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APOL1 associations with nephropathy, atherosclerosis, and all-cause mortality in African Americans with type 2 diabetes

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Abstract

Albuminuria and reduced eGFR associate with two apolipoprotein L1 gene (*APOL1*) variants in non-diabetic African Americans. Whether *APOL1* associates with subclinical atherosclerosis and survival remains unclear. To determine this, 717 African American-Diabetes Heart Study participants underwent computed tomography to determine coronary artery, carotid artery, and aorta calcified atherosclerotic plaque mass scores in addition to the urine albumin:creatinine ratio (UACR), eGFR, and C-reactive protein. Associations between mass scores and *APOL1* were assessed adjusting for age, gender, African ancestry, BMI, HbA1c, smoking, hypertension, use of statins and ACE inhibitors, albuminuria, and eGFR. Participants were 58.9% female with mean age 56.5 years, eGFR 89.5 ml/min/1.73m^2, UACR 169.6 mg/g, coronary artery, carotid artery and aorta calcified plaque mass scores of 610, 171 and 5378, respectively. In fully adjusted models, *APOL1* risk variants were significantly associated with lower levels of carotid artery calcified

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plaque (β −0.42, SE 0.18, dominant model), and marginally lower coronary artery plaque (β −0.36, SE 0.21; dominant model), but not with aorta calcified plaque, C-reactive protein, UACR, or eGFR. After a mean follow-up of 5.0 years, 89 participants died. *APOL1* nephropathy risk variants were significantly associated with improved survival (hazard ratio 0.67 for 1 copy; 0.44 for 2 copies). Thus, *APOL1* nephropathy variants associate with lower levels of subclinical atherosclerosis and reduced risk of death in African Americans with type 2 diabetes mellitus.

Keywords

African Americans; apolipoprotein L1 gene (*APOL1*); atherosclerosis; calcified atherosclerotic plaque; diabetes mellitus; kidney disease

Introduction

Chronic kidney disease (CKD) and cardiovascular disease (CVD) are confounded disorders; each predisposes to and exacerbates the other.[1;2] Jackson Heart Study (JHS) and Women's Health Initiative (WHI) investigators reported that apolipoprotein L1 gene (*APOL1*) nephropathy variants were significantly associated with higher rates of CVD, after adjusting for CKD.[3] Paradoxically, JHS also reported that lower levels of coronary artery calcified atherosclerotic plaque (CAC) were present in those who had two *APOL1* nephropathy risk variants. CAC typically associates with higher rates of CVD, an observation that holds true in many populations including individuals affected by type 2 diabetes mellitus (T2D).[4] In fact, CAC scores can improve the Framingham risk prediction model for CVD in patients with T2D, although they are less useful in individuals known to be at very high or very low risk.[5;6]

Genetic studies can provide an opportunity to clarify complex clinical scenarios such as this. For example, putative hypertension-attributed end-stage kidney disease (ESKD) in African Americans (AAs) proved to be associated with two coding variants in *APOL1*; risk variants that are virtually absent in populations of European ancestry.[7;8] *APOL1* association reveals that this form of ESKD, which occurs more often in AAs, resides in the focal segmental glomerulosclerosis spectrum with secondary hypertension.[9–11] In contrast to *APOL1*-mediated biologic risk for non-diabetic CKD in AAs, European Americans (EAs) have enhanced biologic risk for CVD. This is evident for the subclinical phenotype of calcified atherosclerotic plaque (CP) and incidence rates of myocardial infarction (MI). Despite exposure to more severe conventional CVD risk factors than EAs, AAs have substantially lower levels of CP and 50% lower rates of MI when provided equivalent access to healthcare.[12–19] AAs are an admixed population group, with approximately 80% African and 20% European ancestry. AAs with the highest levels of CAC have higher proportions of European ancestry, demonstrating that European ancestry underlies risk for atherosclerosis and African ancestry is relatively protective.[20;21]

The association between *APOL1* variants with reduced levels of CAC in JHS, despite paradoxically higher risk for CVD warrants additional investigation. Associations between *APOL1* risk variants and C-reactive protein (CRP), CP in the coronary arteries (CAC), carotid arteries, and aorta, nephropathy, and all-cause mortality were assessed in AAs with

T2D from the African American-Diabetes Heart Study (AA-DHS) and Diabetes Heart Study (DHS).

Results

The study sample consisted of 717 participants with T2D. Of these, 533 were unrelated, 69 families had 2 sibs, 11 had 3 sibs, 2 had 4 sibs, and 1 had 5 sibs. The frequencies of individuals with 0, 1, and 2 *APOL1* nephropathy risk alleles, respectively, were 38.5%, 48.8%, and 12.7%, similar to those in general AA populations. T2D duration prior to enrollment was 10.3±8.1 years in unrelated AA-DHS participants and 10.7±7.8 years in family-based DHS participants.

Table 1 contains demographic and laboratory data based on number of *APOL1* nephropathy variants. Overall, participants had a mean±SD age of 56.5±9.6 years and 58.9% were female. T2D duration was 10.4±8.0 years, CKD-EPI (Epidemiology) equation-estimated glomerular filtration rate (eGFR) 89.5±27.8 ml/min/1.73m^2, urine albumin:creatinine ratio (UACR) 169.6±609 mg/g (median 13.9 mg/g), CAC mass score 610.2±1421.5 (median 44), carotid artery CP mass score 171.8±531.4 (median 4.5), and aorta CP mass score 5378.2±10235.5 (median 1023). Women had significantly higher body mass index (BMI) and levels of CRP, HDL and LDL cholesterol; whereas men had higher levels of CAC, eGFR and more current and former smokers. The proportion of African ancestry varied from 0.1 to 1 with an inter-quartile range (IQR) of 0.23 in individuals carrying 0 copies of *APOL1* risk variants, between 0.09 and 1 (IQR 0.21) in individuals carrying 1 copy of an *APOL1* risk variant, and between 0.3 and 1 in *APOL1* 2 risk variant carriers (IQR 0.17). The mean, standard deviation and median for each group is given in Table 1. The distribution of African ancestry proportion was not statistically different between these 3 groups (p=0.11).

In models adjusting for age, sex, ancestry, hemoglobin (Hb) A1c, BMI and angiotensin converting enzyme inhibitor/angiotensin receptor blocker (ACEi/ARB) medications, *APOL1* variants were not significantly associated with albuminuria or kidney function in this diabetic sample (Table 2). *APOL1* variants were significantly and negatively associated with carotid artery CP (parameter estimate [β]=−0.42, SE=0.18, p=0.02) and trended toward negative association with CAC (β=−0.36, SE=0.21; p=0.08) in dominant genetic models adjusting for age, sex, ancestry, HbA1c, BMI, smoking, hypertension, ACEi/ARB and statin medications, eGFR, and UACR. No associations were detected with aorta CP or CRP.

After mean follow-up of 5.0±1.9 years, 89 of 717 AA-DHS participants had died; 43.8% (39/89) of deaths were in those with 0 risk variants; 47.2% (42/89) in those with 1 risk variant, and 9.0% (8/89) in those with 2 risk variants. The survival analysis revealed a significant inverse relationship between death and the number of *APOL1* risk variants (hazard ratio=0.67 for 1 copy and 0.44 for 2 copies of the *APOL1* risk variants; SE=0.14, p=0.005 [additive genetic model]; Figure 1). This analysis also showed a lower rate of death with female gender (β=−0.93; SE=0.21, p=1.4×10^{-5}) and higher eGFR (β −0.02; SE=0.005, p=0.0002) (Table 3). A higher rate of death was seen with presence of hypertension (β=1.31; SE=0.4, p=0.01) and smoking (β=0.33; SE=0.4, p=0.01).

Discussion

This analysis in AAs with T2D confirms negative relationships between *APOL1* nephropathy risk variants and subclinical atherosclerosis as reported by the JHS, with significant effects in the carotid arteries and a trend in the coronary arteries.[3] In contrast to the JHS, where paradoxically *higher* rates of CVD were observed with *APOL1* variants (despite the association with *lower* CAC), we observed improved participant survival based on the number of *APOL1* risk variants, a finding consistent with the known impact of subclinical atherosclerosis on CVD.[4] As such, our data supports that *APOL1* nephropathy risk variants protect from subclinical atherosclerosis and death in AAs with T2D. The JHS sample was larger than AA-DHS with 1959 AAs; the numbers with cardiac imaging for CAC were not specified.[3] In addition, JHS assessed effects of *APOL1* on adjudicated CVD events, while AA-DHS assessed effects on all-cause mortality.

A role for *APOL1* nephropathy variants in kidney disease was present in subjects with diabetes in the Chronic Renal Insufficiency Cohort (CRIC); the G1 and G2 risk variants contributed to nephropathy progression in CRIC participants both with and without hyperglycemia.[22] In contrast, no association exists between chromosome 22q region nephropathy risk variants and diabetic ESKD, including the E1 haplotype of the non-muscle myosin heavy 9 chain gene (*MYH9*) which is in strong linkage disequilibrium with *APOL1* G1 and G2 and serves as a useful surrogate.[9;23;24] AA-DHS results support that diabetic kidney disease in AAs does not reside in the *APOL1* spectrum of CKD (Table 2).

The present analysis was less likely than the JHS to have been impacted by effects of *APOL1* on risk for nephropathy. AA-DHS enrolled participants with T2D with a focus on susceptibility to CVD.[25] As evidenced by the mean eGFR of 89.5 ml/min/1.73 m^2, AA-DHS participants had minimal to absent CKD. Those with end-stage kidney disease (ESKD) or known serum creatinine concentrations ≥2 mg/dl were not targeted for recruitment. Based on the significant association between *APOL1* and CKD in the JHS and WHI, it is possible that effects of *APOL1* risk variants on CVD may be better assessed in the AA-DHS where there was no association with CKD. It is unclear what mechanism(s) could underlie *higher* CVD event rates in JHS participants with two *APOL1* risk variants, despite association with lower levels of CAC.[3] The African American Study of Kidney Disease and Hypertension (AASK) reported significant association between *APOL1* risk variants and the composite end-point of ESKD or doubling of serum creatinine concentration (roughly equivalent to a halving of eGFR).[26] In AASK, *APOL1* was not found to be significantly associated with participant survival, despite markedly lower baseline kidney function and nearly ten year follow-up.[10;22] Despite the markedly lower baseline kidney function in AASK participants (relative to AA-DHS, JHS and WHI), which should have produced far higher risk for CVD, the vast majority of AASK participants met a renal end-point and few deaths were recorded.[27] Only 59 CVD deaths were recorded in AASK and ~70% of the study sample was genotyped; hence, there may have been reduced power to detect an effect. A major difference between AASK and both the JHS and WHI is that individuals with T2D were excluded from AASK. Approximately 25% of JHS and WHI participants had diabetes. As such, the uniformly T2D-affected AA-DHS cohort provides an important contrast.

Relative to European ancestry, African ancestry is protective from development of CP.[20;21] Beyond the known confounding effects of CKD on risk for CVD in JHS and WHI, the effect of overall African ancestry on CP and clinical events such as MI and CVD-related deaths needs to be considered. We note that African ancestry proportion was negatively, but not significantly associated with time to death in AA-DHS participants (p=0.075 unadjusted; p=0.30 model adjusted for age, sex, diabetes duration, HbA1c, BMI, hypertension, lipid medications, urine ACR and eGFR [data not shown]). The consistency of our *APOL1* association with both lower carotid artery CP (and trend towards lower CAC) and improved survival was reassuring. We note that despite significant association of *APOL1* with baseline CKD, CVD events were not different in AA Systolic Pressure Reduction Intervention Trial (SPRINT) participants based on *APOL1* genotypes.[28] Results in the AA-DHS, AASK and SPRINT fail to support excessive rates of CVD based upon *APOL1* nephropathy variants.

Strengths of the present analysis include intensive phenotyping for CVD risk factors, non-invasive measurement of CP in three vascular beds, and complete follow-up for death. Compared to coronary and carotid arteries, levels of CP in the aorta are far higher. As such, discriminatory power to detect association in this bed is reduced. Limitations were that we did not determine whether participants had a MI or stroke post-enrollment or collect death certificates to assess whether CVD was a contributor to death. Death certificates are frequently inaccurate.[29] In addition, CVD-related deaths are known to occur frequently in individuals with T2D.[30] The present analyses relied on surrogate markers of CVD risk (calcified atherosclerotic plaque) and the hard-end point of all-cause mortality, not directly measured CVD events. There was no consistent mode of inheritance of *APOL1* in the significant results. Unfortunately, we only have data on a small subset of siblings which made it difficult to assess the inheritance pattern through familial data; correlations among CP in the three vascular beds ranged from 0.49 to 0.59, yielding R^2 values between 0.25 and 0.35. These proportions of variance are low enough to suggest that other factors likely contribute to relationships with CP in these vascular beds. Therefore, different modes of inheritance with *APOL1* are not entirely unexpected.

We confirm a protective effect of *APOL1* nephropathy risk variants on development of CP in the carotid arteries (with a similar trend in the coronary arteries) in AAs with T2D. In addition, *APOL1* risk variants were associated with a lower risk of death in this cohort, potentially related to lower levels of CP. Our results contrast with those from the JHS and WHI reporting an increased risk for CVD in carriers of two *APOL1* risk variants, but are consistent with results in the AASK and baseline results in SPRINT. Since these results differ from those reported by Ito *et al.*[3] demonstration of a similar effect in other cohorts is required before concluding that *APOL1* renal risk alleles associate with lower mortality in AAs with T2D. We believe it may be premature to conclude that *APOL1* imparts an increased risk for MI and CVD, independent of confounding effects from presence of CKD and albuminuria in AA populations.

Methods

Study Population

Analyses were performed in all unrelated AA-DHS participants, as well as AA siblings concordant for T2D recruited in the DHS.[21] T2D was diagnosed based upon age at onset ≥30 years, in the absence of historical evidence of diabetic ketoacidosis. Participants were actively receiving insulin and/or oral hypoglycemic agents; those with prior MI and strokes were enrolled. Studies were approved by the Institutional Review Board at the Wake Forest School of Medicine (WFSM) and all participants provided written informed consent.

A clinical examination was conducted in the WFSM General Clinical Research Center, including completion of medical questionnaires, measurement of vital signs and clinical chemistries. Fasting glucose, HbA1c, lipid profiles, and UACR were performed at LabCorp, Burlington, NC (methods: www.labcorp.com). High sensitivity CRP was measured in the WFSM Hypertension Center Core Laboratory using an enzyme-linked immunosorbent assay (Alpco Immunoassays; Salem, NH). History of CVD was provided by self-report and chart review. Estimated GFR was computed with the creatinine-based CKD-EPI equation.[31] Hypertension was diagnosed if listed in medical records, participants were treated with anti-hypertensive medications, or blood pressure >140/90 at the study visit. The Social Security Death Index was queried through February 5, 2014 to capture deaths.

Vascular Imaging

As previously reported, CP was measured in the coronary and carotid arteries and infrarenal abdominal aorta using single and multi-detector CT systems incorporating a standardized scanning protocol based on those currently implemented in the National Heart Lung and Blood Institute's Multi-Ethnic Study of Atherosclerosis (MESA).[21;32] Measures of CAC in participants who underwent coronary artery bypass graft surgery (N=21) and carotid artery CP in those who underwent carotid endarterectomy (N=2) were excluded, since scores could be altered by these procedures.

Typically, the traditional Agatston unit (Calcium Score) has been reported; however, compared to volume based measures of CP this system adds noise to CT measures. This report used the calcium mass score based on the milligrams of calcium hydroxyapatite (SmartScore, General Electric [GE] Healthcare, Waukesha, WI) within the plaque and is calculated from the plaque volume score calibrations of the CT number to calcium mass on a pixel by pixel basis. The mass score provides a direct comparison of the amount of CP in each of the vascular territories. Score parameters included a 90 Hounsfield Unit threshold and two adjacent pixels to define the minimum calcified lesion size. The reproducibility of CP measures obtained from sequential scans, as well as the inter- and intra-observer variability in performing the analysis exceeded 0.96.

Genotyping

Two single nucleotide polymorphisms (SNPs) in the *APOL1* G1 nephropathy risk allele (rs73885319; rs60910145) and an insertion/deletion polymorphism for the G2 risk allele (rs71785313) were genotyped in subjects using a custom assay designed in the Center for

Genomics and Personalized Medicine Research at WFSM on the Sequenom platform (San Diego, California). Of the 26 blind duplicates that were genotyped only one was found to be discordant, for a 99.98% concordance rate. The G1 and G2 genotype calls were visually inspected for quality control. One hundred and six bi-allelic ancestry informative markers were genotyped to provide African ancestry proportion estimates. The maximum likelihood approach of Tang *et al*. as coded in the package frequentist estimation of individual ancestry proportion (FRAPPE) was used to obtain the proportion of African and European ancestry in each individual.[33] Genotype data at these markers were obtained from 44 HapMap Yoruba individuals (YRI) and 39 EA controls as anchors and provided starting values for the Expectation-Maximization algorithm in FRAPPE.

Statistical Analyses

Unadjusted comparisons between continuous outcomes were performed using the Wilcoxon two sample test while chi-square tests were used for binary outcomes. Genetic association tests were performed on the 717 AA-DHS participants with *APOL1* variants as the main predictor. The Box-Cox method was applied to identify the appropriate transformation best approximating the distributional assumptions of conditional normality and homogeneity of variance of the residuals.[34] This method suggested taking the natural logarithm of (CAC+1), (carotid artery CP+1), (aorta CP+1), (UACR+1), the square root of the cube of CRP, and no transformation for CKD-EPI eGFR. Linear mixed models were fitted to account for the familial relationship between siblings. The kinship coefficient matrix was estimated using Illumina 5M genome-wide association study (GWAS) data available in these samples. The linear model that we applied is akin to Zhou & Stephens GEMMA model.[35] Associations between *APOL1* and renal disease (UACR and eGFR) were adjusted for age, sex, ancestry, HbA1c, BMI, and ACEi/ARB medications. Associations with CP and CRP were further adjusted for smoking status, hypertension, statin medications, UACR, and eGFR. Covariates were selected to limit confounding effects and ensure that reported effects were not due to other variables not accounted for in the model. Therefore, variables that have previously been associated with these outcomes were included in these models as covariates while controlling the degree of co-linearity. Parameter estimates and corresponding confidence intervals, standard errors, and p-values are provided in Table 2. Proportional hazards models were used to assess the association between *APOL1* variants and time to death following study enrollment. Survival analyses were restricted to 8 years post-enrollment to allow uniform follow-up (participants in AA-DHS had maximum 8 year follow-up). Participants surviving 8 years after enrollment were censored. Cox's proportional hazard model was used to fit the data.[36] Adjustment for familial relationships was performed using Lin's (citation) sandwich estimator.[37] The parameter estimates, hazard ratios and their corresponding confidence intervals are provided in Table 3. Analyses were also repeated on the subset of unrelated (independent) individuals, as previously performed.

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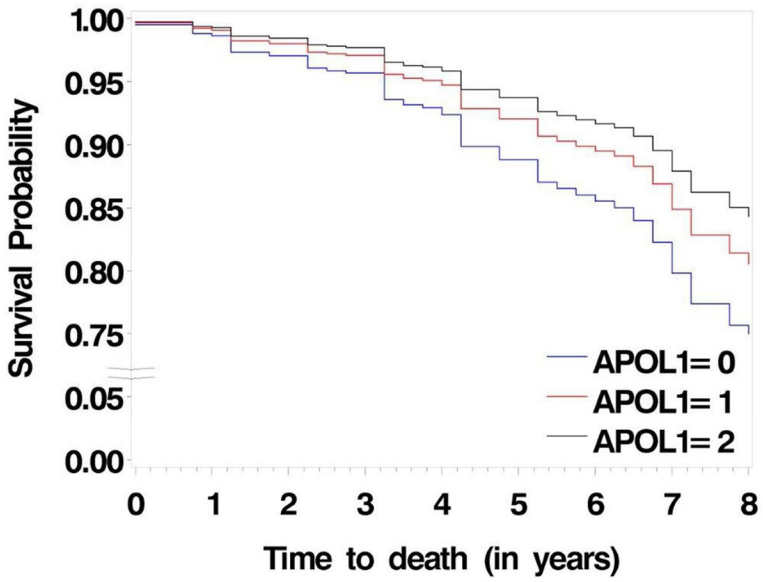

Figure 1.
Kaplan Meier survival curves by the number of *APOL1* nephropathy risk variants.

Table 1

Demographic and laboratory characteristics of the AA-DHS study sample

Variable	0 *APOL1* risk variants (N=276)		1 *APOL1* risk variant (N=350)		2 *APOL1* risk variants (N=91)		P-value
	Mean±SD	Median	Mean±SD	Median	Mean±SD	Median	
Age (years)	56.2±10.1	55.0	56.8±9.0	56.0	56.4±10.2	58.0	0.64
Diabetes duration (years)	10.4±7.9	8.0	10.5±7.9	9.0	10.3±8.6	8.0	0.75
Hemoglobin A1c (%)	8.2±2.0	7.7	8.2±2.1	7.7	8.4±2.4	7.8	0.81
High sensitivity CRP (mg/dl)	0.9±1.5	0.4	1.0±1.4	0.5	0.9±1.2	0.5	0.81
Fasting glucose (mg/dl)	160.0±75.6	143.0	149.1±65.4	134.0	144.7±60.9	127.0	0.15
HDL- cholesterol (mg/dl)	46.8±14.0	45.0	48.9±14.0	47.0	45.8±14.0	42.0	0.04
LDL- cholesterol (mg/dl)	109.4±37.6	107.0	107.4±38.1	103.0	107.2±33.0	102.0	0.61
Triglycerides (mg/dl)	130.7±142.8	100.0	125.9±74.1	108.0	132.2±173.8	97.0	0.35
BMI (kg/m2)	35.0±9.1	33.6	35.1±8.0	33.6	35.5±9.1	33.9	0.80
Survival time (years)	5.0±1.9	5.0	4.9±1.9	5.0	5.3±1.8	5.0	0.17
Yoruban ancestry (%)	0.73±0.16	0.76	0.75±0.16	0.76	0.77±0.14	0.80	0.11
Aorta CP >10 (%)	79.2%		81.5%		75.3%		0.63
Aorta CP (mass score)	6760.7±13375.0	968.0	4287.4±7062.0	979.0	5388.4±9070.8	1249.0	0.94
Carotid artery CP (mass score)	231.2±715.0	7.5	128.0±349.1	2.0	157.9±430.3	5.8	0.08
Carotid artery CP >10 (%)	60.9%		53.7%		60.5%		0.17
Coronary artery CP (mass score)	706.8±1553.2	56.0	555.8±1392.01	45.0	519.8±1047.9	18.0	0.17
Coronary artery CP >10 (%)	65.0%		62.6%		53.0%		0.14
Urine albumin:creatinine ratio (mg/g)	4.0±0.3	4.0	4.0±0.4	4.0	4.0±0.3	4.1	0.63
Serum creatinine (mg/dl)	1.0±0.4	0.9	1.0±0.3	1.0	1.1±0.4	1.0	0.05
CKD-EPI eGFR (ml/min/1.73m2)	92.5±30.1	89.7	88.1±26.1	87.1	85.8±26.2	82.7	0.10
Hypertension (%)	83.3%		84.2%		80.7%		0.72
Past smoker (%)	32.0%		40.7%		35.2%		0.20
Current smoker (%)	23.6%		23.2%		25.3%		
ACEi/ARB medication (%)	47.8%		50.6%		46.2%		0.67
Lipid-lowering medication (%)	45.2%		48.1%		47.2%		0.77
Gender(female)	58.7%		60.0%		54.9%		0.67

eGFR – estimated glomerular filtration rate; ACEi/ARB – angiotensin converting enzyme inhibitor/angiotensin receptor blocker

Table 2

Association tests for *APOL1* G1 and G2 variants with kidney phenotypes, subclinical cardiovascular disease and mortality

Variable	Genetic Model	Effect of *APOL1*			
		Beta	SE	P-value	Confidence Interval
Urine albumin:creatinine ratio*	Additive	−0.07	0.10	0.47	(−0.27, 0.13)
	Dominant	−0.09	0.14	0.49	(−0.37, 0.19)
	Recessive	0.14	0.18	0.46	(−0.21, 0.49)
CKD-EPI estimated GFR*	Additive	−2.02	1.12	0.07	(−4.22, 0.18)
	Dominant	−2.42	1.54	0.12	(−5.45, 0.61)
	Recessive	3.01	2.28	0.19	(−1.47, 7.49)
C-reactive protein#	Additive	0.00	0.02	0.90	(−0.04, 0.04)
	Dominant	−0.01	0.02	0.73	(−0.05, 0.03)
	Recessive	−0.01	0.03	0.85	(−0.07, 0.05)
Carotid artery calcified plaque#	Additive	−0.15	0.13	0.27	(−0.41, 0.11)
	Dominant	−0.42	0.18	0.02	(−0.77, −0.07)
	Recessive	−0.29	0.26	0.27	(−0.80, 0.22)
Coronary artery calcified plaque#	Additive	−0.25	0.15	0.10	(−0.54, 0.04)
	Dominant	−0.36	0.21	0.08	(−0.77, 0.05)
	Recessive	0.34	0.29	0.25	(−0.23, 0.91)
Aorta calcified plaque#	Additive	−0.03	0.16	0.87	(−0.34, 0.28)
	Dominant	−0.20	0.22	0.35	(−0.63, 0.23)
	Recessive	−0.30	0.33	0.36	(−0.95, 0.35)
Time to death	Additive	−0.41	0.14	0.005	(−0.69, −0.13)
	Dominant	−0.43	0.19	0.03	(−0.80, −0.06)
	Recessive	−0.72	0.36	0.04	(−1.43, −0.01)

*adjusted for age, sex, ancestry, HbA1c, BMI, ACEi/ARB medications;

#adjusted for age, sex, ancestry, HbA1c, BMI, smoking, hypertension, ACEi/ARB and statin medications, UACR, and estimated GFR, SE – standard error

Table 3

Multivariable analysis of all-cause mortality using Cox proportional hazards regression models

Parameter	Estimate	Standard Error	P-value	Hazard Ratio	Confidence Interval
APOL1 G1 and G2 variants (additive model)	−0.41	0.14	0.005	0.67	(0.50, 0.89)
Diabetes duration	0.02	0.01	0.16	1.02	(0.99, 1.04)
Age	0.001	0.01	0.97	1.00	(0.97, 1.03)
Female gender	−0.93	0.21	1.14×10^{-5}	0.40	(0.26, 0.60)
Hemoglobin A1c	0.07	0.05	0.12	1.08	(0.98, 1.18)
Body mass index	0.00	0.01	0.86	1.00	(0.97, 1.03)
Smoking	0.33	0.12	0.01	1.39	(1.10, 1.76)
Hypertension	1.31	0.40	0.001	3.70	(1.68, 8.16)
Statin medications	−0.21	0.20	0.29	0.81	(0.54, 1.20)
African ancestry	−0.58	0.58	0.32	0.56	(0.18, 1.77)
Urine albumin:creatinine ratio	1.9×10^{-4}	9.1×10^{-5}	0.04	1.00	(1.00, 1.00)
CKD-EPI estimated glomerular filtration rate	−0.02	0.005	0.0002	0.98	(0.97, 0.99)