

## **Ethnic differences in the relationship between albuminuria and calcified atherosclerotic plaque: African American-Diabetes Heart Study**

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Running Head: Albuminuria-CVD in African Americans

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*Objective:* Despite higher rates of nephropathy, calcified atherosclerotic plaque (CP) is less prevalent in African Americans (AA) with diabetes relative to European Americans (EA). We explored ethnic-specific relationships between albuminuria and CP involving the infra-renal aorta, coronary and carotid artery in 835 EA and 393 AA subjects with type 2 diabetes.

*Research Design and Methods:* Generalized estimating equations with exchangeable correlation and the sandwich estimator of the variance were used to test for association between the principal component of CP in the 3 vascular beds and urine albumin:creatinine ratio (ACR).

*Results:* Mean (SD) age of AA and EA participants was 56.7 (9.6) and 61.7 (9.1) years, respectively, diabetes duration 10.4 (7.4) and 10.0 (7.3) years, and median urine ACR 17.5 and 13.4 mg/g. In AA and EA participants, respectively, median CP mass scores were 53.5 and 291 for coronary artery, 3 and 35.5 for carotid artery, and 761 and 3237 for aorta. Adjusting for age, gender, glomerular filtration rate and body mass index, albuminuria was significantly associated with CP in EA ( $p=3.4 \times 10^{-8}$ ), not in AA ( $p=0.33$ ), with significant ethnic interaction ( $p=0.01$ ). Ethnic differences in this relationship persisted after adjustment for blood pressure, smoking, lipids and use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers.

*Conclusions:* Albuminuria is strongly associated with severity of CP in EA with diabetes, but not in AA. Disparities in this relationship may contribute to ethnic differences in the rates of cardiovascular disease that are observed in subjects with type 2 diabetes.

African Americans (AA) have overall higher rates of type 2 diabetes (1) and greater risk for diabetes-associated renal and cardiovascular complications relative to European Americans (EA) (2,3). In contrast, reports from the Veterans Administration and Kaiser Permanente reveal that when given access to equivalent medical care, AA with diabetes had approximately half the rate of myocardial infarctions as seen in EA (4,5). In concert with this observation, computed tomography (CT)-derived coronary artery calcified plaque (CP) is markedly lower in AA with and without diabetes relative to EA (6-10). Coronary CP correlates with the extent of atherosclerosis and subsequent risk for cardiovascular disease (CVD) events (11). Coronary artery CP scores also predict the risk for CVD events in individuals of all ethnic groups (12) and are higher among patients with renal disease, relative to non-kidney diseased individuals with known coronary artery disease (13).

CVD remains the major cause of morbidity and mortality in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) (2). Among incident dialysis patients, AA had fewer myocardial infarctions and improved survival relative to EA (14). As individuals with diabetes and nephropathy approach ESRD, they typically have albuminuria with falling glomerular filtration rate (GFR) over several years. Associations between albuminuria and coronary artery CP are robust in EA and appear to be at least equivalent to the risk that is associated with other established CVD risk factors (15). We hypothesized that ethnic differences in the relationship between albuminuria and atherosclerosis might contribute to the lower levels of CP that are widely observed in AA with diabetes.

The African American-Diabetes Heart Study (AA-DHS) is assessing ethnic

differences and inherited factors that contribute to development of CP. Herein, we compare the relationship between albuminuria (urine albumin:creatinine ratio; ACR) and CP in the coronary (Cor) and carotid (Car) arteries and infra-renal aorta (Aor) in AA and EA subjects with type 2 diabetes mellitus. We made use of a principal component (PC) that encompasses the burden of calcified atherosclerotic plaque in all three vascular beds. The majority of AA-DHS participants have preserved renal function, allowing for separation of the effects of hyperphosphatemia, uremia, and ingestion of phosphate binders on vascular calcification.

## **RESEARCH DESIGN AND METHODS**

**Study Populations.** Siblings concordant for type 2 diabetes were recruited from internal medicine clinics and community advertising in the Diabetes Heart Study (DHS) (8). Diabetes was diagnosed after the age of 34 years in the absence of historical evidence of ketoacidosis. In addition, 213 unrelated AA subjects were subsequently recruited in the AA-DHS using these same diagnostic criteria, except type 2 diabetes was diagnosed after the age of 30 years. Subjects who underwent prior coronary artery bypass surgery or carotid endarterectomy were excluded from this analysis as it was felt that the CP mass score in relevant arteries would be impacted by these procedures; those with prior myocardial infarction or stroke were included. The study was approved by the Institutional Review Board at the Wake Forest University School of Medicine (WFUSM) and all participants provided written informed consent.

Participant examinations were conducted in the General Clinical Research Center of the WFUSM and included interviews for medical history, current medications and health behaviors, measurements of body size, resting blood

pressure, 12-lead electrocardiogram, fasting blood draw, and morning spot urine collection. Laboratory assays included urine albumin and creatinine for ACR, total cholesterol, LDL, HDL, triglycerides, HbA<sub>1c</sub>, and fasting serum glucose. Renal function was assessed using serum creatinine concentration and MDRD estimation of GFR. History of cardiovascular disease was provided by self-report and chart review. Hypertension was defined as self-report of a physician's diagnosis, blood pressure >140/90 mm Hg, or use of anti-hypertensive medications. Anti-hypertensive medications were grouped into drug classes; particularly angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB), medicines known to reduce urine ACR.

**Vascular Imaging.** Calcified plaque was measured in the coronary and carotid arteries and infra-renal abdominal aorta using single and multidetector CT systems incorporating a standardized scanning protocol based on those currently implemented in the National Heart Lung and Blood Institute's MESA studies and these methods have been reported previously (8,16). Traditionally, the Agatston, also called the Calcium Score, has been used to report results. However, the nature of this scoring system adds noise to the CT measurement of CP when compared to calcified plaque volume based measures (17). This report used the calcium mass score (SmartScore, General Electric [GE] Healthcare, Waukesha, WI) which is derived from the volume score, but in addition accounts for the density of CP on a pixel by pixel basis. Additional scoring parameters included a 90 Hounsefield Unit (H.U.) threshold and two adjacent pixels to define the maximum calcified lesion size and the program accounted for slice thickness.

**Statistical methods.** A series of generalized estimating equations (GEE)

assuming exchangeable correlation and using the empirical estimate of the variance to adjust for familial correlation was computed to test for associations between urine ACR and CP (18). The natural log of (urine ACR + 1) was calculated to minimize the influence of extremely large covariate values on parameter estimates in these models. The Box-Cox method was applied to identify the appropriate transformation of each outcome variable that would best approximate the distributional assumptions of conditional normality and homogeneity of variance of the residuals (19). The natural log of (CorCP + 1), (CarCP + 1) and (AorCP + 1) were analyzed. We applied principal component analysis (PCA) to compute a linear combination of CorCP, CarCP and AorCP that we used as the primary outcome variable. The PC encompasses the burden of calcified atherosclerotic plaque in these three vascular beds. There is strong correlation between the amount of CP in the coronary arteries, carotid arteries and aorta of individuals with diabetes (20). PCA was conducted using the correlation matrix instead of the covariance matrix, in order to account for the differences in measurement scales between the 3 variables. The first PC explained approximately 70% of the total variation observed in these three variables and is computed as:

$$PCAI\_CP = 0.6 \times CarCP + 0.5 \times CorCP + 0.6 \times AorCP$$

The variable  $PCAI\_CP$  was computed using the standardized values of CarCP, CorCP and AorCP. The Box-Cox transformation that best approximated the distributional assumptions of the model was the inverse  $PCAI\_CP$ , i.e.,  $(PCAI\_CP)^{-1}$ . For  $PCAI\_CP$ , models were adjusted for age, gender, body mass index (BMI), and GFR. Subsequent analyses were further adjusted for use of ACEi or ARB medications, blood pressure, lipid levels, HbA<sub>1c</sub> and smoking. Standard

regression diagnostics for collinearity and influence were computed for each model reported.

## RESULTS

A total of 1427 individuals with type 2 diabetes had complete data for analysis. Of these, 1008 were EA from 445 families and 419 were AA from 297 families. Coronary artery bypass grafting or carotid endarterectomy was performed in 173 EA and 26 AA participants and these individuals were excluded. Tables 1 and 2 contain demographic and clinical information in study participants. Urine ACR was <30 mg/g in 60.3% of AA and 71.0% of EA participants; 30-299 mg/g in 29.0% of AA and 23.5% of EA participants; and  $\geq 300$  mg/g in 10.7% of AA and 5.5% of EA participants (Table 1). Median Modification of Diet in Renal Disease (MDRD) estimated GFR was 1.34 mL/sec in AA and 1.09 mL/sec in EA participants (p-value for ethnic difference  $6.3 \times 10^{-22}$ ), with graded reductions in GFR from normoalbuminuric to overt proteinuric participants in both ethnic groups (Table 2).

Coronary CP was detectable in 81.7% and 93.3% of AA and EA participants, respectively (p-value for ethnic difference  $1 \times 10^{-9}$ ). Since distributions of CP mass scores are highly skewed, mean scores should be interpreted cautiously and median values are more reflective of central tendency. In AA subjects the median CorCP mass score was 53.5 (mean 697), median CarCP mass score 3 (mean 170), median AorCP mass score 761 (mean 4934) and median ACR 17.5 mg/g (mean [SD] 230 [758]). In EA subjects the median CorCP mass score was 291 (mean 1277), median CarCP mass score 35.5 (mean 275), median AorCP mass score 3237 (mean 9803) and median ACR 13.4 mg/g (mean [SD] 110 [531]); these ethnic differences were highly significant ( $p=8.2 \times 10^{-11}$  to  $2.39 \times 10^{-14}$ ). Statistically significant and graded increases in median vascular CP mass score

were observed with increasing levels of ACR in European Americans with p-values= $1.6 \times 10^{-4}$ ,  $2.7 \times 10^{-4}$  and  $1.0 \times 10^{-6}$  respectively for AorCP, CorCP and CarCP using traditional ACR cut points <30, 30-299, and >300 mg/g to stratify the sample. When stratification was done using quartiles of urine ACR, p-values improved to  $4.7 \times 10^{-7}$ ,  $1.2 \times 10^{-8}$  for AorCP and CorCP, but decreased to  $4.8 \times 10^{-5}$  for CarCP. In African Americans, only CarCP had a significant positive relationship with urine ACR ( $p=9.6 \times 10^{-3}$  using ACR quartiles,  $p=5.8 \times 10^{-3}$  using traditional ACR cutoff values; Table 2 and Supplemental Table 1 which is available in the online appendix at <http://care.diabetesjournals.org>).

Table 3 focuses on the relationship between urine ACR and CP, separately in each vascular distribution and for the first PC of CP. In age-, gender-, BMI- and GFR-adjusted analyses, significant associations were seen between urine ACR with each vascular bed as well as for the PC in EA; whereas significant relationships were not present in AA. In addition, significant ethnic differences were observed in the relationship between urine ACR and the PC for CP ( $p=0.01$ ), and a trend for urine ACR with CarCP ( $p=0.06$ ).

Table 4 reveals the parameter estimate for the relationship between log urine ACR and the first PC for CP across the three vascular beds, adjusted for additional covariates including ACEi or ARB. The log urine ACR was significantly associated with the first PC for CP in EA (parameter estimate [SE] -0.0387 [0.008];  $p=8.34 \times 10^{-7}$ ); while a significant relationship was not observed in AA (parameter estimate -0.0068 [0.011];  $p=0.54$ ) and there was a significant ethnic interaction ( $p=0.01$ ). The Box-Cox transformation suggested using a decreasing function of the PC; therefore, the direction indicated for sign of the parameter estimate should be inverted when reverting to the original scale. Ethnic differences in the

relationship between gender and CP were also detected ( $p=0.0001$ ). Although there was no association between gender and the first PC for CP in AA ( $p=0.37$ ), gender was strongly associated with CP in EA, with men having greater CP than women ( $p = 6.4 \times 10^{-7}$ ).

## DISCUSSION

This report characterized ethnic differences in the relationship between calcified atherosclerotic plaque and albuminuria in AA and EA with type 2 diabetes mellitus lacking advanced renal dysfunction. Albuminuria and kidney disease are important risk factors for development of atherosclerosis (21). After adjusting for the covariates of age, gender, BMI, and GFR, a significant and positive relationship was observed between albuminuria and CP in EA, but not in AA. Consequently, the ethnic difference in this relationship suggests that lower amounts of CP in AA with diabetes, with attendant reduced risk for myocardial infarction relative to EA, could be related in part to a differential effect of albuminuria. Myocardial infarctions occur significantly less often in AA patients receiving renal replacement therapy compared to EA and CVD is the leading cause of death in subjects with nephropathy (2,14). Our report intentionally examined EA and AA subjects with diabetes and relatively preserved kidney function, thereby minimizing the potential effects of exogenous Vitamin D and Vitamin D analogues, phosphate binders and calcimimetic agents on CP. These medications and associated hyperphosphatemia may impact risk for development of subclinical cardiovascular disease in patients with advanced nephropathy (22).

A recent report confirmed the lower risk of CVD in AA with advanced stages of CKD, relative to EA (23). There is mounting evidence that biological differences may contribute to ethnic differences in risk for

CVD and development of CP with subsequent CVD (6-10). Given equal access to healthcare, AA with T2DM and CKD face lower risks for CVD events than EA (4,5,14,23). In the current report, ACEi, ARB and lipid lowering medications were prescribed nearly equally in AA and EA participants. Previously, biologic factors have been implicated in ethnic disparities in development of kidney failure (24). Ethnic differences in *MYH9* risk allele distribution reveal that inherited factors are capable of causing ethnic differences in incidence in common diseases. It remains possible that other inherited factors contribute to the ethnic differences in development of CP relating to albuminuria.

Markedly lower levels of CP are observed in AA subjects, relative to EA, with and without diabetes mellitus (6-10). Although ethnic differences exist in presence of CP, severity of CP is strongly associated with risk for coronary events among individuals of all ethnic groups. In the Multi-Ethnic Study of Atherosclerosis (MESA), Americans of European, African, Hispanic and Chinese descent demonstrated equivalent risk for CVD events based on level of CP (12). Conventional CVD risk factors may have ethnic-specific effects on risk for CP (20). Therefore, it is important to assess whether ethnic differences in the relationship between albuminuria and CP exist, as AA are known to develop type 2 diabetes-associated nephropathy with resultant albuminuria more often than EA (2). In addition, calcium metabolism clearly differs between AA and EA. Although AA typically ingest less dietary calcium than EA, they have denser bone with lower rates of osteoporosis and skeletal resistance to the effects of parathyroid hormone (25). Related phenomena may prove to be important in development of CP, since vascular endothelial cells assume osteoblastic phenotypes and deposit bone matrix in blood vessels.

Albuminuria markedly increases the risk for CVD in EA with type 2 diabetes (15). The current analyses emphasize the importance of ethnic differences in the effect of albuminuria on risk for CVD. We studied a population of subjects with median 8 year durations of diabetes and diabetes would be expected to magnify atherosclerotic vascular disease. However, there is no *a priori* reason to suspect that the relationship between albuminuria and CP would be different in AA and EA without diabetes. Studies in these individuals remain to be performed. It is possible that the lower levels of CP in African Americans despite presence of similar or more severe conventional CVD risk factors, as well as the differential effects of atherosclerotic risk factors on amounts of CP, relate to inherited factors as CorCP is a heritable trait. The AA-DHS will soon perform Mapping by Admixture Linkage Disequilibrium in an attempt to detect genes underlying development of CP.

Potential weaknesses of this report are reliance on cross-sectional data, a single measurement of albuminuria, and inclusion of solely subjects with diabetes. Equivalent diabetes durations and similar prescription of lipid lowering and proteinuria-reducing medications in AA and EA participants, as well as consistency of CorCP scores when contrasted with other reports, suggest the lack of bias. Albuminuria is both a marker of renal impairment and a sign of systemic endothelial dysfunction. It appears likely that

the balance between these relationships may differ between AA and EA. In the future, it will be important that longitudinal studies clarify the relationship between classic and novel CVD risk factors on ethnic differences in susceptibility to CP. These analyses need to be performed in subjects with and without diabetes.

In conclusion, albuminuria is strongly associated with CP in EA with type 2 diabetes, but not in AA with type 2 diabetes. Ethnic differences in the relationship between CP and albuminuria may contribute to the lower levels of CP and reduced risk for myocardial infarction in AA with diabetes. It remains to be determined whether interventions that reduce albuminuria and preserve renal function will prevent the development of calcified atherosclerotic plaque and reduce CVD rates equally in AA and EA with type 2 diabetes mellitus.

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**Table 1: Demographic characteristics of study population by ethnicity**

Variable	Parameter	European American				African American			
		Urine ACR (mg/g)				Urine ACR (mg/g)			
		<30	30-299	>300	Total	<30	30-299	>300	Total
		(N=593)	(N=196)	(N=46)	(N=835)	(N=237)	(N=114)	(N=42)	(N=393)
Age (years)	Mean (SD)	61.2 (8.9)	62.4 (9.7)	65.4 (8.3)	61.7 (9.1)	56.5 (9.3)	56.9 (10.3)	56.8 (9.7)	56.7 (9.6)
	Median	61	62	65	61.9	57	56	58	57.0
	(p-value) <sup>1</sup>	(1.34x10 <sup>-10</sup> )	(1.05x10 <sup>-5</sup> )	(1.55x10 <sup>-04</sup> )	(8.1x10 <sup>-17</sup> )				
DM duration (years)	Mean (SD)	9.2 (6.6)	11.2 (8.2)	14.7 (8.7)	10.0 (7.3)	9.2 (6.9)	11.9 (8.0)	13 (7.4)	10.4 (7.4)
	Median	7	9	14	8	7	10	13	8
	(p-value)	(0.7)	(0.4)	(0.6)	(0.43)				
BMI (kg/m <sup>2</sup> )	Mean (SD)	32.7 (6.6)	32.9 (7.3)	31.6 (6.4)	32.7 (6.7)	35.3 (7.8)	34.7 (8.1)	34 (9.5)	35 (8.1)
	Median	31.4	32.2	30.5	31.5	34.1	32.6	33.5	33.7
	(p-value)	(8.6 x 10 <sup>-6</sup> )	(0.09 )	(3.05 x 10 <sup>-6</sup> )	(3.8x10 <sup>-6</sup> )				
Systolic BP (mm Hg)	Mean (SD)	137.7 (17.4)	143.4 (18.3)	158.7 (20.0)	140.2 (18.4)	132.5	139.5 (21.4)	154.7 (20.1)	136.9 (20.2)
	Median	136	141	158	139	(17.7)	137.5	151.0	135.0
	(p-value)	(1.08 x 10 <sup>-4</sup> )	(0.04)	(0.03)	(0.002)	131.0			
Diastolic BP (mm Hg)	Mean (SD)	73 (9.6)	73.8 (11.2)	74 (10.0)	74 (10.0)	75.2	76.9 (12.8)	82.7 (10.9)	76.5 (11.9)
	Median	72.5	73.0	74.5	72.5	(11.2)	77	82	76
	(p-value)	(0.02)	(0.04)	(3.29 x 10 <sup>-4</sup> )	(7.1x10 <sup>-6</sup> )	74			
ACEi/ARB	N (%) <sup>2</sup>	266 (44.9)	103 (52.6)	30 (65.2)	399 (47.8)	120 (50.6)	53 (46.5)	26 (61.9)	199 (50.6)
	(p-value) <sup>3</sup>	(0.71)	(0.85)	(0.21)	(0.72)				
Lipid meds	N (%)	244 (41.5)	89 (45.6)	24 (53.3)	357 (43.1)	112 (47.7)	52 (45.6)	24 (58.5)	188 (48.2)
	(p-value) <sup>3</sup>	(0.74)	(0.70)	(0.48)	(0.57)				
Insulin	N (%)	126 (21.3)	60 (30.6)	17 (37.0)	203 (24.3)	95 (40.3)	49 (43.0)	25 (59.5)	169 (43.1)
	(p-value) <sup>3</sup>	(2.3x10 <sup>-8</sup> )	(0.03)	(0.03)	(2.3x10 <sup>-11</sup> )				
Smoking	Former	210 (42.5)	57 (35.2)	16 (41.1)	283 (40.7)	81 (38)	29 (28.2)	14 (34.2)	124 (34.7)
	Current	72 (14.6)	27 (16.7)	10 (25.6)	109 (15.7)	52 (24.4)	22 (21.3)	12 (29.3)	86 (24.1)
	Never	212 (42.9)	78 (48.1)	13 (33.3)	303 (43.6)	80 (37.6)	52 (50.5)	15 (36.6)	147 (41.2)
	(p-value) <sup>4</sup>	(0.01)	(0.72)	(0.96)	(0.02)				

<sup>1</sup>: P-value for the Wilcoxon rank statistic testing for equality of the median of each variable between European and African Americans at each level of ACR.

<sup>2</sup>: (%) for each variable reflects the available sample size.

<sup>3</sup>: P-value for the association between each categorical variable and race.

<sup>4</sup>: P-value for the Armitage trend test for association between smoking status and race.

**Table 2. Laboratory characteristic of the study population by ethnicity**

Variable	Parameter	European American				African American			
		Urine ACR (mg/g)				Urine ACR (mg/g)			
		<30 (N=593)	30-299 (N=196)	≥300 (N=46)	Total (N=835)	<30 (N=237)	30-299 (N=114)	≥300 (N=42)	Total (N=393)
eGFR (mL/sec)	Mean (SD)	1.16 (0.30)	1.11 (0.33)	0.95 (0.38)	1.14 (0.32)	1.45 (0.46)	1.44 (0.44)	1.06 (0.45)	1.40 (0.47)
	Median	1.11	1.07	0.84	1.09	1.38	1.31	1.01	1.34
	(p-value) <sup>1</sup>	(2.8x10 <sup>-18</sup> )	(5.3x10 <sup>-9</sup> )	(0.16)	(6.3x10 <sup>-22</sup> )				
Serum creatinine (umol/L)	Mean (SD)	92.8 (22.1)	97.2 (23.9)	118.5 (41.6)	94.6 (24.8)	89.3 (28.3)	88.4 (24.8)	124.6 (64.5)	92.8 (34.5)
	Median	88.4	97.2	114.9	88.4	88.4	88.4	106.1	88.4
	(p-value) <sup>1</sup>	(0.02)	(0.003)	0.64	(0.003)				
Fasting blood sugar (mmol/L)	Mean (SD)	7.96 (2.9)	8.71(3.4)	9.76 (4.2)	8.24 (3.1)	7.83 (3.0)	10.0 (4.7)	11.27 (5.1)	8.82 (4.0)
	Median	7.33	7.96	8.80	7.49	7.27	9.05	10.55	7.94
	(p-value) <sup>1</sup>	(0.42)	(0.01)	(0.11)	(0.05)				
HbA1c (proportion of total)	Mean (SD)	0.075 (0.02)	0.078 (0.02)	0.085 (0.02)	0.076 (0.02)	0.081 (0.02)	0.090 (0.03)	0.094 (0.02)	0.085 (0.02)
	Median	0.071	0.074	0.082	0.072	0.076	0.084	0.093	0.080
	(p-value) <sup>1</sup>	(9.1x10 <sup>-6</sup> )	(1.8x10 <sup>-5</sup> )	(0.02)	(1.2x10 <sup>-12</sup> )				
Serum calcium (mmol/L)	Mean (SD)	2.33 (0.1)	2.33 (0.1)	2.33 (0.1)	2.33 (0.1)	2.35 (0.1)	2.38 (0.1)	2.30 (0.1)	2.35 (0.1)
	Median	2.33	2.30	2.30	2.33	2.38	2.40	2.30	2.38
	(p-value) <sup>1</sup>	(1.6x10 <sup>-4</sup> )	(5x10 <sup>-5</sup> )	(0.55)	(1.4x10 <sup>-6</sup> )				
Serum phosphorus (mmol/L)	Mean (SD)	1.07 (0.2)	1.07 (0.2)	1.10 (0.2)	1.07 (0.2)	1.10 (0.2)	1.10 (0.2)	1.16 (0.3)	1.10 (0.2)
	Median	1.07	1.07	1.07	1.07	1.10	1.10	1.13	1.10
	(p-value) <sup>1</sup>	(0.003)	(0.26)	(0.20)	(7.5x10 <sup>-4</sup> )				
Coronary CP	Mean (SD)	1165 (2378)	1511 (2813)	1686 (2111)	1277 (2479)	603 (1507)	771 (1678)	1028 (2244)	697 (1649)
	Median	213	411	884	291	37.8	62.5	219.5	53.5
	(p-value) <sup>1</sup>	(2.5x10 <sup>-10</sup> )	(5.4x10 <sup>-5</sup> )	(0.001)	(2.39x10 <sup>-14</sup> )				
Coronary CP >0%	N (%)	519 (93.2)	174(92.1)	44(100)	737(93.3)	187(79.9)	92(82.1)	37(90.2)	316(81.7)
	(p-value) <sup>3</sup>	(3.8x10 <sup>-8</sup> )	(0.009)	(0.03)	(1.0x10 <sup>-9</sup> )				
Carotid CP	Mean (SD)	244 (627)	334 (660)	407 (524)	275 (631)	138 (463)	211 (749)	236 (550)	170 (569)
	Median	23.5	78.5	202	35.5	0.5	8.5	48	3
	(p-value) <sup>1</sup>	(7.7x10 <sup>-8</sup> )	(7.2x10 <sup>-5</sup> )	(0.002)	(8.2x10 <sup>-11</sup> )				
Carotid CP > 0%	N (%)	395 (72)	148 (78.7)	41 (93.2)	584 (74.8)				
	(p-value) <sup>3</sup>	(9.7x10 <sup>-9</sup> )	(0.003)	(0.01)	(3.1x10 <sup>-10</sup> )	118 (50.6)	70 (63.1)	30 (73.2)	218(56.6)
Aorta CP	Mean (SD)	8478 (13192)	12383 (16691)	14201 (13692)	9803 (14339)	4009 (7509)	6355 (13422)	6105 (8593)	4934 (9856)
	Median	2751	4470	10194	3237	713	742	2053	761
	(p-value) <sup>1</sup>	(7.7x10 <sup>-8</sup> )	(7.06x10 <sup>-5</sup> )	(0.002)	(1.03x10 <sup>-14</sup> )				
Aorta CP > 0%	N (%)	388 (95.1)	148 (95.5)	32 (100)	568 (95.5)	170 (80.6)	95 (86.4)	29 (87.9)	294 (83.1)
	(p-value) <sup>3</sup>	(9.0 x10 <sup>-9</sup> )	(0.008)	(0.04)	(1.5x10 <sup>-11</sup> )				

HDL (mmol/L)	Mean (SD)	1.10 (0.3)	1.11 (0.3)	1.14 (0.3)	1.11 (0.3)	1.26 (0.4)	1.19 (0.4)	1.33 (0.4)	1.25 (0.4)
	Median	1.06	1.04	1.11	1.06	1.19	1.17	1.35	1.19
	(p-value) <sup>1</sup>	(5.2x10 <sup>-9</sup> )	(0.03)	(0.01)	(1.9 x10 <sup>-11</sup> )				
LDL (mmol/L)	Mean (SD)	2.70 (0.8)	2.78 (0.9)	2.78 (0.9)	2.72 (0.8)	2.81 (0.9)	2.86 (1.0)	3.26 (1.3)	2.87 (1.0)
	Median	2.64	2.72	2.69	2.64	2.82	2.72	3.06	2.80
	(p-value) <sup>1</sup>	(0.12)	(0.65)	(0.09)	(0.03)				
TG (mmol/L)	Mean (SD)	2.34 (1.5)	2.47 (1.7)	2.82 (2.0)	2.40 (1.6)	1.28 (0.7)	1.81 (2.1)	1.88 (1.4)	1.50 (1.4)
	Median	1.99	2.05	2.31	2.00	1.07	1.32	1.62	1.14
	(p-value) <sup>1</sup>	(6.3 x10 <sup>-34</sup> )	(1.8 x10 <sup>-8</sup> )	(0.002)	(2.4 x10 <sup>-40</sup> )				

<sup>1</sup>: P-value for the Wilcoxon rank statistic testing for equality of the median of each variable between European and African Americans at each level of ACR.

<sup>2</sup>: (%) for each variable reflects the available sample size. <sup>3</sup>: P-value for the association between each categorical variable and race.

**Table 3. Relationships between albuminuria and calcified atherosclerotic plaque**

Vascular Bed	Ethnicity	Adjusted for age and gender				Adjusted for age, gender, BMI and GFR			
		Main effect		Ethnic Interaction		Main effect		Ethnic Interaction	
		Estimate	P-value	Estimate	P-value	Estimate	P-value	Estimate	P-value
Aorta	African American	0.17	5.1x10 <sup>-2</sup>	-0.08	0.42	0.13	1.9x10 <sup>-1</sup>	-0.11	0.34
	European American	0.26	7.3 x10 <sup>-6</sup>			0.28	3.5 x10 <sup>-6</sup>		
Carotid Artery	African American	0.18	6.0 x10 <sup>-3</sup>	-0.13	0.12	0.14	7 x10 <sup>-2</sup>	-0.13	0.06
	European American	0.31	1.0 x10 <sup>-9</sup>			0.33	1.0 x10 <sup>-10</sup>		
Coronary Artery	African American	0.16	1.1 x10 <sup>-2</sup>	-0.02	0.84	0.11	1.4 x10 <sup>-1</sup>	-0.05	0.53
	European American	0.18	1.0 x10 <sup>-4</sup>			0.19	4.7 x10 <sup>-5</sup>		
First Principal Component for Aorta, Carotid and Coronary Artery Calcified Plaque#	African American	-0.02	5.8 x10 <sup>-2</sup>	0.03	0.03	-0.01	3.3 x10 <sup>-1</sup>	0.03	0.01
	European American	-0.04	4.3 x10 <sup>-8</sup>			-0.04	3.4 x10 <sup>-8</sup>		

#Box-Cox transformation suggested using a decreasing function of the principal component. Therefore, direction indicated by the sign of the parameter estimate for relationships between parameters and CP should be inverted when reverting to the original scale.

**Table 4. Generalized estimating equation for the first principal component of aorta, carotid and coronary artery calcified plaque#**

Parameter	Level	African American			European American			Ethnic Interaction (African American : European American)*		
		Estimate	SE	P-value	Estimate	SE	P-value	Estimate	SE	P-value
Intercept		1.8343	0.2499	2.15E-13	1.5561	0.2234	3.31E-12	---	---	---
Log ACR		-0.0068	0.0110	0.54	-0.0387	0.0079	8.34E-07	0.03	0.01	0.01
Age		-0.0165	0.0024	0.00	-0.0142	0.0018	1.55E-15	-0.002	0.00	0.54
Gender	Female	-0.0339	0.0379	0.37	0.1460	0.0293	6.4E-07	-0.18	0.05	0.0001
BMI		0.0019	0.0022	0.37	-0.0016	0.0021	0.45	0.0035	0.0029	0.22
Diastolic BP		-0.0012	0.0022	0.59	0.0040	0.0017	0.02	-0.0039	0.0027	0.14
Systolic BP		0.0006	0.0013	0.63	-0.0005	0.0010	0.58	0.0008	0.0015	0.58
eGFR		0.0004	0.0007	0.61	-0.0003	0.0008	0.73	-0.001	0.0010	0.29
ACEi-ARB		-0.0921	0.0534	0.08	-0.0396	0.0366	0.28	-0.005	0.04	0.90
LDL		-0.0007	0.0005	0.11	0.0000	0.0004	0.97	-0.0005	0.0006	0.38
HDL		0.0009	0.0013	0.49	0.0004	0.0012	0.75	0.001	0.0017	0.49
HbA1c		0.0016	0.0055	0.77	-0.0122	0.0086	0.16	0.008	0.01	0.24
smoking	Never	0.2050	0.0418	4.69E-07	0.1860	0.0369	2.31E-07	-0.0064	0.0571	0.91
smoking	Former	0.1001	0.0473	0.03	0.1250	0.0341	1.23E-04	-0.0397	0.0605	0.51

#Box-Cox transformation suggested using a decreasing function of the principal component. Therefore, direction indicated by the sign of the parameter estimate for relationships between parameters and CP should be inverted when reverting to the original scale.

\* Except gender comparison; testing the interaction between African American females vs. others

ACR = urine albumin:creatinine ratio; BMI = body mass index; BP = blood pressure; eGFR = estimated glomerular filtration rate; ACEi-ARB = use of angiotensin converting inhibitors or angiotensin receptor blockers; LDL = low density lipoprotein; HDL = high density lipoprotein; HbA1c = hemoglobin A1c.