6,935 (5.2)
Others	9,701 (4.0)	6,719 (3.3)	6,941 (4.1)	6,920 (5.1)
Unknown	35,425 (14.0)	34,748 (17.0)	24,604 (15.0)	13,942 (10.4)
Insurance Type				
Private	30,540 (12.0)	29,739 (15.0)	27,177 (16.4)	22,814 (16.6)
Medicare	187,917 (72.8)	151,871 (73.6)	124,362 (74.0)	102,874 (77.0)
Medicaid	27,158 (10.6)	14,878 (7.3)	10,311 (6.2)	5,294 (3.9)
Self-Pay	6,627 (2.6)	4,490 (2.2)	2,858 (1.7)	1,747 (1.3)
Other	5,057 (2.0)	3,959 (1.9)	2,896 (1.7)	1,661 (1.2)
Mode of Admission				
Elective	116,042 (45.0)	97,599 (48.0)	79,232 (47.0)	61,140 (46.0)
Emergency	140,686 (55.0)	107,206 (52.0)	88,003 (53.0)	73,111 (54.0)
Cardiac co-morbidities				
Present	124,202 (48.0)	100,898 (49.0)	85,270 (51.0)	70,319 (52.0)
Chronic Obstructive Pulmonary Disease				
Present	52,580 (20.0)	44,398 (22.0)	34,359 (20.0)	24,417 (18.0)
End-Stage Renal Disease				
Present	39,885 (15.0)	26,908 (13.0)	21,704 (13.0)	17,250 (13.0)
Diabetes mellitus				
Present	151,702 (59.0)	115,804 (56.0)	93,558 (56.0)	74,028 (55.0)
Charlson Co-morbidity Index				
0 – 1	103,241 (40.0)	83,067 (40.5)	67,713 (40.3)	54,253 (40.0)
2 – 3	94,627 (37.0)	76,121 (37.1)	61,465 (36.6)	48,509 (36.0)
> 3	59,772 (23.0)	46,064 (22.4)	38,668 (23.1)	31,726 (24.0)
Location/teaching status of hospital				
Rural	31,129 (12.0)	17,408 (8.5)	4.965 (3.0)	816 (0.6)
Urban Non-teaching	87,093 (34.0)	82,456 (40.5)	70,864 (42.0)	57,608 (42.9)
Urban Teaching	137,772 (54.0)	104,361 (51.0)	91,494 (55.0)	75,963 (57.5)

Table 3: Severity of Critical Limb Ischemia by Household Income Quartiles

Severity of Presentation	Median Household Income Quartile for Patient ZIP Code, n (%)			
	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile
Rest Pain	58,856 (22.8)	48,238 (23.5)	38,597 (23.0)	28,383 (21.1)
Tissue Loss	198,784 (77.2)	157,014 (76.5)	129,249 (77.0)	106,106 (78.9)

Table 4: Demographic and Clinical Characteristics of Patients with Critical Limb Ischemia by Mode of Management

Characteristic	Mode of Management, n (%)	
	Revascularization (n = 536,165)	Amputation (n = 229,061)
Median Household Income Quartile for Patient ZIP Code		
1st Quartile	169,825 (66.0)	87,814 (34.0)
2nd Quartile	143,330 (70.0)	61,922 (30.0)
3rd Quartile	122,072 (73.0)	45,774 (27.0)
4th Quartile	100,938 (75.0)	33,550 (25.0)
Sex		
Male	304,176 (69.0)	94,436 (31.0)
Female	231,934 (71.0)	134,612 (29.0)
Age Category		
40 – 64	177,481 (70.0)	74,538 (30.0)
65 – 84	295,634 (71.0)	121,571 (29.0)
≥ 85	63,050 (66.0)	32,952 (34.0)
Race/Ethnicity		
White	317,908 (75.0)	107,821 (25.0)
Black	80,091 (58.0)	57,362 (42.0)
Hispanic	41,503 (66.0)	21,542 (34.0)
Others	21,361 (71.0)	8,919 (29.0)
Unknown	75,302 (69.0)	33,417 (31.0)
Insurance Type		
Private	85,001 (77.0)	25,268 (23.0)
Medicare	390,268 (69.0)	176,756 (31.0)
Medicaid	38,629 (67.0)	19,011 (33.0)
Self-Pay	11,583 (74.0)	4,138 (26.0)
Other	10,025 (74.0)	3,549 (26.0)
Mode of Admission		
Elective	279,548 (79.0)	74,465 (21.0)
Emergency	254,987 (62.0)	154,018 (38.0)
Charlson Co-morbidity Index		
0 – 1	233,399 (76.0)	74,876 (24.0)
2 – 3	190,875 (68.0)	89,847 (32.0)
> 3	111,891 (63.0)	64,338 (37.0)
Location/teaching status of hospital		
Rural	33,924 (62.0)	20,395 (38.0)
Urban Non-teaching	207,326 (70.0)	90,695 (30.0)
Urban Teaching	292,803 (71.0)	116,787 (29.0)

Table 5: Outcomes of Patients with Critical Limb Ischemia by Household Income Quartile and by Severity of Presentation

Patient Category	Mortality, n (%)	Amputation, n (%)	Complications, n (%)
1st Quartile	7,176 (2.8)	87,814 (34.0)	36,074 (14.0)
2nd Quartile	5,713 (2.8)	61,922 (30.0)	30,958 (15.0)
3rd Quartile	4,576 (2.7)	45,774 (27.0)	25,910 (15.0)
4th Quartile	4,299 (3.2)	33,550 (25.0)	22,046 (16.0)
Rest Pain	2,183 (1.3)	8,720 (5.0)	34,511 (20.0)
Tissue Loss	19,582 (3.3)	220,341 (37.0)	80,478 (14.0)

Table 6: Multivariate Analysis of Factors associated with Severity of Presentation of Critical Limb Ischemia

Characteristic	Adjusted Odds of Tissue Loss vs. Rest Pain (95% Confidence Interval)	P-value
Median Household Income for ZIP code		
1st Quartile	Ref	-
2nd Quartile	1.04 (1.00 – 1.09)	0.068
3rd Quartile	1.07 (1.01 – 1.13)	0.013
4th Quartile	1.19 (1.11 – 1.27)	<0.001
Sex		
Female	Ref	-
Male	1.24 (1.20 – 1.27)	<0.001
Age Category		
40 – 64	Ref	-
65 – 84	1.22 (1.17 – 1.26)	<0.001
≥ 85	2.63 (2.48 – 2.80)	<0.001
Race/Ethnicity		
White	Ref	-
Black	1.60 (1.51 – 1.68)	<0.001
Hispanic	1.90 (1.76 – 2.06)	<0.001
Others	1.37 (1.22 – 1.52)	<0.001
Unknown	1.15 (1.06 – 1.24)	0.001
Insurance Type		
Private	Ref	-
Medicare	1.44 (1.38 – 1.50)	<0.001
Medicaid	1.35 (1.28 – 1.44)	<0.001
Self-Pay	1.35 (1.22 – 1.48)	<0.001
Other	1.19 (1.07 – 1.33)	0.001
Charlson Co-morbidity Index		
0 – 1	Ref	-
2 – 3	2.00 (1.93 – 2.06)	<0.001
> 3	3.86 (3.70 – 4.03)	<0.001

Model is adjusted for all variables in the table

Table 7: Association between Median Household Income and Severity of Presentation of Critical Limb Ischemia stratified by Mode of Presentation

		Tissue Loss vs. Rest Pain			
Income Quartile		1st Quartile	2nd Quartile	3rd Quartile	4th Quartile
Emergency Presentation	aOR (95% CI)	Ref	1.01 (0.94 – 1.09)	1.06 (0.98 – 1.16)	1.21 (1.11 – 1.33)
	P-value	-	0.738	0.149	<0.001
Elective Presentation	aOR (95% CI)	Ref	1.07 (1.01 – 1.14)	1.08 (1.01 – 1.15)	1.14 (1.05 – 1.24)
	P-value	-	0.017	0.030	0.002

All models are adjusted for age, sex, race, insurance type, Charlson Co-morbidity Index and household income quartile
aOR, adjusted Odds Ratio; CI, Confidence Interval

Chapter 3: PAPER 2 – NHANES STUDY

The Relationship Between PAD Severity and Allostatic Load: A National Health and Nutrition Examination Survey Study

Introduction

Major disparities persist in the management of peripheral artery disease (PAD) in the United States. 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).[1] 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.[3-6] This disparity has persisted for decades. In one study, utilizing a statewide database, Huber, et al. 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.[6] While some have suggested that this disparity is largely explained by an increased burden of diabetes mellitus in the Black population,[9] it has been shown that this disparity exists and is even more pronounced among patients who do not have diabetes.[5] 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."[10] 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, I and others have documented that these differences persist among patients seeking care at institutions with significant vascular surgical capability.[10, 65] 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.[18] 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.[18]

In a study utilizing the Area Resource File, Hayanga, et al., after categorizing each county in the US into most, moderately or least segregated, performed multivariate linear regression analysis to examine the association between access to surgical services and the proportion of minorities living in a particular county. These authors identified that each percentage point increase in Blacks and/or Hispanics was associated with a significant decrease in surgeons, and surgical volume.[8] Decreased access to health care by Blacks in the United States has long been reported.[14] This is particularly true for cardiovascular disease.[15] More specifically, it has been well described that even when presenting with similar symptoms, Blacks are significantly less likely to receive cardiovascular interventions.[15, 16] 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,[11] and that

Black race is a strong and independent risk factor for PAD.[12] Indeed, using the Vascular Quality Initiative, a prospectively-maintained regional database, we have recently shown that Black patients present with more advanced vascular disease at the time of their initial major vascular operation.[13] 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.[39, 40] Allostasis is an extension of the concept of homeostasis, and represents successful physiologic adaptation to socio-environmental stress. While the notion of allostasis is comparable to homeostasis, homeostasis aims at reducing variability while allostasis places specific emphasis on the capacity to adapt to stressful stimuli.[3] 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.[43] Whether a greater allostatic load is associated with more severe PAD and a greater risk

of amputation in Blacks is currently unknown. I, therefore, undertook this study in order to evaluate if allostatic load is associated with PAD severity.

Methods

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, noninstitutionalized US population.[90] 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 $\leq$ 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.[91] 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.[92] 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.[92] 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. 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.[93]

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). Effect 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 following submission of an IRB application (Appendix A).

Statistical Analyses: Because there are no widely accepted thresholds for high or low allostatic loads in the literature, all participants in the survey were divided into three roughly equal parts (tertiles) based on their allostatic loads. 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.

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 1. The sample had an equal split of male to female proportions for allostatic load scores representing the second and third tercile. Females, however, 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 PAD, i.e., an ABI $\leq$ 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 2. In each allostatic load tertile, the overwhelming majority (99%) of PAD diagnosed was mild or moderate, Table 3. 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 4. A statistically significant correlation 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, Figure 1. A multivariate analysis of factors associated with a diagnosis of PAD is shown in Table 5. In Table 4, the distribution of allostatic load components across levels of PAD severity is illustrated, and a multivariate analysis of factors associated with allostatic load is represented in Table 7.

Discussion

The current study was unable to identify an association between PAD severity and allostatic load, Table 5. 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. using an earlier NHANES wave that showed that individuals with PAD had higher allostatic load scores.[59] Furthermore, this corroborates the previously reported finding associating a higher PAD prevalence in the setting of a higher allostatic load.[59, 60] 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.[39, 40] It represents the cumulative effect of chronic "wear and tear" leading to a failure of allostasis that results 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.[41] Other investigators have long described this phenomenon of "weathering" in Blacks related to the long-term effect of perceived discrimination.[42] 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.[94] 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.[43] My current study supports this hypothesis, and places allostatic load 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. 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.[19] In fact, certain authors have proposed that race may simply be a surrogate for socioeconomic status. It is postulated that lower 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.[20, 21] 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.[28, 29, 95] 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.[17] 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 this amputation-revascularization disparities. Blacks have a significantly higher prevalence of traditional cardiovascular risk factors such as diabetes, hypertension and dyslipidemia as compared to Whites.[24] 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.[25] Furthermore, there is significant under-utilization of statins[26] in Blacks so that this population is not fully benefitting from the tremendous advantages of statins in combatting vascular disease.

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,[38] the role of physician bias has been increasingly recognized as playing a role in healthcare disparities. Furthermore, racism and perceived discrimination have been described as determinants of health in general, and of cardiovascular events in particular.[31, 32] The Multi-Ethnic Study of Atherosclerosis reported that, while controlling for chronic stress and depression, perceived discrimination was associated with an increased incidence of cardiovascular events.[34] It has been suggested that this may be the reason why Blacks in West Africa and the Caribbean have a lower prevalence of certain cardiovascular diseases, such as hypertension, as compared to African Americans.[35] While the literature remains

unclear as to whether PAD is more prevalent and more severe in African-Americans as compared to native Africans and/or Afro-Caribbean,[36] data indicates that foreign-born Blacks may have a health advantage in allostatic load.[96]

One key limitation of my second (NHANES) study is that the NHANES wave used 2003 – 2004 – is relatively dated. I utilize these data, however, as this is the most recent NHANES wave that includes Doppler occlusion pressures that allows 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.[97] Moreover, data suggests that while overall national amputation rates have decreased over the past two decades, amputation rates among Blacks have not decreased.[98] 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. My 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[44, 45] and endothelial dysfunction. In vitro and in vivo racial differences in inflammation have been identified,[48] and Blacks, with early life adversity, have been noted to have high

concentrations of inflammatory biomarkers in mid-life.[49] There are studies that suggest race-specific differences in endothelial function and a propensity of Blacks towards endothelial dysfunction.[53-56] 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. My current study was unable to identify a clear association between PAD severity and allostatic load. Therefore, I was unable to establish allostatic load as a probable down-stream factor in the amputation-revascularization disparities pathway.

Tables

Table 1: Demographic and Clinical Characteristics of All Survey Respondents by Level of Allostatic Load, NHANES 2003-04

	Represented Population in Millions (%)		
Allostatic Load Tertile	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)
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)
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)
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)
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)
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)
Hypertension	4.6 (10)	13.0 (21)	32.0 (51)
Diabetes Mellitus	0.3 (1)	2.5 (4)	10.0 (17)

Table 2: Distribution of Individuals with Peripheral Artery Disease across Tertiles of Allostatic Load

	PAD Status, Represented Population in Millions (%)	
Allostatic Load Tertile	PAD	No PAD
1st Tertile	0.3 (6)	10.0 (14)
2nd Tertile	1.4 (28)	28.0 (36)
3rd Tertile	3.3 (66)	39.0 (50)

PAD, Peripheral Artery Disease

Table 3: Association between Levels of Allostatic Load and Degree of Peripheral Artery Disease Severity

	Peripheral Artery Disease Severity, number in 10^5 (%)		
Allostatic Load Tertile	Mild ($n = 26.0 \times 10^5$)	Moderate ($n = 24.0 \times 10^5$)	Severe ($n = 0.3 \times 10^5$)
1st Tertile	1.9 (60)	1.3 (40)	0 (0)
2nd Tertile	8.1 (58)	5.7 (41)	0.1 (1)
3rd Tertile	16.0 (48)	17.0 (51)	0.2 (1)

Table 4: Distribution of Allostatic Load Components Across Levels of Peripheral Artery Disease Severity

	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 (≥ 30)	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 5: 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

Table 6: 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

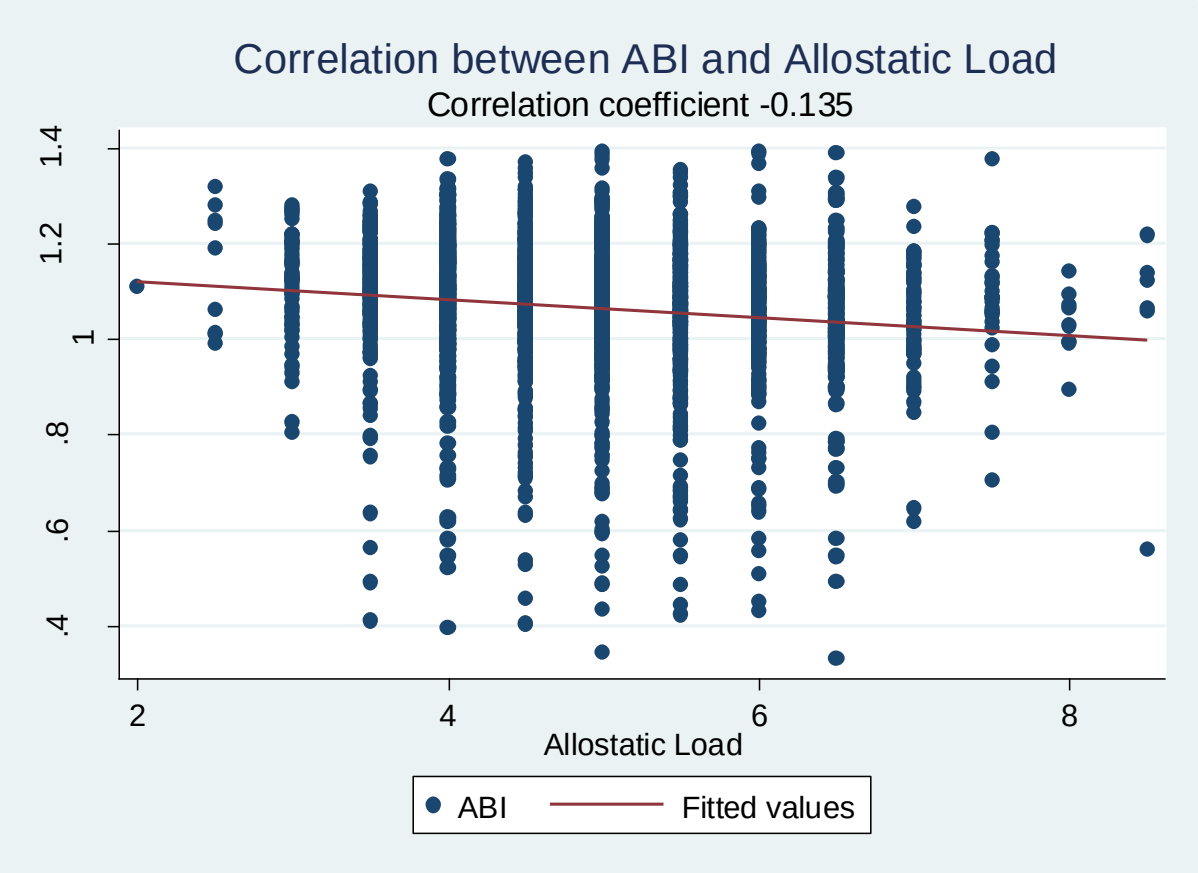
Table 7: Multivariate Analysis of Factors associated with Allostatic Load

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

Figure

Figure 1: Relationship between Allostatic Load and Ankle Brachial Index (ABI) for Individuals with and without PAD



Chapter 4: PAPER 3 – NRD STUDY

The Effect of Socioeconomic Status on Outcomes of Lower Extremity Arterial Reconstruction: A Nationwide Readmission Databases Study

Introduction

Significant socioeconomic disparities exist in the management of peripheral artery disease (PAD).[99] Patients with severe PAD - referred to as critical limb ischemia - are at particularly high risk for major leg amputation with estimates of losing their leg within six months of diagnosis as high as 40%.[1] For this group of severe PAD patients, expeditious restoration of blood flow (i.e., revascularization) is essential in order to save the endangered leg. Data suggests that there is a greater prevalence of PAD in individuals of lower socioeconomic status (SES).[19] Evidence also indicates that among patients presenting with severe PAD, low SES is an independent predictor of the likelihood of amputation rather than revascularization.[17, 100] In one statewide study, individuals living in a low income neighborhood were ten times more likely to undergo an amputation as compared to individuals living in more affluent communities.[30]

Distressed neighborhoods have been associated with a range of negative health outcomes in general and cardiovascular health outcomes in particular.[27] It is believed that this may be due to the stress of high unemployment rates, high crime as well as limited opportunities for exercise and purchasing healthy food in these neighborhoods.[28] Neighborhood socioeconomic deprivation has been described as a marker of the prevalent contextual characteristics that affect one's health. Deprived neighborhoods have, therefore, been associated with increased risk of cardiovascular disease[29] and death.[27] While little specific work has been done to determine a specific

relationship between PAD and neighborhood stress, the impact that neighborhood stress has on overall cardiovascular disease would suggest that there may be some correlation between neighborhood stress and PAD. Specific mechanisms by which neighborhood stress may impact PAD, however, have not been systematically examined.

In a recent nationwide study, I reported that patients of low income are more likely to undergo an amputation versus revascularization, and that this disparity occurs in a highly linear fashion.[22] After stratifying patients who presented with severe PAD into four income quartiles based on ZIP codes, I showed that the likelihood of amputation increased in a step-wise fashion as one moved from one ZIP code income quartile to a lower one. In this same study, I also demonstrated that Medicaid insurance and uninsured status were associated with a higher likelihood of amputation while private insurance was associated with a lower likelihood of amputation and a higher likelihood of revascularization. Clearly, lower income also affects access to care given that poor patients are less likely to have private insurance and more likely to have no insurance or Medicaid (which is not universally accepted by clinicians). The report that diabetics in lower income neighborhoods of California are ten times more likely to undergo an amputation as compared to diabetics from more affluent areas in the state unequivocally underscores this disparity.[23] What is not clear from the literature is if it is individual low income that actually affects the severity of PAD and the likelihood of amputation or if it is living in a lower income ZIP code that leads to more severe PAD. Furthermore, it is not known if individuals of low SES have more severe PAD or if low SES individuals will have similar outcomes when lower extremity arterial

reconstruction is undertaken. While there is some data that for individuals undergoing coronary artery bypass grafting, socioeconomic deprivation is associated with worse outcomes,[101] similar data has not been reported for the peripheral circulation. Furthermore, there is a paucity of data on the association of SES and post-discharge outcomes among patients undergoing lower extremity arterial reconstruction. Given this background, I undertook this study to determine if SES influences outcomes following lower extremity arterial reconstruction.

Methods

Study Population: A query of the Agency for Healthcare Research and Quality's (AHRQ) Healthcare Cost and Utilization and Project (HCUP) Nationwide Readmissions Databases (NRD) was performed to identify all patients with critical limb ischemia who underwent surgical bypass for PAD from 2010 - 2014. The NRD is one of the largest sources of hospital readmission information in the US aggregating hospital records in 22 states comprising more than 50% of all hospitalizations in the country.[102] The NRD includes discharges for patients with and without repeat hospital visits in a given year as well as those who died while being hospitalized. Since patients are assigned a specific identifier, it is possible to track subjects for a given year.

Patients with severe PAD were identified with International Classification of Diseases, 9th Edition (ICD-9) diagnosis codes of 440.22, 440.23, and 440.24, and surgical revascularization procedures were identified using ICD-9 procedure codes 39.25 and 39.29. To eliminate atypical etiologies necessitating surgical revascularization, patients younger than 40 years old were excluded.

Patient and Hospital Characteristics: The median household income (MHI) quartile was determined *a priori* for each of these study subjects based on their ZIP codes. The MHI quartile was the most appropriate measure of socioeconomic status provided by the database and was present in more than 99% of patients in the database. Because SES is the central focus of the study, patients without MHI quartile information were not included in further analyses.

Demographic data, co-morbid conditions and hospital characteristics were recorded for these subjects. Demographic data included sex, insurance type (Private, Medicare, Medicaid, Self-pay, Other), and age category. Co-morbidity burden was measured with the Charlson Co-morbidity Index (CCI), which uses an aggregate measure based on 19 chronic conditions to predict long-term outcomes in longitudinal data.[69, 70] The CHARLSON module in Stata was used in calculating the CCI from ICD-9 diagnosis codes and then CCI was classified as 0-1, 2-3, and >3.[71] Hospital location and teaching status were classified by the database as Non-Metropolitan, Metropolitan, Teaching and Non-teaching.

Outcome Measures: The primary outcome variable was the need for additional procedures following revascularization i.e., the need for repeat revascularization efforts and/or amputation. Readmission data and clinical outcomes were tracked for each patient specifically focusing on re-admission for repeat revascularization attempts and readmission for leg amputation. Repeat revascularization procedures included open revascularization procedures (ICD-9 codes: 39.25, 39.29) and endovascular procedures (ICD-9 codes: 39.50, 39.90). For patients with multiple admissions for open revascularization, the earliest admission was selected as the index admission. Only

major amputations were included i.e., above and/or below knee amputations alone (ICD-9 codes: 84.15, 84.17). Amputations were characterized separately during the index admission and during the subsequent admissions. Secondary outcomes included mortality during the index admission and 30-day all-cause readmission.

Statistical Analyses: Variations in the patient and hospital characteristics of patients across income quartiles were evaluated using Pearson chi-square tests. Similarly, the differences in outcomes across the quartiles were evaluated using Pearson chi-square tests. To evaluate the independent associations between household income and the outcomes measured, logistic multivariate models were created. The associations of other demographic factors such as insurance type and sex were also evaluated using these models. Since amputations were considered as adverse outcomes regardless of when they occurred, amputations during the index admission and amputations during the subsequent admissions were examined as an aggregate measure for the multivariate analyses. All analyses were done using STATA Statistical software: 14.2 (College Station, TX: StataCorp LLC) and the level of significance was set at $P < 0.05$.

Institutional Review Board (IRB): Given that this study, utilized de-identified patient data, an IRB waiver was granted following submission of an IRB application (Appendix A).

Results

The NRD identified 131,529 individuals 40 and older who had a diagnosis of severe PAD (critical limb ischemia) and underwent an open lower extremity arterial

reconstructive procedure between 2010 and 2014 (793 patients younger than 40 were excluded). This was a primarily male (61%) population with an average age of 68.5 years old. Most of these patients were on Medicare (70%). The next most common insurance was Private insurance (16%) followed by Medicaid (9%). Table 1.

Across income quartiles, there were 42,908 (33.0%) in the 1st quartile, 35,414 (27.0%) in the 2nd quartile, 29,993 (23.0%) in the 3rd quartile and 23,214 (18.0%) in the 4th quartile. Differences in characteristics across income quartiles are shown in Table 1. Of note, patients in the lower income quartiles were significantly younger than patients in higher quartiles with 44.0% of patients in the 1st quartile less than 65 years old compared to only 27.4% in the 4th quartile (P<0.001). Also, while up to 12.0% of patients in the 1st quartile were treated in rural hospitals, only 0.3% of those in the 4th quartile were treated in similar hospitals (P<0.001).

There was a significantly increased likelihood of readmission leading to a major amputation (i.e., above knee or below knee amputation) as one moved from a higher income ZIP code to a lower ZIP code: i.e 6.7% for 4th MHI, 7.9% for 3rd MHI, 7.9% for 2nd MHI and 9.2% for 1st MHI, (P<0.001) (Table 2). There was also a significantly increased likelihood of undergoing an amputation at the same admission following an initial leg bypass as one's income decreased (3.2% in the 4th quartile vs. 4.1% in the 1st quartile, (P= 0.006). This indicates that a lower revascularization success rate is associated with a lower income. There were no significant differences identified for readmission for a repeat revascularization procedure based on MHI (11.0% in the 4th quartile vs. 11.0% in the 1st quartile, P= 0.754) or for 30-day all-cause readmission (23.0% in the 4th quartile vs. 23.0% in the 1st quartile, P= 0.521) or for

hospital mortality (2.4% in the 4th quartile vs 2.0% in the 1st quartile, *P*= 0.111), Table 2.

Multivariate analysis, adjusting for multiple factors including age, sex, insurance type and comorbidity index indicates that compared to the 1st median household income quartile, a 2nd or 3rd median household income quartile is associated with a 16% decreased likelihood of undergoing an amputation while a 4th median income quartile is associated with a 30% decreased likelihood of undergoing an amputation following an open lower extremity arterial reconstructive procedure, Table 3. Similar analyses showed that household income was not associated with subsequent revascularization procedures or with mortality during the index admission. However, compared to the 1st compared income quartile, patients in the 4th income quartile had significantly lower 30-day all-readmission (Adjusted Odds Ratio; 95% Confidence Interval: 0.91; 0.84 – 0.99).

Additional independent factors shown to be associated with the outcomes of interest are outlined in Table 4. While being age 65 and older was associated with increased mortality, it was associated with lower odds of amputation and subsequent revascularization. Higher Charlson Co-morbidity Indices were associated with higher odds of occurrence for all the outcomes measured. Additionally, compared to discharge home without home health, all other discharge dispositions were independently associated with higher amputation rates and 30-day readmission rates.

Discussion

The current study is a retrospective analysis utilizing data from the Agency for Healthcare Research and Quality's (AHRQ Healthcare Cost and Utilization Project (HCUP) Nationwide Readmission Databases (NRD). The NRD is a member of a family of health care databases established through a federal-state-industry partnership to create a multistate health database.[103] In this study, I demonstrate that socioeconomic neighborhood stress, as defined by MHI quartile per ZIP code, is directly related to the long-term outcomes of surgical revascularization for severe PAD. Specifically, the lower one's SES the greater the likelihood that one would be unsuccessful following surgical revascularization at the index operation leading to an amputation during that admission as well as subsequent re-admissions within that year. This implies that individuals living in lower SES neighborhoods are more likely to have unsuccessful revascularization operations. This study is a significant contribution to the body of knowledge that indicates that the MHI of one's neighborhood is an independent predictor of long-term outcomes following surgical revascularization for severe PAD.

Socioeconomic neighborhood stress is increasingly recognized as playing a critical role in health disparities in general[58, 64, 73-75] and cardiovascular health disparities in particular.[76] I and others have recently reported that individuals with PAD of lower SES have a greater likelihood of undergoing amputation and a lower likelihood of undergoing revascularization.[17, 22, 23] Yet, emerging evidence suggests that it may not only be individual socioeconomic characteristics that impact on health but, perhaps more importantly, one's neighborhood characteristics.[77-79] It is increasingly recognized that neighborhood stress associated with high unemployment

rates, high crime as well as limited opportunities for exercise and purchasing healthy food in these neighborhoods work together to create a uniquely stressful environment that "gets under the skin".[28, 41] In fact, Stevens et. al. reported that diabetics in low-income neighborhoods in California are ten times more likely than diabetics from wealthier neighborhoods to undergo an amputation.[30] Previous reports have indicated that neighborhood socioeconomic deprivation – judged by MHI - is associated with a higher prevalence of, and worse outcomes for, cardiovascular disease.[62, 63] This is true even after adjusting for individual-level risk factors.[64] What is not clear is if a lower median household income specifically correlates with more severe PAD. Even though the current study is unable to answer this specific question, this study, nonetheless, clearly shows that outcomes following surgical bypass are worse for those in the lower SES strata. While we must refrain from concluding that inferior surgical outcomes in individuals of lower SES necessarily implies more severe PAD, it is, nonetheless a well-known fact in the vascular community that one of the primary determinants of long-term graft patency is the character of the outflow vessels, i.e., the severity of a patient's vascular disease.[104] This suggests that while primarily sociologic issues such as access to care may continue to play a role in this amputation-revascularization disparity, it may well be that a primary driver is the biologic response to environmental stress: i.e., the socioeconomic neighborhood stressful milieu may have created a "biology of poverty"[105] that has extended to the vascular system so that individuals thus affected by this biology do, indeed, have more severe PAD. This may lead to a greater failure rate following leg bypass and a subsequent greater likelihood of amputation. While the role of a biologic response pattern to stress is increasingly recognized as a

major contributor to cardiovascular disease including ischemic heart disease and stroke[57] this, however, has not been previously reported for PAD. This study further emphasizes the role of place in health care disparities.[106, 107] Data suggests that neighborhood characteristics such as high unemployment rates, high crime as well as limited opportunities for exercise and purchasing healthy food combine together to create a contextual milieu of socioeconomic deprivation that affect one's health.[28, 106]

Given that in the United States, Blacks are significantly more likely to live in socioeconomically deprived neighborhoods as compared to Whites,[61] a similar mechanism may also explain why Blacks have often been shown to present with a greater burden of vascular disease as compared to Whites.[11, 108] Unfortunately, the absence of race/ethnicity data in the NRD database does not allow us to explore the race/ethnic question in this current study.

There are several limitations associated with this study. The first major limitation is an inability to review any preoperative angiograms. I am, therefore, not able to determine if, in fact, any outcomes may have been related to the quality of the outflow arteries preoperatively. Thus, we are left to infer that these individuals of lower SES who had worse outcomes following surgical revascularization may have had worse vascular disease. Second, the NRD has readmission data only for a given year. Therefore, an individual who may have had an operation in one year and who was readmitted in another year would not have been captured by this database. This is obviously a significant limitation. Third, the absence of racial data does not allow an exploration of race/ethnicity which has often been closely linked to SES and income in previous studies of amputation-revascularization disparities.[67] Fourth is the pervasive

problem of coding and potential sampling errors present in administrative databases,[89] and fifth is the reality that these large sample sizes can yield statistically significant data which bear little clinical utility. Notwithstanding, the large sample size afforded by this national database and the fact that these patients can be reliably tracked across multiple hospital admissions still allow us to draw some meaningful conclusions from this study.

A further limitation involves the use of ZIP codes to capture neighborhood socioeconomic stress - i.e., MHI. This assumes that all individuals living in a particular ZIP code necessarily belong to that "ZIP code's socioeconomic deprivation bracket". Even though this may be typical, this assumption is unlikely to be universally accurate. Another limitation in using ZIP-code based MHI is the question as to whether these disparities may simply be reflective of local practice patterns. Studies indicate that amputation and revascularization rates vary nationwide not only according to income and race, but also according to according to the hospital referral region.[87] Unfortunately, by using ZIP-code based MHI, it is not possible to determine how much of this disparity was simply related to local practice patterns of that hospital referral region as opposed to low SES-mediated health disparities. Notwithstanding these limitations, there is good data that indicates that the ZIP-code based MHI specifically is an excellent indicator of SES and is useful for monitoring health disparities. Furthermore, ZIP-code based MHI is generally noted to be less likely to have missing data as compared to other parameters such as block group and census tract.[88]

In conclusion, lower SES, specifically living in a lower MHI ZIP code, is associated with worse outcomes following lower extremity arterial reconstruction for severe PAD. Individuals who live in low SES neighborhoods are more likely to be readmitted following a failed leg bypass resulting in a major amputation. These data highlight the need for including the reduction of socioeconomic disparities among efforts to improve outcomes of treatment for PAD and reduce amputations.

Tables

Table 1: Patient Demographics and Hospital Characteristics

Characteristic	Median Household Income Quartile for Patient ZIP Code, n (%)			
	1st Quartile [n=42,908]	2nd Quartile [n=35,414]	3rd Quartile [n=29,993]	4th Quartile [n=23,214]
Sex				
Male	25,480 (59.0)	21,852 (62.0)	18,092 (60.0)	14,181 (61.0)
Female	17,429 (41.0)	13,562 (38.0)	11,900 (40.0)	9,033 (39.0)
Age Category				
40 – 64	18,887 (44.0)	13,718 (38.7)	10,379 (35.0)	6,351 (27.4)
65 – 84	21,494 (50.0)	18,746 (53.0)	16,636 (55.1)	14,016 (69.4)
≥ 85	2,528 (6.0)	2,950 (8.3)	2,978 (9.9)	2,847 (12.2)
Insurance Type				
Private	5,492 (13.0)	5,787 (16.0)	5,626 (19.0)	4,412 (19.0)
Medicare	29,325 (69.0)	24,644 (70.1)	20,948 (69.7)	16,887 (72.8)
Medicaid	5,452 (13.1)	3,088 (8.7)	2,129 (7.1)	1,137 (4.9)
Self-Pay	1,276 (3.0)	890 (2.5)	538 (1.8)	317 (1.4)
Other	1,258 (2.9)	945 (2.7)	718 (2.4)	442 (1.9)
Charlson Co-morbidity Index				
0 – 1	19,736 (46.0)	16,380 (46.0)	13,526 (45.0)	9,963 (43.0)
2 – 3	14,841 (35.0)	12,152 (34.0)	10,249 (34.0)	7,946 (34.0)
> 3	8,332 (19.0)	6,881 (19.0)	6,218 (21.0)	5,305 (23.0)
Location/teaching status of hospital				
Rural	5,294 (12.0)	2,382 (6.7)	506 (1.7)	72 (0.3)
Urban Non-teaching	11,552 (27.0)	11,537 (32.6)	10,123 (33.7)	8,149 (34.7)
Urban Teaching	26,063 (61.0)	21,496 (60.7)	19,364 (64.6)	14,993 (65.0)
Discharge Disposition				
Home	17,681 (42.0)	13,891 (40.0)	11,214 (38.0)	7,639 (34.0)
Short-term hospital	263 (0.6)	233 (0.7)	273 (0.9)	388 (1.7)
SNF, ICF, Other facility	11,289 (27.1)	10,672 (31.0)	9,270 (32.0)	8,128 (36.0)
Home Health Care	12,682 (30.0)	9,819 (28.0)	8,524 (28.9)	6,440 (28.2)
AMA	131 (0.3)	89 (0.3)	43 (0.2)	28 (0.1)

AMA, Against Medical Advice; ICF, Intermediate Care Facility; SNF, Skilled Nursing Facility

Table 2: Outcomes Following Lower Extremity Arterial Reconstruction

Outcome	Median Household Income Quartile for Patient ZIP Code, n (%)			
	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile
Mortality	838 (2.0)	663 (1.9)	642 (2.1)	564 (2.4)
Major amputation – index or subsequent admission	5,486 (13.0)	3,885 (11.0)	3,281 (11.0)	2,238 (9.6)
Amputation during index admission	1,762 (4.1)	1,225 (3.5)	1,018 (3.4)	750 (3.2)
Amputation during subsequent admission	3,927 (9.2)	2,805 (7.9)	2,362 (7.9)	1,559 (6.7)
Subsequent Revascularization Procedure	4,542 (11.0)	3,885 (11.0)	3,306 (11.0)	2,501 (11.0)
Open Revascularization Procedure	2,625 (6.1)	2,190 (6.2)	1,927 (6.4)	1,307 (5.6)
Percutaneous Revascularization Procedure	2,570 (6.0)	2,219 (6.3)	1,867 (6.2)	1,495 (6.4)
30-day Readmission	10,028 (23.0)	8,026 (23.0)	7,010 (23.0)	5,259 (23.0)

Table 3: Multivariate Analysis of Outcomes of Patients with Lower Extremity Arterial Bypass by Income Category

		Median Household Income Quartile for Patient ZIP Code			
Outcome		1st Quartile	2nd Quartile	3rd Quartile	4th Quartile
Mortality	aOR (95% CI)	Ref	0.89 (0.73 – 1.09)	0.97 (0.78 – 1.22)	1.01 (0.79 – 1.28)
	P-value	-	0.266	0.819	0.959
Any Amputation	aOR (95% CI)	Ref	0.84 (0.76 – 0.92)	0.84 (0.76 – 0.92)	0.70 (0.63 – 0.77)
	P-value	-	<0.001	<0.001	<0.001
Subsequent Revascularization Procedure	aOR (95% CI)	Ref	1.04 (0.94 – 1.15)	1.05 (0.95 – 1.15)	1.04 (0.94 – 1.15)
	P-value	-	0.409	0.366	0.433
30-day Readmission	aOR (95% CI)	Ref	0.96 (0.89 – 1.03)	0.99 (0.91 – 1.06)	0.91 (0.84 – 0.99)
	P-value	-	0.209	0.715	0.028

aOR, adjusted Odds Ratio; CI, Confidence Interval

All models are adjusted for age, sex, insurance type, Charlson Co-morbidity Index and hospital type; discharge disposition included in all models except for mortality

Table 4: Multivariate Analysis of Outcomes of Patients with Lower Extremity Arterial Bypass by Patient and Hospital Characteristics

Characteristic	Outcome, aOR (95% CI)			
	Mortality	Any Amputation	Subsequent Revascularization	30-day Readmission
Sex				
Female	Ref	Ref	Ref	Ref
Male	0.97 (0.84 – 1.13)	1.11 (1.02 – 1.20)	0.98 (0.91 – 1.05)	0.94 (0.89 – 0.99)
Age Category				
40 – 64	Ref	Ref	Ref	Ref
65 – 84	2.33 (1.87 – 2.92)	0.74 (0.68 – 0.82)	0.85 (0.77 – 0.93)	0.92 (0.85 – 0.99)
≥ 85	3.57 (2.63 – 4.84)	0.58 (0.50 – 0.68)	0.67 (0.57 – 0.79)	0.97 (0.87 – 1.08)
Insurance Type				
Private	Ref	Ref	Ref	Ref
Medicare	0.96 (0.69 – 1.33)	1.09 (0.97 – 1.24)	1.07 (0.96 – 1.19)	1.26 (1.15 – 1.38)
Medicaid	0.82 (0.54 – 1.24)	1.31 (1.14 – 1.52)	0.96 (0.84 – 1.11)	1.22 (1.09 – 1.37)
Self-Pay	1.44 (0.81 – 2.54)	1.31 (1.03 – 1.67)	1.08 (0.86 – 1.35)	1.10 (0.90 – 1.35)
Other	1.55 (0.86 – 2.80)	1.02 (0.80 – 1.30)	0.81 (0.64 – 1.02)	0.93 (0.77 – 1.14)
Charlson Co-morbidity Index				
0 – 1	Ref	Ref	Ref	Ref
2 – 3	2.16 (1.77 – 2.65)	1.16 (1.06 – 1.27)	1.13 (1.04 – 1.22)	1.30 (1.22 – 1.38)
> 3	4.16 (3.37 – 5.12)	1.34 (1.22 – 1.48)	1.09 (0.99 – 1.20)	1.71 (1.60 – 1.83)
Location/teaching status of hospital				
Rural	Ref	Ref	Ref	Ref
Urban Non-teaching	1.18 (0.76 – 1.83)	0.93 (0.78 – 1.12)	1.34 (1.13 – 1.58)	0.97 (0.85 – 1.11)
Urban Teaching	1.23 (0.80 – 1.90)	0.87 (0.72 – 1.04)	1.33 (1.13 – 1.56)	1.07 (0.93 – 1.23)
Discharge Disposition				
Home	-	Ref	Ref	Ref
Short-term hospital	-	3.53 (2.58 – 4.83)	0.78 (0.56 – 1.10)	1.97 (1.58 – 2.46)
SNF, ICF, Other facility	-	3.50 (3.20 – 3.84)	0.90 (0.82 – 0.98)	1.73 (1.62 – 1.85)
Home Health Care	-	1.86 (1.69 – 2.05)	1.01 (0.92 – 1.10)	1.37 (1.29 – 1.46)
AMA	-	3.19 (1.78 – 5.73)	0.98 (0.52 – 1.86)	2.00 (1.15 – 3.45)

AMA, Against Medical Advice; aOR, adjusted Odds Ratio; CI, Confidence Interval; ICF, Intermediate Care Facility; SNF, Skilled Nursing Facility All models are adjusted for variables in the tables and for median household income quartile for patient ZIP code

Chapter 5: Conclusion

Study Summary

The disturbing reality that Blacks in the US are several times more likely to undergo an amputation as compared to Whites is largely because Blacks presenting with the most severe form of PAD are more likely to be treated by amputation rather than revascularization.[66] With evidence supporting both a sociologic[6, 8] versus a biologic phenomenon,[10,13] I embarked on investigating whether biologic response patterns to stress would explain this disparity. I theorized that the social determinants of health[109] result in a specific biologic milieu that lead to increased PAD severity resulting in disparate amputation rates in Blacks.[57,58] Given that US Blacks are more likely to live in socioeconomically deprived neighborhoods as compared to Whites,[61] I hypothesized that **exposure to higher socioeconomic neighborhood stress, as demonstrated by lower MHI, creates a more severe PAD and a greater risk for amputation. I further posited that this increased PAD severity is associated with a higher allostatic load.** My specific aims were: 1. to evaluate if a lower MHI is associated with more severe PAD; 2. to evaluate if allostatic load is associated with PAD severity; and 3. to determine if MHI influences outcomes following surgical revascularization. In proving my hypotheses from these studies, I sought to answer the question as to if biologic response patterns to stress play a defining role in this racial/ethnic disparity in amputation-revascularization.

For my first aim, I used the *Nationwide Inpatient Sample (NIS) Database* in a retrospective study to test the hypothesis that among hospitalized patients, a lower MHI correlates with more severe PAD. This study reveals that low SES actually does

correlate with less severe clinical PAD. Paradoxically, however, patients with low SES are more likely to be selected for an amputation rather than limb-saving revascularization. Thus, my study went beyond accepting the null hypothesis to proving the definite opposite of my hypothesis.

For my second aim, I used a cross-sectional study design to test the hypothesis that, among patients participating in the *National Health and Nutrition Examination Survey (NHANES)*, the severity of PAD, as determined by the ABI, is associated with the level of allostatic load. This study was unable to identify an association between allostatic load burden and PAD severity.

For my third aim, I tested the hypothesis that among patients undergoing surgical revascularization in the *Nationwide Readmission Databases (NRD)*, MHI will affect surgical outcomes. This study indicates that low SES is, in fact, associated with worse outcomes, specifically a greater likelihood for a failed operation leading to amputation during the initial admission as well as a greater likelihood for later failure leading to readmission for an amputation. For this third aim, the null hypothesis is clearly rejected.

Study Limitations

There are several limitations in this study. For my first (NIS) and third (NRD) studies, using ZIP codes to capture neighborhood socioeconomic stress - i.e., MHI - assumes that all individuals living in a particular ZIP code necessarily belong to that "ZIP code's socioeconomic deprivation bracket". Even though this may be typical, this assumption is unlikely to be universally accurate. A further limitation in using ZIP-

code based MHI is the question as to whether these disparities may simply be reflective of local practice patterns. Studies indicate that amputation and revascularization rates vary nationwide not only according to income and race, but also according to according to the hospital referral region.[87] Unfortunately, by using ZIP-code based MHI, it is not possible to determine how much of this disparity was simply related to local practice patterns of that hospital referral region as opposed to low SES-mediated health disparities. Notwithstanding these limitations, there is good data that indicates that the ZIP-code based MHI specifically is an excellent indicator of SES and is useful for monitoring health disparities. Furthermore, ZIP-code based MHI is generally noted to be less likely to have missing data as compared to other parameters such as block group and census tract.[88]

A further limitation in using ZIP-code based MHI is the possibility that the disparities observed may simply be reflective of variation in patterns of clinical practice. Studies indicate that amputation and revascularization rates vary nationwide not only according to income and race, but also according to according to the hospital referral region.[87] As a result, it is not possible to determine how much of this disparity resulted from local practice patterns in hospital referral regions as opposed to low SES-mediated health disparities. Notwithstanding these limitations, ZIP-code based MHI is a well validated indicator of SES and is useful for monitoring health disparities. Furthermore, ZIP-code based MHI is generally noted to be less likely to have missing data as compared to other parameters such as block group and census tract.[88]

Another limitation is that given that the NIS and NRD are exclusively inpatient databases, I am unable to comment on any potential outpatient revascularization efforts

that may have been undertaken. This is particularly pertinent because as regarding endovascular (minimally invasive) revascularization, there has been an increasing shift from inpatient to outpatient and office-based revascularization over the study period.[110] Currently, a third of revascularization procedures are performed in the outpatient setting.[111] Unfortunately, it is not clear from the existing literature whether there is any systematic demographic bias in selection for outpatient versus inpatient revascularization. In an effort to mitigate this limitation, I restricted my cohort to the one percent of most severe PAD patients, critical limb ischemia patients. These patients are the ones who are most likely to be admitted to the hospital.[97] Furthermore, for the NRD study, I limited my cohort only to patients who underwent surgical revascularization. Given that all surgically revascularized patients are admitted to the hospital, this limitation was fully overcome in the NRD study. Yet another significant limitation is an inability to review any preoperative arteriograms. I am, therefore, unable to determine if, in fact, the quality of the arteries preoperatively may have determined the decision to amputate versus revascularize. In order to limit this inadequacy, I excluded limb ischemia patients who did not undergo any procedures during their admission so that presumably only those who required a relatively prompt procedure were included. This approach in itself could have introduced bias. Another limitation is the ubiquitous drawback of coding errors inherent in large database studies.[89] Since these databases were created with a primary administrative rather than clinical intent, certain clinical data may be coded incorrectly or may be missing. In order to mitigate this, I excluded all patients who did not have the most pertinent data i.e. ZIP code information. Notwithstanding, the large sample size afforded by these

national databases yielded immense statistical power in a real-life setting so that meaningful inferences could be drawn.

One key limitation of my second (NHANES) study is that the NHANES wave used 2003 – 2004 – is relatively dated. I utilize these data, however, as this is the most recent NHANES wave that includes Doppler occlusion pressures that allows 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.[97] Moreover, data suggests that while overall national amputation rates have decreased over the past two decades, amputation rates among Blacks have not decreased.[98] This suggests that this amputation-revascularization disparity is at least as bad today as it was during the 2003-2004 NHANES survey period.

Study Conclusions

In conclusion, this dissertation indicates that low SES is associated with both a greater selection for amputation rather than revascularization as well as a greater likelihood for amputation following revascularization. The studies further suggest that allostatic load – i.e., a biologic response to stress - may potentially be involved in the pathway of this amputation-revascularization disparity. Moreover, for the very first time, a critical parodox has been identified: the fact that individuals with low SES while more likely to undergo an amputation do, in fact, present with less severe clinical disease. This latter finding highlights the significant complexities involved in this

disparity and suggests that other factors such as the issue of physician bias need to be further examined.

My research unambiguously underscores the central role that social determinants of health play in America's healthcare and submits that if we, as a nation, are to adequately address this embarrassing disparity and avoid unnecessary amputations, major investments would need to be made not only in healthcare *per se*, but also in our national social infrastructure.[109, 112]

Appendices

Appendix A

INSTITUTIONAL REVIEW BOARD WAIVER

UNIVERSITY OF MARYLAND
INSTITUTIONAL REVIEW BOARD

1204 Marie Mount Hall
College Park, MD 20742-5125
TEL 301.405.4212
FAX 301.314.1475
irb@umd.edu
www.umresearch.umd.edu/IRB

DATE:	April 21, 2020
TO:	Kakra Hughes
FROM:	University of Maryland College Park (UMCP) IRB
PROJECT TITLE:	[1596071-1] Racial/Ethnic Disparities in Amputation & Revascularization: The Roles of Socioeconomic Neighborhood Stress and Allostatic Load
REFERENCE #:	
SUBMISSION TYPE:	New Project
ACTION:	DETERMINATION OF NOT RESEARCH
DECISION DATE:	April 21, 2020

Thank you for your submission of New Project materials for this project. The University of Maryland College Park (UMCP) IRB has determined this project does not meet the definition of human subject research under the purview of the IRB according to federal regulations.

We will retain a copy of this correspondence within our records.

If you have any questions, please contact the IRB Office at 301-405-4212 or irb@umd.edu. Please include your project title and reference number in all correspondence with this committee.

This letter has been electronically signed in accordance with all applicable regulations, and a copy is retained within University of Maryland College Park (UMCP) IRB's records.

Appendix B

STATA ANALYTIC DATA FOR PAPER 1
NIS STUDY

```
*Patient Selection
gen cli= 0 /*critical limb ischemia*/
forvalues c=1/15 {
replace cli=1 if dx`c'=="44022"|dx`c'=="44023"|dx`c'=="44024"
}

gen open_revasc= 0
forvalues c=1/15 {
replace open_revasc=1 if pr`c'=="3925"|pr`c'=="3929"
}

gen perc_revasc= 0
forvalues c=1/15 {
replace perc_revasc=1 if pr`c'=="3950"|pr`c'=="3990"
}

gen revasc= 0 /*revascularization*/
replace revasc=1 if open_revasc==1|perc_revasc==1


gen amputation= 0 /*amputation*/
forvalues c=1/15 {
replace amputation=1 if pr`c'=="8415"|pr`c'=="8417"
}



keep if cli==1 & (revasc==1|amputation==1) /*cli patients who had
revascularization or amputation*/

*Defining Variables (after appending years)

gen severity= 0
forvalues c=1/30 {
replace severity= 1 if dx`c'=="44023"|dx`c'=="44024"
}

label define severe 0 "rest pain" 1 "tissue loss"
label values severity severe


gen severity_3=1

forvalues c=1/30 {
replace severity_3=2 if dx`c'=="44023"
}

forvalues c=1/30 {
```

```
replace severity_3=3 if dx`c'=="44024"
}

label define severe3 1 "rest pain" 2 "ulceration" 3 "gangrene"
label values severity_3 severe3

gen mgt_mode=.
replace mgt_mode=1 if revasc==1
replace mgt_mode=2 if amputation==1

label define mode 1 "revascularization" 2 "amputation"
label values mgt_mode mode


gen age_cat=.
replace age_cat=1 if age<65
replace age_cat=2 if age>64
replace age_cat=3 if age>84

label define agecate 1 "40-64" 2 "65-84" 3 ">=85"
label values age_cat agecate


recode female (0=4) (1=5)
recode female (4=1) (5=0)
rename female male


gen race_cat=.
replace race_cat=1 if race==1 /*white*/
replace race_cat=2 if race==2 /*black*/
replace race_cat=3 if race==3 /*hispanic*/
replace race_cat=4 if race==4|race==5|race==6 /*others*/
replace race_cat=5 if race==. /*unknown*/
label define race4 1 "white" 2 "black" 3 "hispanic" 4 "others" 5
"unknown" /*race categories*/
label values race_cat race4


recode pay1 (1=7)(2=8)(3=9)
recode pay1 (9=1)(7=2)(8=3)(6=5)
label define insurancet 1 "private" 2 "medicare" 3 "medicaid" 4
"self-pay" 5 "other"  /*insurance*/
label values pay1 insurancet

label define dispos 1 "home" 2 "short-term hospital" 5 "SNF, ICF,
other facility" 6 "Home Health Care" 7 "AMA"
label values dispuniform dispos
replace dispuniform=. if dispuniform==99
replace dispuniform=. if dispuniform==20 /*died*/
replace dispuniform=. if dispuniform==21

label define lteach 1 "rural" 2 "urban non-teaching" 3 "urban
teaching"
label values hosp_locteach lteach
```

```
ssc install charlson
order dx1 dx2 dx3 dx4 dx5 dx6 dx7 dx8 dx9 dx10 dx11 dx12 dx13 dx14
dx15 dx16 dx17 dx18 dx19 dx20 dx21 dx22 dx23 dx24 dx25 dx26 dx27
dx28 dx29 dx30
charlson dx1-dx30, index(c) assign0 noshow /*Charlson Score*/
gen charlcat=0
replace charlcat=1 if charlindex>1 & charlindex<4
replace charlcat=2 if charlindex>3
replace charlcat=. if charlindex==.

label define charlsoncat 0 "0-1" 1 "2-3" 2 ">3"
label values charlcat charlsoncat


forval x=1/30 {
gen dxgrp_`x' = substr(dx`x',1,3)
}/*to create 3-number variables*/

gen hrt_failure=0 /*heart failure*/
forvalues c=1/30 {
replace hrt_failure=1 if dxgrp_`c'=="428"
}

gen prior_cabgpci=0 /*prior cabg or pci*/
forvalues c=1/30 {
replace prior_cabgpci=1 if dx`c'=="V4582"|dx`c'=="V4581"
}

gen cad=0 /*cad*/
forvalues c=1/30 {
replace cad=1 if
dx`c'=="41401"|dx`c'=="4142"|dx`c'=="4143"|dx`c'=="4144"
}


gen cardiac=0
replace cardiac=1 if hrt_failure==1|prior_cabgpci==1|cad==1


gen copd=0 /*copd*/
forvalues c=1/30 {
replace copd=1 if
dxgrp_`c'=="490"|dxgrp_`c'=="491"|dxgrp_`c'=="492"|dxgrp_`c'=="496"
}


gen esrd=0 /*esrd*/
forvalues c=1/30 {
replace esrd=1 if dx`c'=="5856"|dx`c'=="5855"
}

gen dm=0 /*dm*/
forvalues c=1/30 {
replace dm=1 if dxgrp_`c'=="250"
}
gen smoking=0 /*smoking*/
```

```
forvalues c=1/30 {
replace smoking=1 if dx`c'=="3051"
}
      gen comp=0
      forvalues c=1/30 {
            replace comp=1 if inlist(dx`c', "99800", "99801",
"99802")
            replace comp=2 if inlist(dx`c', "99811", "99812")
            replace comp=3 if inlist(dx`c', "99830", "99831",
"99832")
            replace comp=4 if inlist(dx`c', "9985", "99859",
"99851")
            replace comp=5 if inlist(dx`c', "9961", "99652")
            replace comp=6 if inlist(dx`c', "99662", "99674")
            replace comp=7 if inlist(dx`c', "99700", "99701")
            replace comp=8 if inlist(dx`c', "99702", "9971")
            replace comp=9 if inlist(dx`c', "9972", "99779")
            replace comp=10 if inlist(dx`c', "99731", "99732",
"99739")
replace comp=11 if inlist(dx`c', "99760")
            }
      label define comp 0 "No Complication" 1 "Shock" 2 "Hemorrhage/
Hematoma" 3 "Wound Dis" 4 "Wound Inf" 5 "Vascular Graft Defect" 6
"Vascular Graft Infection" 7 "Neuro comp" 8 "Cardio Comp" 9
"Vascular Comp" 10 "Resp Comp" 11 "Urinary Comp"
      label values comp comp
gen complic=0
replace complic=1 if comp!=0
****

*Analysis


gen discwt2 = trendwt if
year==2005|year==2006|year==2007|year==2008|year==2009|year==2010|ye
ar==2011
replace discwt2 = discwt if year==2012|year==2013|year==2014

replace hospid = hosp_nis if missing(hospid)


svyset [pweight=discwt2], strata(nis_stratum) psu(hospid)
singleunit(scaled)


svy: tab cli if age<40, count cellwidth(15) format(%15.2g)


drop if age< 40


tab cli /*overall*/

svy: tab cli, count cellwidth(15) format(%15.2g) /*weighted*/
```

```
svy: tab zipinc_qrtl, count cellwidth(15) format(%15.2g) col
/*weighted - study sample*/

svy: tab severity if zipinc_qrtl!=., count cellwidth(15)
format(%15.2g) col /*2 categories of severity*/

svy: tab severity_3 if zipinc_qrtl!=., count cellwidth(15)
format(%15.2g) col /*3 categories of severity*/
*Characteristics by Income Quartile
svy: tab zipinc_qrtl male, count cellwidth(15) format(%15.2g) row
col
svy: tab zipinc_qrtl age_cat, count cellwidth(15) format(%15.2g) row
col
svy: mean age if zipinc_qrtl==1
svy: mean age if zipinc_qrtl==2
svy: mean age if zipinc_qrtl==3
svy: mean age if zipinc_qrtl==4
svy: tab zipinc_qrtl race_cat, count cellwidth(15) format(%15.2g)
row col
svy: tab zipinc_qrtl pay1, count cellwidth(15) format(%15.2g) row
col
svy: tab zipinc_qrtl hosp_locteach, count cellwidth(15)
format(%15.2g) row col
svy: tab zipinc_qrtl elective, count cellwidth(15) format(%15.2g)
row col
svy: tab zipinc_qrtl cardiac, count cellwidth(15) format(%15.2g) row
col
svy: tab zipinc_qrtl copd, count cellwidth(15) format(%15.2g) row
col
svy: tab zipinc_qrtl esrd, count cellwidth(15) format(%15.2g) row
col
svy: tab zipinc_qrtl dm, count cellwidth(15) format(%15.2g) row col
svy: tab zipinc_qrtl smoking, count cellwidth(15) format(%15.2g) row
col
svy: tab zipinc_qrtl charlcat, count cellwidth(15) format(%15.2g)
row col


*Severity by Income Quartile
svy: tab zipinc_qrtl severity, count cellwidth(15) format(%15.2g)
row col


corr severity zipinc_qrtl


*Characteristics of Patients by Mgt mode
svy: tab mgt_mode zipinc_qrtl, count cellwidth(15) format(%15.2g)
row col
svy: tab mgt_mode male if zipinc_qrtl!=., count cellwidth(15)
format(%15.2g) row col
svy: tab mgt_mode age_cat if zipinc_qrtl!=., count cellwidth(15)
format(%15.2g) row col
svy: mean age if mgt_mode==1 & zipinc_qrtl!=.
svy: mean age if mgt_mode==2 & zipinc_qrtl!=.
```

```
svy: tab mgt_mode race_cat if zipinc_qrtl!=., count cellwidth(15)
format(%15.2g) row col
svy: tab mgt_mode pay1 if zipinc_qrtl!=., count cellwidth(15)
format(%15.2g) row col
svy: tab mgt_mode hosp_locteach if zipinc_qrtl!=., count
cellwidth(15) format(%15.2g) row col
svy: tab mgt_mode elective if zipinc_qrtl!=., count cellwidth(15)
format(%15.2g) row col
svy: tab mgt_mode cardiac if zipinc_qrtl!=., count cellwidth(15)
format(%15.2g) row col
svy: tab mgt_mode copd if zipinc_qrtl!=., count cellwidth(15)
format(%15.2g) row col
svy: tab mgt_mode esrd if zipinc_qrtl!=., count cellwidth(15)
format(%15.2g) row col
svy: tab mgt_mode dm if zipinc_qrtl!=., count cellwidth(15)
format(%15.2g) row col
svy: tab mgt_mode smoking if zipinc_qrtl!=., count cellwidth(15)
format(%15.2g) row col
svy: tab mgt_mode charlcat if zipinc_qrtl!=., count cellwidth(15)
format(%15.2g) row col



*Outcomes
svy: tab zipinc_qrtl died, count cellwidth(15) format(%15.2g) row

svy: tab zipinc_qrtl amputation, count cellwidth(15) format(%15.2g)
row /*amputation*/

svy: tab zipinc_qrtl complic, count cellwidth(15) format(%15.2g) row
/*complication*/


svy: tab severity died if zipinc_qrtl!=., count cellwidth(15)
format(%15.2g) row

svy: tab severity amputation if zipinc_qrtl!=., count cellwidth(15)
format(%15.2g) row /*amputation*/

svy: tab severity complic if zipinc_qrtl!=., count cellwidth(15)
format(%15.2g) row /*complication*/
*Univariate analyses (not included in tables for paper)
svy: logistic severity zipinc_qrtl
svy: logistic severity male
svy: logistic severity i.race_cat
svy: logistic severity i.age_cat
svy: logistic severity i.pay1
svy: logistic severity smoking
svy: logistic severity i.charlcat
*Multivariate analyses
svy: logistic severity i.zipinc_qrtl male i.age_cat i.race_cat
i.pay1 i.charlcat



*Sensitivity analyses - only emergency cases
```

```
svy: logistic severity i.zipinc_qrtl male i.age_cat i.race_cat
i.pay1 i.charlcat if elective==0

*Sensitivity analyses - only elective cases
svy: logistic severity i.zipinc_qrtl male i.age_cat i.race_cat
i.pay1 i.charlcat if elective==1
```

Appendix C

STATA ANALYTIC DATA FOR PAPER 2
NHANES STUDY

```
**********************************************merging
files************************************************************
***********
log using "C:\Users\Desktop\Nhanes2003-2004\Nhansedata\stata\nhanes
stata\merge.smcl"
use "C:\Users\Nhanes2003-2004\Nhansedata\stata\nhanes
stata\DEMO_C.dta", clear
merge 1:1 seqn using "C:\Users\Desktop\Nhanes2003-
2004\Nhansedata\stata\nhanes stata\BMX_C.dta"
drop _merge
merge 1:1 seqn using "C:\Users\Desktop\Nhanes2003-
2004\Nhansedata\stata\nhanes stata\BPX_C.dta"
drop _merge
merge 1:1 seqn using "C:\Users\Desktop\Nhanes2003-
2004\Nhansedata\stata\nhanes stata\CDQ_C.dta"
drop _merge
merge 1:1 seqn using "C:\Users\Desktop\Nhanes2003-
2004\Nhansedata\stata\nhanes stata\L10_C.dta"
drop _merge
merge 1:1 seqn using "C:\Users\Desktop\Nhanes2003-
2004\Nhansedata\stata\nhanes stata\L11_C.dta"
drop _merge
merge 1:1 seqn using "C:\Users\Desktop\Nhanes2003-
2004\Nhansedata\stata\nhanes stata\L13_C.dta"
drop _merge
merge 1:1 seqn using "C:\Users\Desktop\Nhanes2003-
2004\Nhansedata\stata\nhanes stata\L40_C.dta"
drop _merge
merge 1:1 seqn using "C:\Users\Desktop\Nhanes2003-
2004\Nhansedata\stata\nhanes stata\LEXAB_C.dta"
drop _merge
merge 1:1 seqn using "C:\Users\Desktop\Nhanes2003-
2004\Nhansedata\stata\nhanes stata\SMQMEC_C.dta"
drop _merge
save "C:\Users\Desktop\Nhanes2003-2004\Nhansedata\stata\nhanes
stata\merged.dta"
merge 1:1 seqn using "C:\Users\Desktop\Nhanes2003-
2004\Nhansedata\stata\nhanes stata\DIQ_C.dta"
drop _merge
merge 1:1 seqn using "C:\Users\Desktop\Nhanes2003-
2004\Nhansedata\stata\nhanes stata\BPQ_C.dta"
drop _merge
merge 1:1 seqn using "C:\Users\Desktop\Nhanes2003-
2004\Nhansedata\stata\nhanes stata\DIQ_C.dta"
lookfor diq050
drop _merge
merge 1:1 seqn using "C:\Users\Desktop\Nhanes2003-
2004\Nhansedata\stata\nhanes stata\BPQ_C.dta"
```

```
use "C:\Users\Desktop\Nhanes2003-2004\Nhansedata\stata\nhanes
stata\DEMO_C.dta", clear
merge 1:1 seqn using "C:\Users\Desktop\Nhanes2003-
2004\Nhansedata\stata\nhanes stata\mergedAllostasis.dta"
drop _merge
merge 1:1 seqn using "C:\Users\Desktop\Nhanes2003-
2004\Nhansedata\stata\nhanes stata\SMQMEC_C.dta"
drop _merge
merge 1:1 seqn using "C:\Users\Desktop\Nhanes2003-
2004\Nhansedata\stata\nhanes stata\DIQ_C.dta"
drop _merge
merge 1:1 seqn using "C:\Users\Desktop\Nhanes2003-
2004\Nhansedata\stata\nhanes stata\BPQ_C.dta"

merge 1:1 seqn using "C:\Users\Desktop\Nhanes2003-
2004\Nhansedata\stata\nhanes stata\DIQ_C.dta"
drop _merge
merge 1:1 seqn using "C:\Users\Desktop\Nhanes2003-
2004\Nhansedata\stata\lLO6COT.dta"



**************************************************generating
systolic and diastolic
variables************************************************************
log using "C:\Users\Desktop\Nhanes2003-2004\Nhansedata\stata\nhanes
stata\allostasisdummy1.smcl"
gen n_sbp= !missing(bpxsy1)+ !missing(bpxsy2)+ !missing(bpxsy3)+
!missing(bpxsy4)

gen n_dbp= !missing(bpxdi1)+ !missing(bpxdi2)+ !missing(bpxdi3)+
!missing(bpxdi4)

foreach i in bpxdi1 bpxdi2 bpxdi3 bpxdi4 {
    replace `i' =. if `i'==0
}
******Use the egen command with the rowmean function to calculate
the mean systolic and diastolic blood pressures.
egen mean_sbp = rowmean(bpxsy1 bpxsy2 bpxsy3 bpxsy4)
egen mean_dbp = rowmean(bpxdi1 bpxdi2 bpxdi3 bpxdi4)


gen systolic=.
replace systolic=1 if mean_sbp<120
replace systolic=2 if mean_sbp>=120 & mean_sbp<=150
replace systolic=3 if mean_sbp>=150
tab systolic


gen  diastolic=.
replace diastolic=1 if mean_dbp<80
replace diastolic =2 if mean_dbp >=80 & mean_dbp < 90
replace diastolic =3 if mean_dbp >=90
tab  diastolic
```

```
**********************************************generating and
recoding other demographic and clinical
variables****************************************
rename riagendr sex
tab sex
recode ridreth2 (1 = 1 "White") (2 = 2 "Black") (3 4 = 3 "Hispanic")
(5 = 4 "Other"), generate(race)
tab race
recode dmdeduc2 (1 / 2 = 1  "< High School") (3 = 2  "High School")
(4 = 3 "Some College") (5 =4  "College Grad and above") ( 7 / 9= 5
"missing"), generate(educ)
tab educ
recode ridageyr (0/59.999 = 1 "<60") (60/69.999 = 2 "60's")
(70/79.999 = 3 "70's") (80/100 = 4 "80+l"), generate(age)
tab age


gen BMI=.
replace BMI=1 if bmxbmi>=18 & bmxbmi<25
replace BMI=2 if bmxbmi>=25 & bmxbmi<30
replace BMI=3 if bmxbmi>=30 & bmxbmi!=.
tab BMI

recode BMIcat (1 = 1 "Underweight") (2 = 2 "Normal")(3 = 3
"Overweight")(4 5 = 4 "Obese"), generate(BMIcat1)
tab BMIcat1

gen Glycohemo=.
replace Glycohemo=1 if lbxgh < 5.7
replace Glycohemo = 2 if lbxgh >= 5.7 &  lbxgh < 6.5
replace Glycohemo =3 if lbxgh >= 6.5 & lbxgh !=.
tab Glycohemo

gen Tcholesterol=.
replace Tcholesterol=1 if lbxsch  < 200
replace Tcholesterol =2 if lbxsch   >=200 & lbxsch  < 240
replace Tcholesterol =3 if  lbxsch  >= 240 & lbxsch !=.
tab Tcholesterol

gen HDLcholesterol=.
replace HDLcholesterol=1 if lbxhdd  < 40
replace HDLcholesterol =2 if lbxhdd   >=40 & lbxhdd  < 60
replace HDLcholesterol =3 if  lbxhdd  >= 60 & lbxhdd !=.
tab HDLcholesterol


gen cholratio = lbxsch/lbxhdd
gen cholesRatio=.
replace cholesRatio=1 if cholratio  < 5
replace cholesRatio =2 if cholratio    >=5 & cholratio   < 6
replace cholesRatio =3 if  cholratio   >= 6 & cholratio !=.
tab cholesRatio

gen Creactivep = .
replace Creactivep=1 if Creactivep < 1
replace Creactivep=1 if  lbxcrp < 1
```

```
replace Creactivep =2 if  lbxcrp  >=1 & lbxcrp  < 3
replace Creactivep  =3 if  lbxcrp   >= 3 & lbxcrp !=.
tab Creactivep

gen albumin=.
replace albumin=1 if lbxsal < 3.0
replace albumin=2 if lbxsal  >=3 & lbxsal < 3.8
replace albumin=3 if  lbxsal  >= 3.8 & lbxsal!=.
tab albumin

gen crcl=.
replace crcl=1 if  lbdscrsi < 30
replace crcl=2 if lbdscrsi   >=30 & lbdscrsi < 60
replace crcl=3 if  lbdscrsi  >= 60 & lbdscrsi !=.
tab crcl

gen smoking=0
replace smoking=1 if race==1 & lbxcot>=5.92
replace smoking=1 if race==2 & lbxcot>=0.84
replace smoking=1 if race==3 & lbxcot>=4.85
replace smoking=1 if race==4 & lbxcot>=5.92
tab smoking


****************************************generating dummy
variables************************************************************
*****************
quietly tabulate diastolic , generate(diastolic_) missing
quietly tabulate systolic, generate(systolic_) missing
tab BMI,gen(BM1_)

tab Glycohemo, gen(Glycohemo_)
tab Tcholesterol , gen( Tcholesterol_)
tab HDLcholesterol , gen(HDLcholesterol_)
tab cholesRatio , gen( cholesRatio_)
 tab Creactivep , gen( Creactivep_)
quietly tabulate albumin , generate( albumin_) missing
 quietly tabulate crcl , generate( crcl_) missing


 gen BMIcat3 = 1 if BMIcat1==1|BMIcat1==2
 replace BMIcat3 = 2 if BMIcat1==3
 replace BMIcat3 = 3 if BMIcat1==4

************************************************************genera
ting Allostatic
load*************************************************************
*************************************************************
*************************************************************
**********************************************
generate Allostasis = 1* systolic_3 + 0.5*systolic_2 + 0*systolic_1
+ 1*diastolic_3 + 0.5* diastolic_2  +  0* diastolic_1  +  1* BM1_3
+ 0.5* BM1_2  + 0* BM1_1  + 1* Glycohemo_3  +  0.5* Glycohemo_2  +
0* Glycohemo_1  +  1* Tcholesterol_3  + 0.5* Tcholesterol_2  +  0*
Tcholesterol_1  +  1* HDLcholesterol_3  + 0.5* HDLcholesterol_2  +
0* HDLcholesterol_1  + 1* cholesRatio_3  +  0.5* cholesRatio_2  + 0*
```

```
cholesRatio_1  + 1* Creactivep_3  +  0.5* Creactivep_2  +  0*
Creactivep_1  +  1* albumin_3  +  0.5* albumin_2  +  0* albumin_1  +
1* crcl_3  +  0.5* crcl_2  + 0* crcl_1
gen allostatic = Allostasis + 0.5 if diq050==1 |  bpq050a==1 |
bpq100d==1 & Glycohemo==1 | systolic==1 | diastolic==1 |
HDLcholesterol==1
xtile allostatic_tert= allostatic,nq(3)
tab allostatic_tert



**********************************generating
PAD*****************************************************************
********************
gen LtABI= lexlptsm/lexbrpm
gen LtABI= lexlptsm/lexbrpm


gen ABI = LtABI
replace ABI = RtABI if RtABI<LtABI

gen pad= 0
replace pad=1 if ABI <=0.9


***********************************************generating
continuous and categorical PAD variable(for data restricted for
ABI<=0.9)***********************************************

gen pad_cat3=1 if ABI >=0.8 & ABI <=0.9
replace pad_cat3=2 if ABI >=0.4 & ABI <0.8
replace pad_cat3=3 if ABI <0.4

label define pad_3 1 "Mild" 2 "Moderate" 3 "Severe"
label values pad_cat3 pad_3

recode pad_cat3 (1=0)(2=1)(3=1), generate(pad_cat2)


gen abi_round = round(ABI,.1)

gen abi_reverse = 1 - abi_round


gen allostatic_round = round(allostatic, 1.0)



*****************************************************Scatter Plot
of Allostatic load and
PAD*********************************************************

corr ABI allostatic if ABI<=0.9
local corr : di %4.3f r(rho)
```

```
twoway scatter ABI allostatic if ABI<=0.9, title("Correlation
between ABI and Allostatic Load") xtitle("Allostatic Load")
ytitle("Ankle Brachial Index (ABI)")|| lfit ABI allostatic if ABI
<=0.9, subtitle(Correlation coefficient `corr')

corr ABI allostatic if ABI<1.4
local corr : di %4.3f r(rho)

twoway scatter ABI allostatic if ABI<1.4, title("Correlation between
ABI and Allostatic Load") xtitle("Allostatic Load") ytitle("Ankle
Brachial Index (ABI)")|| lfit ABI allostatic if ABI <1.4,
subtitle(Correlation coefficient `corr')



**************************************Crosstabutions and Chisquare
test*****************************************************************
********************
use "C:\Users\Desktop\Nhanes2003-2004\Nhansedata\stata\nhanes
stata\mergedAllostasis.dta", clear

svy linearized : tabulate sex allostatic_tert, cell count column row
obs
svy linearized : tabulate age allostatic_tert, cell count column row
obs
svy linearized : tabulate race allostatic_tert, cell count column
row obs
svy linearized : tabulate BMIcat1 allostatic_tert, cell count column
row obs
svy linearized : tabulate educ allostatic_tert if educ !=5, cell
count column row obs
svy linearized : tabulate smoking allostatic_tert, cell count column
row obs
svy linearized : tabulate bpq020 allostatic_tert if bpq020 !=9, cell
count column row obs
svy linearized : tabulate diq010 allostatic_tert if diq010 !=3  &
diq010 !=9, cell count column row obs




**

svy: tab pad if ABI<1.4, cell count column obs
svy: tab allostatic_tert, cell count column obs

sum allostatic if allostatic_tert==1, detail
sum allostatic if allostatic_tert==2, detail
sum allostatic if allostatic_tert==3, detail


svy: tab pad allostatic_tert if ABI<1.4, cell count column row obs
```

```
svy: tab pad_cat3 allostatic_tert if pad==1, cell count column row
obs


svy linearized : tabulate allostatic_tert pad_cat3 if pad==1, cell
count column row obs
svy linearized : tabulate systolic pad_cat3 if pad==1, cell count
column row obs
svy linearized : tabulate diastolic pad_cat3 if pad==1, cell count
column row obs
svy linearized : tabulate BMIcat3 pad_cat3 if pad==1, cell count
column row obs
svy linearized : tabulate Glycohemo pad_cat3 if pad==1, cell count
column row obs
svy linearized : tabulate creactivecat pad_cat3 if pad==1, cell
count column row obs
svy linearized : tabulate creatineclcat pad_cat3 if pad==1, cell
count column row obs
svy linearized : tabulate HDLcholesterol pad_cat3 if pad==1, cell
count column row obs
svy linearized : tabulate Tcholesterol pad_cat3 if pad==1, cell
count column row obs
svy linearized : tabulate CholesRatio pad_cat3 if pad==1, cell count
column row obs
svy linearized : tabulate albumin pad_cat3 if pad==1, cell count
column row obs



**********************************************************************mo
delling**************************************************

logistic pad_cat2 i.allostatic_tert sex i.age i.race ib2.BMIcat1
i.educ i.smoking ib2.bpq020 ib2.diq010 if educ ! =5 & bpq020 !=9 &
diq010 !=3 & diq010 !=9 & pad==1

regress abi_reverse i.allostatic_tert sex i.age i.race ib2.BMIcat1
i.educ i.smoking ib2.bpq020 ib2.diq010 if educ ! =5 & bpq020 !=9 &
diq010 !=3 & diq010 !=9 & pad==1


svy: logistic pad i.allostatic_tert sex i.age i.race ib2.BMIcat1
i.educ i.smoking ib2.bpq020 ib2.diq010 if educ ! =5 & bpq020 !=9 &
diq010 !=3 & diq010 !=9 & ABI<1.4


svy: regress allostatic_round sex i.age i.race ib2.BMIcat1 i.educ
i.smoking if educ ! =5 & bpq020 !=9 & diq010 !=3 & diq010 !=9
```

Appendix D

STATA ANALYTIC DATA FOR PAPER 3
NRD STUDY

```
*Patient Selection
gen cli= 0 /*critical limb ischemia*/
forvalues c=1/25 {
replace cli=1 if dx`c'=="44022"|dx`c'=="44023"|dx`c'=="44024"
}

gen open_revasc= 0
forvalues c=1/15 {
replace open_revasc=1 if pr`c'=="3925"|pr`c'=="3929"
}

gen perc_revasc= 0
forvalues c=1/15 {
replace perc_revasc=1 if pr`c'=="3950"|pr`c'=="3990"
}

gen revasc= 0 /*revascularization*/
replace revasc=1 if open_revasc==1|perc_revasc==1


gen amputation= 0 /*amputation*/
forvalues c=1/15 {
replace amputation=1 if pr`c'=="8415"|pr`c'=="8417"
}



*creating sequence of admissions
sort nrd_visitlink nrd_daystoevent

by nrd_visitlink: gen admitn=1 if _n==1 /*creating an indicator for
the sequence of admissions*/
forvalues i = 2/50 {
by nrd_visitlink: replace admitn = `i' if _n==`i'
}

by nrd_visitlink: gen diff=nrd_daystoevent-nrd_daystoevent[_n-1]
/*difference in admitting days*/

by nrd_visitlink: gen gap=diff-los[_n-1] /*days between discharge
and next admission (subtracting length of stay)*/

*coding 30-day readmissions
gen readmission=1 if gap < 31
replace readmission=0 if readmission==.
/*replace readmission=0 if dxgrp1=="V" /*to exclude planned
readmissions*/ */
```

```
by nrd_visitlink: replace readmission=0 if gap < 1 /*to exclude
those that were transferred from one hospital to another*/
by nrd_visitlink: replace readmission=0 if
nrd_daystoevent[_n]==nrd_daystoevent[_n-1] & dx1[_n]==dx1[_n-1] /*to
eliminate duplicates*/

*to create a variable that says that a diagnosis was followed by a
readmission within 30 days
by nrd_visitlink: gen readmitff=1 if readmission[_n+1]==1
replace readmitff=0 if readmitff==.


*to identify earliest open revascularization admission
recode open_revasc (0=2) /*to allow for sorting*/
sort nrd_visitlink open_revasc nrd_daystoevent

gen open_revasc_seq=.
forvalues i = 1/20 {
by nrd_visitlink: replace open_revasc_seq = `i' if _n==`i'
}
*to exclude prior admissions
by nrd_visitlink: gen firstday= nrd_daystoevent[_n==1]
replace firstday=0 if firstday==.

by nrd_visitlink: egen firstday2= total(firstday) /*to copy firstday
to every patient encounter*/

gen admission_diff = nrd_daystoevent-firstday2

drop if admission_diff <0


*to identify subsequent open revascularization
by nrd_visitlink: gen subsequent_open_revasc=1 if
open_revasc[_n+1]==1|open_revasc[_n+2]==1|open_revasc[_n+3]==1|open_
revasc[_n+4]==1|open_revasc[_n+5]==1|open_revasc[_n+6]==1|open_revas
c[_n+7]==1|open_revasc[_n+8]==1|open_revasc[_n+9]==1|open_revasc[_n+
10]==1|open_revasc[_n+11]==1|open_revasc[_n+12]==1|open_revasc[_n+13
]==1|open_revasc[_n+14]==1|open_revasc[_n+15]==1|open_revasc[_n+16]=
=1|open_revasc[_n+17]==1|open_revasc[_n+18]==1|open_revasc[_n+19]==1
|open_revasc[_n+20]==1
replace subsequent_open_revasc=0 if subsequent_open_revasc==.

*to identify subsequent percutaneous revascularization
by nrd_visitlink: gen subsequent_perc_revasc=1 if
perc_revasc[_n+1]==1|perc_revasc[_n+2]==1|perc_revasc[_n+3]==1|perc_
revasc[_n+4]==1|perc_revasc[_n+5]==1|perc_revasc[_n+6]==1|perc_revas
c[_n+7]==1|perc_revasc[_n+8]==1|perc_revasc[_n+9]==1|perc_revasc[_n+
10]==1|perc_revasc[_n+11]==1|perc_revasc[_n+12]==1|perc_revasc[_n+13
]==1|perc_revasc[_n+14]==1|perc_revasc[_n+15]==1|perc_revasc[_n+16]=
=1|perc_revasc[_n+17]==1|perc_revasc[_n+18]==1|perc_revasc[_n+19]==1
|perc_revasc[_n+20]==1
replace subsequent_perc_revasc=0 if subsequent_perc_revasc==.


*any subsequent revascularization
```

```
gen multi_revasc=1 if
subsequent_open_revasc==1|subsequent_perc_revasc==1
replace multi_revasc=0 if multi_revasc==.


*to identify subsequent amputations
by nrd_visitlink: gen subsequent_ampu=1 if
amputation[_n+1]==1|amputation[_n+2]==1|amputation[_n+3]==1|amputati
on[_n+4]==1|amputation[_n+5]==1|amputation[_n+6]==1|amputation[_n+7]
==1|amputation[_n+8]==1|amputation[_n+9]==1|amputation[_n+10]==1|amp
utation[_n+11]==1|amputation[_n+12]==1|amputation[_n+13]==1|amputati
on[_n+14]==1|amputation[_n+15]==1|amputation[_n+16]==1|amputation[_n
+17]==1|amputation[_n+18]==1|amputation[_n+19]==1|amputation[_n+20]=
=1
replace subsequent_ampu=0 if subsequent_ampu==.

*all amputations (index admission and subsequent admissions)
gen any_amputation=0
replace any_amputation=1 if amputation==1|subsequent_ampu==1


keep if cli==1 & open_revasc==1 & open_revasc_seq==1 /*cli patients
who had the earliest revascularization procedure - study cohort*/

*Defining Variables (after appending years)

gen age_cat=.
replace age_cat=1 if age<65
replace age_cat=2 if age>64
replace age_cat=3 if age>84

label define agecate 1 "40-64" 2 "65-84" 3 ">=85"
label values age_cat agecate


recode female (0=4) (1=5)
recode female (4=1) (5=0)
rename female male

recode pay1 (1=7)(2=8)(3=9)
recode pay1 (9=1)(7=2)(8=3)(6=5)
label define insurancet 1 "private" 2 "medicare" 3 "medicaid" 4
"self-pay" 5 "other"  /*insurance*/
label values pay1 insurancet


label define dispos 1 "home" 2 "short-term hospital" 5 "SNF, ICF,
other facility" 6 "Home Health Care" 7 "AMA"
label values dispuniform dispos
replace dispuniform=. if dispuniform==99
replace dispuniform=. if dispuniform==20 /*died*/
replace dispuniform=. if dispuniform==21
recode hosp_ur_teach (0=4) (1=5) (2=6)
recode hosp_ur_teach (6=1) (4=2) (5=3)
label define lteach 1 "non-metropolitan" 2 "metropolitan non-
teaching" 3 "metropolitan teaching"
```

```
label values hosp_ur_teach lteach


ssc install charlson
order dx1 dx2 dx3 dx4 dx5 dx6 dx7 dx8 dx9 dx10 dx11 dx12 dx13 dx14
dx15 dx16 dx17 dx18 dx19 dx20 dx21 dx22 dx23 dx24 dx25 dx26 dx27
dx28 dx29 dx30
charlson dx1-dx30, index(c) assign0 noshow /*Charlson Score*/
gen charlcat=0
replace charlcat=1 if charlindex>1 & charlindex<4
replace charlcat=2 if charlindex>3
replace charlcat=. if charlindex==.

label define charlsoncat 0 "0-1" 1 "2-3" 2 ">3"
label values charlcat charlsoncat


****

*Analysis

svyset [pweight=discwt], strata(nrd_stratum) psu(hosp_nrd)
singleunit(scaled)

svy: tab cli if age<40, count cellwidth(15) format(%15.2g)

drop if age< 40

tab cli /*overall*/

svy: tab cli, count cellwidth(15) format(%15.2g) /*weighted*/

svy: tab zipinc_qrtl, count cellwidth(15) format(%15.2g) col
/*weighted - study sample*/

*Characteristics
svy: tab zipinc_qrtl male, count cellwidth(15) format(%15.2g) row
col
svy: tab zipinc_qrtl age_cat, count cellwidth(15) format(%15.2g) row
col
svy: mean age if zipinc_qrtl==1
svy: mean age if zipinc_qrtl==2
svy: mean age if zipinc_qrtl==3
svy: mean age if zipinc_qrtl==4
svy: tab zipinc_qrtl pay1, count cellwidth(15) format(%15.2g) row
col
svy: tab zipinc_qrtl charlcat, count cellwidth(15) format(%15.2g)
row col
svy: tab zipinc_qrtl hosp_ur_teach, count cellwidth(15)
format(%15.2g) row col
svy: tab zipinc_qrtl dispuniform, count cellwidth(15) format(%15.2g)
row col


*Outcomes
svy: tab zipinc_qrtl died, count cellwidth(15) format(%15.2g) row
```

```
svy: tab zipinc_qrtl amputation, count cellwidth(15) format(%15.2g)
row /*amputation during same admission*/
svy: tab zipinc_qrtl subsequent_ampu, count cellwidth(15)
format(%15.2g) row /*amputation during subsequent admission*/
svy: tab zipinc_qrtl any_amputation, count cellwidth(15)
format(%15.2g) row /*amputation during same or subsequent
admission*/

svy: tab zipinc_qrtl subsequent_open_revasc, count cellwidth(15)
format(%15.2g) row
svy: tab zipinc_qrtl subsequent_perc_revasc, count cellwidth(15)
format(%15.2g) row
svy: tab zipinc_qrtl multi_revasc, count cellwidth(15)
format(%15.2g) row

svy: tab zipinc_qrtl readmitff, count cellwidth(15) format(%15.2g)
row


*Univariate analyses (not to be included in tables for paper)
svy: logistic died i.zipinc_qrtl
svy: logistic died male
svy: logistic died i.age_cat
svy: logistic died i.pay1
svy: logistic died i.charlcat
svy: logistic died i.hosp_ur_teach


svy: logistic any_amputation i.zipinc_qrtl
svy: logistic any_amputation male
svy: logistic any_amputation i.age_cat
svy: logistic any_amputation i.pay1
svy: logistic any_amputation i.charlcat
svy: logistic any_amputation i.hosp_ur_teach
svy: logistic any_amputation i.dispuniform

svy: logistic multi_revasc i.zipinc_qrtl
svy: logistic multi_revasc male
svy: logistic multi_revasc i.age_cat
svy: logistic multi_revasc i.pay1
svy: logistic multi_revasc i.charlcat
svy: logistic multi_revasc i.hosp_ur_teach
svy: logistic multi_revasc i.dispuniform


svy: logistic readmitff i.zipinc_qrtl
svy: logistic readmitff male
svy: logistic readmitff i.age_cat
svy: logistic readmitff i.pay1
svy: logistic readmitff i.charlcat
svy: logistic readmitff i.hosp_ur_teach
svy: logistic readmitff i.dispuniform
```

```
*Multivariate analyses
svy: logistic died i.zipinc_qrtl male i.age_cat i.pay1 i.charlcat
i.hosp_ur_teach

svy: logistic any_amputation i.zipinc_qrtl male i.age_cat i.pay1
i.charlcat i.hosp_ur_teach i.dispuniform

svy: logistic multi_revasc i.zipinc_qrtl male i.age_cat i.pay1
i.charlcat i.hosp_ur_teach i.dispuniform

svy: logistic readmitff i.zipinc_qrtl male i.age_cat i.pay1
i.charlcat i.hosp_ur_teach i.dispuniform
```

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