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An abstract of
a thesis submitted to the Faculty of Emory College of Arts and Sciences
of Emory University in partial fulfillment
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Abstract

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Background: Cardiovascular disease (CVD) is the leading cause of death in the United States. Prevalence of cardiovascular risk factors differs among races, and South Asians tend to have higher rates of CVD and diabetes. The aims of the study are to estimate the prevalence of cardiovascular risk factors in South Asian immigrants, and compare indices of vascular function by pulse wave velocity (PWV), augmentation index (Aix), and carotid intima-media thickness (CIMT) between South Asians, Caucasians, and African Americans.

Methods: 715 South Asians, 1032 Caucasians, and 620 African Americans were included in the study. Study participants were enrolled at community health fairs (CHF) or as part of the Center for Health Discovery and Well Being (CHDWB) at Emory University. Questionnaire responses, blood test results, PWV, Aix, and CIMT were obtained from study subjects. Independent t-tests and chi-tests were used to compare clinical characteristics between races. Multivariable analysis was used to determine predictors of arterial stiffness and atherosclerosis, including the influence of race, on the complete sample size and a healthy subset of each race.

Results: Multivariable analysis of the complete sample size indicated that the South Asian race predicted significantly higher Aix values ($p<0.001$). Analysis of healthy subsets showed similar results for Aix ($p<0.001$), and that the South Asian race correlated with lower PWV compared to the Caucasian ($p=0.04$) and African American ($p=0.003$) races. Healthy South Asian subjects ($n=33$) had lower CIMT than healthy African American subjects ($n=77$) (0.54 ± 0.10mm vs. 0.60 ± 0.12mm, $p=0.03$).

Conclusions: The analysis suggests South Asians may have stiffer arteries than Caucasians and African Americans due to higher Aix, but lower atherosclerosis compared to African Americans through CIMT. These findings suggest that South Asians have a unique cardiovascular risk factor profile that warrant further study to determine whether the effectiveness of therapies established for other races is equivalent in this population. Future studies with larger sample sizes and standardized recruiting methods are necessary for more conclusive results.

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Background

Heart disease is the leading cause of death worldwide and in the United States according to the Centers for Disease Control and Prevention (CDC).[1] More than 70% of Americans between the ages of 60 and 79 in 2013 have cardiovascular disease (CVD), and the percentage increases with age.[2] Various landmark studies have identified the many factors used today in the clinical setting to risk-stratify patients. These include age, gender, family history, hypertension, diabetes, high cholesterol levels, obesity, depression and smoking amongst others.[3-5] While the prevalence of these risk factors differs between ethnicities and socioeconomic status, race has been identified as a strong and independent modifier of cardiovascular risk.[6-8] For example, studies have shown that African Americans have a greater prevalence of risk factors for CVD than Caucasians, including higher prevalence of diabetes mellitus, metabolic syndrome, and uncontrolled hypertension.[9-12] African Americans also have been observed to have a greater overall rate of cardiovascular-related mortality.[1] Despite significant advances in the field of cardiovascular diseases, the mechanisms that underlie the differences in CVD risk among races are still not well understood.

Among various races within the United States, South Asians are one of the fastest growing groups.[7] However, there is a paucity of data regarding CVD risk factors and disease in South Asians residing in the United States. The South Asian population, specifically descendants from India, Pakistan, Sri Lanka, Nepal, and Bangladesh, is known to have higher rates of vascular disease, cardiovascular-related mortality, and diabetes when compared to people from other ethnicities.[4, 13, 14] Researchers have found higher risk of cardiovascular events, including myocardial infarction and CVD-associated death, in South Asian immigrants living in a wide array of countries across the world when compared to other ethnicities.[4, 8, 14, 15] Another study on first-generation Asian Indians in the U.S. showed that South Asians are likely to develop coronary heart disease at an earlier age than other races.[16] There was also an increased rate of diabetes among South Asian immigrants in the U.S. compared to other immigrant groups. In 2004, researchers found that the prevalence of diabetes in Asian Indians living in the metro-Atlanta area was higher than that of the local Caucasian, African American, and Hispanic groups. This rate in the South Asian immigrant population was believed to be the result of urbanization, as it reflects the rate of diabetes in Asian Indians living in urban areas within India as opposed to the rural prevalence of diabetes in the country. Similarly, immigrants that come to the U.S. leave traditional lifestyles behind and tend to have a higher rate of diabetes.[7] Acclimation and the duration of time spent in a new country have both been associated with development of cardiovascular risk factors as studied among other immigrant groups including Japanese Americans and Hispanics [6, 17-19] and may produce similar effects in the South Asian immigrant population.

Further research on South Asians has provided evidence suggesting South Asians have stiffer arteries. Studies conducted in the Indian state of Gujarat showed that South Asian individuals tended to have advanced vascular “aging” – estimated by combining cardiovascular risk factors rather than their actual chronological age.[20] These studies suggest that South Asians are likely to develop stiffer arteries and CVD at an earlier onset than other groups.[5, 21] Arterial stiffness is believed to be an important characteristic for determining risk of CVD. As arterial stiffness increases, the risk for development of hypertension, left ventricular hypertrophy and heart failure increases, as the heart must pump harder to circulate blood. Atherosclerosis on the other hand is the accumulation of plaque inside arteries. Plaque consists of fat, cholesterol, fibrous tissue and matrix that invade the arterial wall from the blood stream. As plaque accumulates on arterial walls, it obstructs the flow of blood through the lumen of the vessel. This plaque can rupture, exposing the contents of the plaque to the bloodstream. This leads to clotting and abrupt closure of the arterial lumen leading to ischemia and infarction or death of the heart muscle.[22, 23]

With the advancement of technology, non-invasive physiologic and imaging techniques examining the human vasculature have allowed us to identify subclinical factors that are associated with future development of CVD. Arterial stiffness, which affects the ability of vessels to compensate for changes in blood volume and results in increased blood pressure, can be readily measured using ultrasound and tonometry to derive pulse wave velocity (PWV). Pulse wave velocity is the speed at which the arterial pulse pressure wave propagates through the body from the heart to peripheral sites.[24] Using a tonometer to measure waveforms at the carotid, radial, and femoral arteries, along with an electrocardiogram (ECG), the PWV can be calculated based on the time that is required for the wave to travel between the sites and a measurement of the distance separating the sites.[25] Another common method to measure arterial stiffness is by pulse wave analysis (PWA). Pulse wave analysis measures the waveform of the radial artery and determines the central pressure waveform, or aortic waveform. The waveform provides information about the augmentation index (Aix), which is given as a percentage for the additional increase in blood pressure due to the reflection of waves from arterial branch points.[21, 25, 26] Stiffer arteries lead to higher values for PWV as the energy waves travel faster in solid-like mediums versus elastic or liquid-like mediums. Arterial stiffness would decrease the elasticity of the vessels leading to higher values for Aix as the arterial walls increase the speed of the reflected waveform and increases the pulse pressure during systole.[27, 28]

Studies have shown that stiffer arteries, measured using PWV and Aix, are a predictor of cardiovascular events in patients with cardiac disease, hypertension and diabetes.[29-33] Furthermore, in diabetic patients, PWV was a predictor for mortality.[34] Aging is associated with increases in both PWV and Aix.[35] Females tend to have higher values for PWV.[36] A study conducted on South Asians found increased arterial stiffness in South Asians compared to Caucasians, and showed that increases in mean arterial blood pressure were also an indicator of arterial stiffness.[37] Another study conducted on young and healthy South Asians and European Caucasians found that South Asians had higher arterial stiffness on the basis of Aix.[21]

Atherosclerosis and inflammation are also associated with an increased risk of various cardiovascular conditions, including stroke and acute coronary syndromes.[38] As a measure of arterial wall thickness the carotid intima-media thickness (CIMT) provides information useful for predicting CVD and related mortality. CIMT can be measured using ultrasound that also provides information on plaque within the common carotid artery (CCA).[38] Carotid ultrasound also enables imaging of the carotid bulb that is immediately before the CCA splits into the internal and external carotid arteries. Turbulent flow at the bifurcation enhances accumulation of plaque. Measurement of CIMT in South Asians would thus be important in characterizing the vasculature in this group.

Factors that influence CIMT include age, gender, high blood pressure and cholesterol levels.[39] High levels of low-density lipoprotein (LDL) and low levels of high-density lipoprotein (HDL) have been associated with increased rates of CVD, as oxidation of LDL leads to atherosclerosis. HDL, in turn, is protective against atherosclerosis and important for the removal of LDL from cells and transporting them to the liver for excretion.[40-44]

Both HDL and LDL particles circulate in the bloodstream. In a 1999 publication, researchers found smaller LDL particles in South Asian individuals, which are believed to be more easily oxidized and promote inflammatory responses and eventually atherosclerosis.[45] Other studies have found an association of higher CIMT values and atherosclerosis with dysfunctional HDL, as is the case with South Asians, who are known to have lower HDL levels and more dysfunctional forms of HDL than other populations.[46, 47] Diabetics also have lower levels of HDL, which coincides with higher CIMT measurements, suggesting that similar effects occur in patients with metabolic syndrome.[48] In a 2004 study, researchers found that South Asians not only had dysfunctional HDL, but also had smaller particles of HDL, reducing its protective effectiveness.[49] Apart from lipid levels, increases in saturated fat and trans fats were related to CIMT suggesting the importance of diet and lifestyle on atherosclerosis.[50] The Study of Health Assessment and Risk in Ethnic groups (SHARE) found that South Asians had a higher occurrence of atherosclerosis.[51] Whether the high rate of diabetes and low HDL levels observed in South Asians leads to changes in CIMT remains to be studied.[52] Thus, South Asians have a higher burden of cardiovascular risk factors and increased CVD, similar to the observations in African Americans. Whether pre-clinical indices of vascular function are altered in South Asians compared to Caucasians and African Americans, independent of traditional risk factors is unknown.

Study Aims

1. To estimate the prevalence of cardiovascular risk factors in the South Asian population of the Atlanta area.
2. To measure subclinical indices of vascular structure and function, including arterial stiffness, using pulse wave analysis (PWA), pulse wave velocity (PWV), and carotid intima-media thickness (CIMT) in South Asians.
3. To compare risk factor profiles and vascular function indices between South Asian, Caucasians, and African Americans.

Hypothesis

I hypothesize that South Asians immigrants, compared to other races, will have:

1. Increased prevalence of cardiovascular risk factors
2. Increased arterial stiffness as measured by arterial pulse wave analysis (PWA) and pulse wave velocity (PWV)
3. Increased carotid intima-media thickness (CIMT)

Methodology and Experimental Design

This study was funded through resources provided by the Emory Clinical Cardiovascular Research Institute (ECCRI).

Subject Enrollment

a) Community Health Fair (CHF)- South Asian Immigrant Group

The research study enrolled South Asian individuals who attended a community health fair in metro Atlanta, Georgia. The health fairs were held at a local physician's clinic and open to anyone, regardless of income or citizenship status. The event occurred once in the spring and once in the fall, and each of these events consisted of two consecutive Sundays. The purpose of the event was to provide medical attention to underserved populations and address health concerns that are prevalent in the population.

For the study, attendees of the health fair were informed about the research study and asked for their participation. Those who expressed interest were asked for consent by an authorized researcher and then enrolled. The subjects provided their contact information for the purpose of creating or locating their medical charts to receive medical care upon each return. Individuals were also required to sign a consent form to receive medical treatment and to indicate comprehension of any risks involved, while releasing any medical professionals and volunteers from being held liable.

b) Criteria

Both males and females over the age of 18 years were enrolled, as well as individuals from any race or ethnicity. The populations that the health fair served included refugees and low-income communities, and predominately people from South Asian countries. All subjects who chose to enroll received free arterial stiffness and atherosclerosis testing, which includes carotid plaque scan, CIMT, and arterial stiffness by PWA and PWV measurements. In addition, all attendees received free physician consultations. There was no monetary compensation for the study. Individuals received their test results.

c) Predictive Health Initiative's Center for Health Discovery and Well Being (CHDWB)-Caucasian and African American Group

The enrollment of Caucasian and African American subjects in this study was completed through the CHDWB. All subjects were employees at Emory University or Emory-affiliated entities who received a medical check-up. Individuals were asked for their consent to participate in the study by authorized personnel. Same criteria as above were followed. There was no monetary compensation for the study. Individuals received their test results.

Data Collection

a) <u>Questionnaire</u>

The questionnaire was provided as the subjects enrolled into the study. The questionnaire was a nine page packet that consisted of questions covering the following topics:

1. Identification/Demographics/Income
2. Current Health History
3. Past Medical and Surgical History
4. Health Perception Questionnaire
5. Sleep Questionnaire (Epworth Sleepiness Scale)
6. Behavior- Alcohol/Tobacco Use
7. Exercise
8. Mood (PHQ-9 Survey)
9. Family History
10. Perceived Stress Scale (PSS by Sheldon Cohen)
11. Medication History
12. Weight Perception (Weight Perception and Control Scale)
13. Tea Consumption
14. Food Intake

The questionnaire was self-administered. Translators were available for those who were unable to understand the English language. For the CHDWB subjects, only the following components were included in the questionnaire:

1. Identification/Demographics/Income
2. Subject Health History
3. Behavior- Alcohol/Tobacco Use
4. Family History
5. Types of Medication

b) Vital Signs and Baseline Measurements

Baseline measurements were made immediately after subjects had completed the consent forms and questionnaires. The measurements for the CHF group were administered by volunteers, including nurses, nursing students, medical school students, and undergraduates who were trained prior to the event. Both the CHF and CHDWB groups had the same measurements made. An electronic sphygmomanometer was used while the individual remained in a seated position to determine blood pressure and heart rate. The measurements were repeated based on judgment of the administering volunteer, or the subject. Subjects were asked to take off their shoes and stand on a stadiometer to measure height (feet and inches). A balance beam weighing scale was used to determine weight (pounds). For BMI calculations, height and weight were converted to meters and kilograms, respectively, and input into the formula: $\frac{\text{weight (kilograms)}}{\text{height (meters)}^2} = BMI$.

c) Blood Tests

Health fair attendees who requested blood tests had blood drawn for specific tests and for research purposes. CHDWB subjects underwent blood tests as well. The study focused specifically on results from a lipid panel, comprehensive metabolic panel (CMP) and complete blood count (CBC). A phlebotomist or nurse administered each blood draw, and the tubes were sent for processing at the Quest Diagnostics laboratory.

d) Arterial Characterization Tests

1. Arterial Stiffness Testing

Using a SphygmoCor® system (PWV Medical, NSW, Australia), subjects were tested for arterial stiffness by the measuring of PWV and PWA.

The system was equipped with a tonometric probe. To measure PWV, a three lead EKG tracing was obtained. The distance from the suprasternal notch to both the carotid and femoral arteries were measured and input into the system. The tonometer was first placed on the femoral artery to measure pulse waveforms. After ten near identical waveforms were recorded by the system, the tonometer was placed on the carotid artery, and ten near identical waveforms were once again recorded. The time difference from when the heart ECG peaks to when the pulse peaks at these regions was recorded by the system. With the measured distance recorded, the system was used to calculate the PWV based on the time it took for the waveform to travel and the distance between the two sites.

The PWA, which provides information and measurements for Aix, was performed in a similar manner. The tonometer was placed on the radial artery site to measure the waveform produced by the changes in pressure as blood pumped through the arteries. After ten consecutive waveforms, the system calculated the corresponding Aix. The measurements were accepted if they were obtained with an operator index greater than 90, otherwise the measurements were retaken. The system also standardized the Aix for a heart rate of 75 beats per minute (Aix@75). [53]

2. Carotid Intima-Media Thickness

Patients who enrolled into the study were asked to participate in carotid plaque scan and CIMT evaluations using a Panasonic CardioHealth® Station (Panasonic Healthcare Co., Ltd. Tokyo, Japan). Individuals were placed in a supine position and asked to place their cheek against a wedge pillow for optimal positioning of the opposite carotid artery. For each patient, right and left carotid arteries were tested.

An ultrasonic plaque scan was performed using a transverse view by moving the probe along the neck, screening for the presence of plaque. The carotid artery was located, and the intima and media were identified by a double line pattern along the vessel wall. The probe was positioned at the point of bifurcation, the location at which the carotid artery split into the external and internal branches. From this location, the probe was moved to image the carotid sinus, or carotid bulb, of the common carotid artery (CCA), where the image of the plaque scan was taken. If plaque was present, as noted by hyperechoic areas along the wall, the image was frozen and saved. A circle on the screen was aligned with the circular cross-sectional view of the carotid artery and a digital pen was used to trace the edges of the observed plaque within the circle. The percentage of plaque in the cross-sectional view of the carotid artery was recorded by the system. This process was repeated for each carotid artery.

For the second test, the IMT measurements, the probe was rotated 90 degrees from the plaque scan configuration, to provide a longitudinal view of the artery. The probe was positioned at the carotid bulb so that the vertical dotted line displayed on the live feed screen was at the bifurcation. For consistency in measurements, the dotted line remained at a set distance from a rectangular analysis box that contained the section of the arterial wall that was analyzed to determine the intima media thickness. At this point, the device automatically measured the maximum, minimum, and average IMT in millimeters. A visual guide on the screen provided real time probe angle for additional consistency for reporting and repeating measurements.

e) Statistical Analysis

Continuous variables are presented as means (standard deviation) and categorical variables as proportions (%). Independent samples t-tests and chi-square tests were used to compare continuous and categorical variables, respectively. A normal distribution was assumed for continuous variables. Hypercholesterolemia was defined by LDL > 130 mg/dL, statin use, or subject's medical history. Hypertension was defined by systolic pressure > 140 mmHg, diastolic pressure > 90mmHg, blood pressure medication, or patient's medical history. Diabetes mellitus was defined by a fasting plasma glucose > 126 mg/dL, diabetic medication, or patient's medical history. Obesity was defined by a BMI > 30 kg/m^2. Subjects categorized as "healthy" were defined as not being a smoker, obese, hypertensive, diabetic, or hypercholesterolemic.

To identify independent predictors of arterial stiffness and atherosclerosis, multivariable analysis was performed using linear regression with either PWV, AIX or CIMT as the dependent variables adjusting for the following covariates: age, gender, BMI, hypertension, hypercholesterolemia, diabetes, race, and smoking status. Covariates among healthy patients included age, gender, BMI, and race.

<u>Results</u>

Clinical Characteristics of Subjects:

The demographic and clinical characteristics of South Asians (n=715), Caucasians (n=1032), and African Americans (n=620) are listed in Table 1.

Table 1. Demographics and Clinical Characteristics

Variables	South Asians (n=715)	Caucasians (n=1032)	African Americans (n=620)
Age, years	48 (13)	**49 (11)***	47 (10)
Male, n (%)	353 (51%)	**446 (43%)****	**222 (36%)*****
Body Mass Index, kg/m^2	26 (5)	**27 (6)***	**31 (8)*****
Clinical Characteristics			
Systolic Pressure, mm Hg	131 (20)	**119 (15)*****	**124 (18)*****
Diastolic Pressure, mm Hg	78 (14)	**75 (11)*****	79 (12)
Heart Rate, bpm	74 (11)	**64 (10)*****	**66 (10)*****
Current Smokers, n (%)	29 (7%)	**93 (9.6%)**	**140 (24%)*****
Hypertension, n (%)	281 (39%)	**302 (29%)****	276 (45%)
Diabetes Mellitus, n (%)	153 (21%)	**133 (13%)*****	127 (20%)
Hypercholesterolemia, n (%)	218 (30%)	**606 (59%)*****	**330 (53%)*****
Low-Density Lipoprotein, mg/dL	107 (31)	**112 (31)****	**114 (35)****
High-Density Lipoprotein, mg/dL	51 (13)	**62 (19)*****	**61 (17)*****
Triglycerides, mg/dL	140 (88)	**111 (69)*****	**93 (43)*****
Plasma Glucose, mg/dL	109 (42)	**90 (16)*****	**92 (25)*****
Creatinine, mg/dL	0.84 (0.21)	0.85 (0.18)	**0.92 (0.63)****
Measures of Vascular Function and Atherosclerosis			
Pulse Wave Velocity, m/s[‡]	7.1 (2.0)	7.1 (1.5)	**7.6 (1.7)****
Central Augmentation Index corrected for HR of 75 bpm[§]	27.0 (10.7)	**18.9 (12.1)*****	**22.0 (11.8)*****
Carotid Intima-Media Thickness, mm*	0.62 (0.15)	0.62 (0.12)	0.63 (0.12)

Statistical significance between South Asians and either Caucasians or African Americans, with a p<0.05 are highlighted in bold. *Values are statistically significant with p<0.03. **Values that are statistically significant with p<0.01. ***Values that are significant with p<0.001. [†]Values are mean (SD) or n (%) where appropriate. [‡]PWV was obtained for 105 South Asian subjects, 860 Caucasians, and 426 African Americans. [§]Central AIX was obtained for 463 South Asian subjects, 984 Caucasians, and 592 African Americans. [¶]Carotid IMT was obtained for 138 South Asian subjects, 612 Caucasians, and 210 African Americans.

South Asian subjects had a higher prevalence of males (51%) and lower average BMI (26 kg/m^2) than the Caucasian (43%; 27 kg/m^2) and African American (36%; 31 kg/m^2) groups, respectively. There were fewer smokers (7%) and hypercholesterolemic subjects (30%) among the South Asians, while African Americans had the highest prevalence (24%, 53%), respectively. Both South Asians and African Americans had a greater proportion of hypertensive individuals (39% and 45%, respectively) and diabetics (21% and 20%, respectively) when compared to the Caucasian group (39% hypertensive; 13% diabetic). South Asians had the highest mean fasting plasma glucose concentration (106±16 mg/dL, $p<0.001$) among the group. On average, South Asian subjects had lower HDL levels (51 mg/dL, $p<0.001$) and higher triglyceride levels (140 mg/dL, $p<0.001$) than the other groups.

Among the vascular function tests, the Aix appeared to be significantly higher in South Asians (27.0% compared to 18.9% in Caucasians and 22.0% in African Americans, $p<0.001$). Both South Asians and Caucasians had lower PWV (7.1 m/s in both groups) than African Americans (7.6 m/s, $p<0.01$), while CIMT was similar between all three groups with 0.62 mm, 0.62 mm, 0.63 mm for South Asians, Caucasians, and African Americans, respectively.

Multivariable Analysis:

We performed a multivariable analysis for all vascular measures (PWV, Aix, and CIMT) after adjusting for age, gender, BMI, hypertension, hypercholesterolemia, diabetes, race, and smoking status. Results are shown in Table 2.

Table 2. Multivariable Predictors of Arterial Stiffness and CIMT in All Subjects

Predictors	Pulse Wave Velocity*, ‡		Augmentation Index (at HR 75)*, §		Carotid Intima-Media Thickness*, †	
	ß (95% CI)	p-value	ß (95% CI)	p-value	ß (95% CI)	p-value
Age	0.04 (0.03, 0.05)	**<0.001**	0.49 (0.45, 0.54)	**<0.001**	0.007 (0.006, 0.007)	**<0.001**
Male	0.45 (0.28, 0.62)	**<0.001**	-10.4 (-11.3, -9.5)	**<0.001**	0.03 (0.02, 0.04)	**<0.001**
Body Mass Index	0.01 (0.00, 0.02)	0.14	-0.08 (-0.15, -0.01)	**0.03**	0.004 (0.003, 0.005)	**<0.001**
Clinical Characteristics						
Current Smokers	0.01 (-0.24, 0.25)	0.96	4.2 (2.9, 5.5)	**<0.001**	0.02 (-0.01, 0.04)	0.28
Hypertension	0.46 (0.27, 0.65)	**<0.001**	2.9 (1.9, 3.9)	**<0.001**	0.02 (0.00, 0.03)	**0.03**
Diabetes Mellitus	0.28 (0.05, 0.52)	**0.01**	-1.6 (-2.8, -0.3)	**0.01**	0.02 (0.00, 0.04)	**0.01**
Hypercholesterolemia	0.02 (-0.16, 0.20)	0.81	1.5 (0.6, 2.5)	**0.002**	-0.01 (-0.02, 0.00)	0.06
South Asian vs Caucasians	-0.33 (-0.68, 0.01)	0.06	10.9 (9.4, 12.5)	**<0.001**	-0.02 (-0.04, 0.00)	0.08
South Asian vs African Americans	-0.74 (-1.11, -0.38)	**<0.001**	8.0 (6.3, 9.6)	**<0.001**	-0.05 (-0.07, -0.02)	**<0.001**
Interactions						
Race-Hypertension	-	0.27	-	**0.005**	-	0.12
Race-Diabetes	-	0.85	-	0.50	-	0.12
Race-Hypercholesterolemia	-	0.81	-	**0.02**	-	0.56

Statistically significant values are highlighted in bold. *Covariates included in the model for PWV, Aix, and CIMT include age, gender, BMI, hypertension, hypercholesterolemia, diabetes, race, and smoking status. ‡PWV was obtained for 105 South Asian subjects, 860 Caucasians, and 426 African Americans. §Central AIX was obtained for 463 South Asian subjects, 984 Caucasians, and 592 African Americans. †Carotid IMT was obtained for 138 South Asian subjects, 612 Caucasians, and 210 African Americans.

The multivariable analysis shows that age (β= 0.04, p<0.001), male gender (β= 0.45, p<0.001), hypertension (β= 0.46, p<0.001), and diabetes (β= 0.28, p=0.01) were positive predictors for higher PWV. The African American race, when compared to the South Asian race, predicted higher PWV ($\beta = 0.74$, $p<0.001$). Significant predictors for higher Aix included age ($\beta = 0.49$, $p<0.001$), smoking status ($\beta = 4.2$, $p<0.001$), hypertension ($\beta = 2.9$, $p<0.001$), hypercholesterolemia ($\beta = 1.5$, $p=0.002$), and the South Asian race ($\beta = 10.9$ vs Caucasian race and $\beta = 8.0$ vs African American race; $p<0.001$). Male gender ($\beta = -10.4$, $p<0.001$), BMI ($\beta = -0.08$, $p=0.03$), and diabetes ($\beta = -1.6$, $p=0.01$) were predictors of lower Aix. Analysis of interactions between race and hypertension as well as race and hypercholesterolemia were significantly associated with Aix. Specifically, Caucasians with hypertension or hypercholesterolemia had significantly higher Aix than Caucasians without these conditions. This relationship was absent in South Asians and African Americans. For CIMT, age ($\beta = 0.007$, $p<0.001$), male gender ($\beta = 0.03$, $p<0.001$), BMI ($\beta = 0.004$, $p<0.001$), hypertension ($\beta = 0.02$, $p= 0.03$), diabetes ($\beta = 0.02$, $p=0.01$), and the African American race ($\beta = 0.05$, $p<0.001$) when compared to South Asians predicted thicker measurements.

Vascular Function in Healthy Subjects

Since the distribution of risk factors varied among the races, and may have accounted for the variation in vascular function and structure we observed, we additionally compared vascular function in subjects free of all cardiovascular risk factors within each racial group. The healthy subset included non-smokers free of hypertension, diabetes, obesity, and hypercholesterolemia.

Clinical Characterization of Healthy Subjects:

The characteristics of the healthy subsets among each race are listed in Table 3. The healthy group includes 258 total South Asians, 286 total Caucasians, and 111 total African Americans.

Table 3. Demographics and Clinical Characteristics for Healthy Subjects

Variables	**South Asians (n=258)**	**Caucasians (n=286)**	**African Americans (n=111)**
Age, years	42 (13)	43 (12)	41 (12)
Male, n (%)	113 (45%)	114 (40%)	40 (36%)
Body Mass Index, kg/m^2	24 (3)	23 (3)	**25 (3)***
Clinical Characteristics			
Systolic Pressure, mm Hg	119 (12)	**111 (11)*****	**114 (11)*****
Diastolic Pressure, mm Hg	72 (10)	**69 (8)****	72 (8)
Heart Rate, bpm	72 (11)	**61 (10)*****	**65 (10)*****
Low-Density Lipoprotein, mg/dL	97 (20)	**92 (19)***	**88 (21)*****
High-Density Lipoprotein, mg/dL	54 (14)	**64 (15)*****	**64 (14)*****
Triglycerides, mg/dL	114 (75)	**72 (27)*****	**66 (28)*****
Plasma Glucose, mg/dL	91 (15)	**85 (7)*****	**83 (7)*****
Creatinine, mg/dL	0.79 (0.15)	**0.83 (0.14)****	**0.86 (0.16)*****
Measures of Vascular Function and Atherosclerosis			
Pulse Wave Velocity, m/s‡	6.0 (1.8)	6.7 (1.2)	**6.9 (1.4)***
Central Augmentation Index corrected for HR of 75 bpm§	24.6 (12.0)	**13.5 (14.2)*****	**16.4 (12.2)*****
Carotid Intima-Media Thickness, mm¶	0.54 (0.08)	0.56 (0.10)	**0.58 (0.13)**

Statistical significance between South Asians and either Caucasians or African Americans, with a p<0.05 are highlighted in bold. *Values are statistically significant with p<0.03. **Values that are statistically significant with p<0.01. ***Values that are significant with p<0.001. †Values are mean (SD) or n (%) where appropriate. ‡PWV was obtained for 28 South Asian subjects, 239 Caucasians, and 77 African Americans. §Central AIX was obtained for 173 South Asian subjects, 265 Caucasians, and 104 African Americans. ¶Carotid IMT was obtained for 41 South Asian subjects, 208 Caucasians, and 66 African Americans.

The mean age and percentage of males between the three races were not significantly different with the healthy subjects, while BMI was higher in healthy African Americans ($p<0.03$) than the other two races. Systolic pressure ($p<0.001$), heart rate ($p<0.001$), triglycerides ($p<0.001$), plasma glucose ($p<0.001$), and Aix ($p<0.001$) were all significantly higher in healthy South Asians when compared to Caucasians and African Americans. Diastolic pressure in healthy South Asians (72 mm Hg) was similar to African Americans (72 mm Hg), but higher when compared to Caucasians (69, $p<0.01$). Healthy South Asians had higher LDL levels (97 mg/dL) than healthy Caucasians (92 mg/dL, $p<0.03$) and healthy African Americans (88 mg/dL, $p<0.001$). Levels of HDL were significantly lower in South Asians (54 mg/dL, $p<0.001$). Healthy African Americans have higher PWV (6.9 m/s, $p<0.03$) and CIMT (0.58 mm, $p<0.05$) than South Asians, though South Asians have similar measurements to Caucasians for PWV and CIMT.

Comparison of Arterial Stiffness and Atherosclerosis in Healthy Subjects

The values and differences in PWV, Aix, and CIMT for healthy subjects are shown in Table 4.

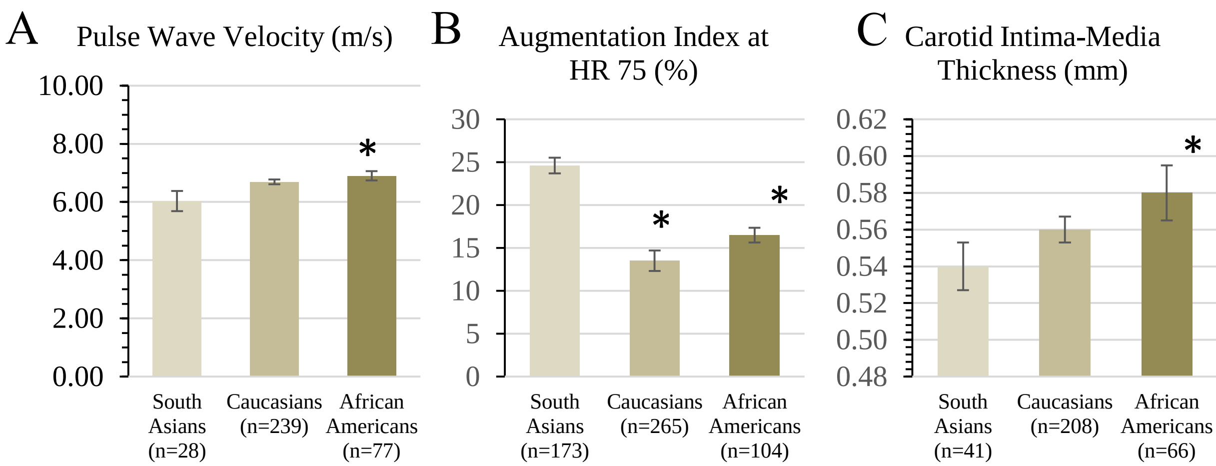
Table 4. Arterial Stiffness and Carotid IMT in Healthy South Asians, Caucasians and African Americans

Variables	Value (SD)	p-value
Pulse Wave Velocity (m/s)		
South Asians (n=28)	6.03 (1.82)	
Caucasians (n=239)	6.69 (1.24)	0.07
African Americans (n=77)	6.90 (1.43)	**0.01**
Augmentation Index at HR 75 (%)		
South Asians (n=173)	24.6 (12.0)	
Caucasians (n=265)	13.5 (14.2)	**<0.001**
African Americans (n=104)	16.5 (12.2)	**<0.001**
Carotid Intima-Media Thickness (mm)		
South Asians (n=41)	0.54 (0.08)	
Caucasians (n=208)	0.56 (0.10)	0.13
African Americans (n=66)	0.58 (0.13)	**0.04**

Statistically significant values are highlighted in bold and in comparison to South Asians. †Factors used for designated subjects included lack of hypertension, diabetes, hypercholesterolemia, obesity, and smoking.

When comparing the healthy subsets between the different races, healthy African Americans had higher PWV (6.90±1.43 m/s) compared to both healthy South Asians (6.03±1.82 m/s) and healthy Caucasians (6.69±1.24 m/s). Aix in healthy South Asians (24.6%) was significantly greater ($p<0.001$) than the other races. The healthy African American subgroup had significantly greater CIMT values (0.58 mm, $p=0.04$) compared to healthy South Asians (0.54 mm). Figure 1 shows a visualization of the results with standard error bars.

Figure 1. Pulse Wave Velocity, Augmentation Index and Carotid Intima-Media Thickness Compared



*Statistically significant differences in comparison to South Asians with $p<0.05$. The bars represent standard error of the mean.

Multivariable Analysis with Healthy Subjects

A multivariable analysis was performed in the healthy subset to adjust for covariates including age, gender, height (for Aix) and race (Table 5).

Table 5. Multivariable Predictors of Arterial Stiffness and CIMT in Healthy Subjects

Predictors	Pulse Wave Velocity*		Augmentation Index (at HR 75)*		Carotid Intima-Media Thickness*	
	ß (95% CI)	**p-value**	**ß (95% CI)**	**p-value**	**ß (95% CI)**	**p-value**
Age	0.05 (0.04, 0.06)	**<0.001**	0.49 (0.45, 0.52)	**<0.001**	0.007 (0.006, 0.007)	**<0.001**
Male	0.50 (0.33, 0.66)	**<0.001**	-6.2 (-7.4, -5.1)	**<0.001**	0.03 (0.02, 0.04)	**<0.001**
Height	-	-	-0.56 (-0.70, -0.41)	**<0.001**	-	**-**
South Asian vs Caucasians	-0.15 (-0.48, 0.17)	0.36	7.4 (6.2, 8.6)	**<0.001**	-0.01 (-0.03, 0.01)	0.38
South Asian vs African Americans	-0.71 (-1.05, -0.36)	**<0.001**	4.1 (2.8, 5.3)	**<0.001**	-0.05 (-0.07, -0.03)	**<0.001**

Statistically significant values are highlighted in bold. *Covariates included in the model for PWV, Aix, and CIMT include age, gender, and race. Height was also a covariate for Aix. After the healthy patients were screened, there were 258 South Asians, with 28 PWV, 173 Aix, and 41 CIMT results that were available. There were 286 Caucasians, with 239 PWV, 265 Aix, and 208 CIMT results available. The screen left 111 African Americans with 77 PWV, 104 Aix, and 66 CIMT results.

Among the healthy subjects, age (β= 0.05, p<0.001) and male gender (β= 0.50, p<0.001) were significant predictors of increased PWV. The South Asian race (β= -0.71, p<0.001) was a predictor for lower PWV when compared to African Americans. Age (β= 0.49, p<0.001) and the South Asian race (β= 7.4, p<0.001 vs Caucasian race; β= 4.1, p<0.001 vs African American race) were positive predictors of Aix, while male gender (β= -6.2, p<0.001) and taller height (β= -0.56, p<0.001) were correlated with lower Aix. Predictors for higher CIMT in healthy subjects included age (β= 0.007, p<0.001) and the male gender (β= 0.03, p<0.001). The South Asian race (β= -0.05, p<0.001) was a predictor of lower CIMT when compared to the African American race.

Discussion

In a multiethnic cross-sectional study, we compared the risk factor profile and vascular structure and function including arterial stiffness and carotid intima-media thickness between South Asians, Caucasians and African Americans. Overall, South Asians had a similar risk factor profile to African Americans, and a higher than Caucasians. Compared to Caucasians, South Asians had a higher prevalence of diabetes and hypertension. Most importantly, South Asians had higher Aix compared to both Caucasians and African Americans, but lower CIMT compared to African Americans. These differences persist in a subgroup of healthy subjects from the three ethnicities. These findings suggest that South Asian immigrants have a unique cardiovascular risk factor profile and thus warrant further study to determine whether the effectiveness of therapies established for other races are appropriate in this population.

In this study, subjects were surveyed and risk factors were measured among a total sample size of over 2300 South Asians, Caucasians, and African Americans. Some of our findings are in agreement with previous reports. Thus, as previously reported, South Asians were less likely to be smokers, likely due to cultural influences, but had a high prevalence of hypertension and diabetes. [4, 7, 8, 13-15, 45-47, 49, 52] The predictors of PWV had included age, gender, hypertension, and diabetes are similar to previous studies. [29-36] Predictors for Aix in this study also parallel previous findings and include age, female gender, smoking, hypertension, and hypercholesterolemia.[27-29, 31, 33, 35-37] Finally, CIMT was independently associated with increasing age, male gender, and BMI, as previously reported. [39-44, 48, 49] Studies have suggested that South Asians living in India and European countries have greater arterial stiffness than other races.[20, 21]

The analysis for PWV in healthy subjects suggests greater arterial stiffness in African Americans compared to South Asians, though the finding is limited by a small sample size. The exact causes for higher PWV in African Americans are beyond the scope of this study, but may be attributed to the high levels of hypertension in the African American population. [45, 50] The average PWV for each healthy group shows no significant different, even though multivariable analysis suggests that the African American race is a predictor for increased PWV when compared to South Asians. Aix was significantly greater in the South Asian group, both among healthy subjects and the total sample size, when compared to the Caucasian and African American groups. The South Asian race was a predictor of greater Aix measurements as well, upholding the notion that South Asians may have greater arterial wave reflections. While South Asians may have stiffer arteries, CIMT is lower than that in African Americans, but similar to levels as seen in Caucasians. A study in 2015 identified a correlation between PWV and CIMT, which can be seen in this study as African Americans have greater arterial stiffness and carotid artery thickness as defined by those two measurements.[54]

Clinical characteristics of South Asians may explain the increased arterial stiffness in comparison to the other groups. The South Asian group had relatively lower HDL levels, higher triglycerides levels, and higher concentration of plasma glucose, which are common in South Asians.[39-44, 48, 49] In prior studies, South Asians have been shown to have smaller particles of LDL which oxidize readily and lead to inflammatory responses.[40, 41, 43, 45] Low levels of HDL and dysfunctional forms of HDL in this group reduce the capacity and ability to remove lipids from peripheral tissue and blood and promote arterial stiffness and atherosclerosis.[45-49] LDL is an important factor for atherosclerosis. The African American group had the highest concentration of LDL in our study. Compounded with a high prevalence of hypertension and diabetes, that is similar to South Asians, increased CIMT in African Americans may be expected as these conditions have been associated with increased atherosclerosis.[39-44, 48, 49]

The PWV, Aix, and CIMT of the South Asian group suggests that they are a very distinct group in terms of clinical characteristics, as PWV measurements suggested less stiff arteries but Aix suggested stiffer arteries in comparison to the other races. Due to the differences in recruitment of these subjects, the socioeconomic statuses of the groups may have been a factor in the health of the subjects. The South Asians were not a randomly chosen group as recruitment occurred at community health fairs that targeted lower income and underserved individuals. Many conditions may not have been diagnosed or remained untreated. The lack of access to health care may have led to an underestimation for prevalence of hypertension, diabetes, and hypercholesterolemia in this group. Many South Asian subjects were not able to access all tests necessary for this study, leading to a smaller total sample size, as well as less available data for the vascular characterization tests of PWV, Aix, and CIMT. The sample size was further reduced when analyzing healthy subjects as well, since most South Asian participants attended the event to receive treatment for conditions and illnesses.

The South Asian group internally is very diverse as religion, lifestyle, and diet can vary by region. Generalization cannot be made about the entire South Asian populations due to these differences. Compared to Caucasians and African Americans, there tend to be a greater number of vegetarians within South Asian groups due to the influences of culture, which also contributes to less smoking and alcohol use. The influence of acculturation and length of time in the U.S. should be considered in future studies to examine changes in risk factors. Depression, stress, and dietary intake could also contribute to the health of this group and should be analyzed. Further studies on South Asian vasculature may provide unique characteristics that could be noted for therapies. Finally, analysis at the cellular and biochemical levels could examine necessary enzymes and markers to provide further insight about the influence of race on arterial stiffness and atherosclerosis.

Research Advisor

Dr. Arshed A. Quyyumi, who is a Professor of Medicine in the Division of Cardiology at Emory University School of Medicine, and the Co-Director for the Emory Clinical Cardiovascular Research Institute (ECCRI) will be advising me in my research pursuits. I will also be advised by Dr. Salim Hayek, who is a cardiology research fellow in the ECCRI. Dr. Hayek will be overseeing my progress regularly and ensuring appropriate procedures are followed for the completion of this project. Emory IRB- 00000343.

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