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APOL1 Nephropathy Risk Alleles and Mortality in African American Adults: A Cohort Study

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Abstract

Rationale & Objective: *APOL1* nephropathy risk alleles are associated with the development of chronic kidney disease (CKD) in African Americans. Although CKD is an established risk factor for mortality, associations of *APOL1* risk alleles with mortality are uncertain.

Study Design: Prospective cohort

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Settings & Participants: 10,380 African-American and 17,485 white-American participants of the REasons for Geographic and Racial Differences in Stroke (REGARDS) study.

Exposures: *APOL1* nephropathy risk alleles

Outcomes: All-cause and cause-specific mortality

Analytical Approach: Cox proportional hazards models were used to examine the association of *APOL1* high-risk genotypes (2 risk alleles) vs. *APOL1* low-risk genotypes (0/1 risk alleles) with all-cause and cause-specific mortality in African Americans; and to examine the risk of all-cause mortality in African Americans with high-risk genotypes vs. African Americans with low-risk genotypes and white Americans.

Results: *APOL1* high-risk participants were younger and had higher prevalence of albuminuria than low-risk participants. There was no statistically significant association of *APOL1* high-risk vs. low-risk genotypes with all-cause mortality in models adjusted for sociodemographic variables, comorbidities and kidney function (HR, 0.88; 95% CI, 0.77-1.01). After further adjustment for genetic ancestry in a subset with available data, a statistically significant association emerged (HR, 0.81; 95%CI, 0.69-0.96). The associations differed by CKD status ($p_{interaction}$ =0.04), with African Americans with high-risk genotypes having lower risk of mortality than those with low-risk genotypes in fully adjusted models (HR, 0.78; 95%CI, 0.62-0.99) among those with CKD, but not those without CKD (HR, 0.84; 95%CI, 0.66-1.05). Compared to white Americans, African Americans with high-risk genotypes had a similar rate of mortality, whereas African Americans with low-risk genotypes had a higher rate of mortality (HR, 1.07; 95%CI, 1.00-1.14) in fully-adjusted models.

Limitations: Lack of follow-up measures of kidney function.

Conclusions: African Americans with high-risk *APOL1* genotypes had lower mortality than those with low-risk genotypes in multivariable-adjusted models including genetic ancestry.

Keywords

apolipoprotein L1 (APOL1); racial/ethnic disparities; chronic kidney disease (CKD); genetic risk factor; African American; risk allele; mortality; *APOL1* genotype; CKD progression; nephropathy; genetic differences; survival

INTRODUCTION

Two coding alleles in the apolipoprotein L1 gene (*APOL1*) are associated with the development and progression of kidney disease in African Americans.[1, 2] Chronic kidney disease (CKD) is an established risk factor for all-cause mortality,[3] suggesting that *APOL1* nephropathy risk alleles may shorten survival in African Americans with high-risk genotypes comprising any combination of the two risk alleles. Consistent with this possibility, a report from the Cardiovascular Health Study (CHS) showed that carriage of high-risk *APOL1* genotypes was associated with higher risk of mortality than carriage of low-risk *APOL1* genotypes (zero or one risk allele).[4] In contrast, other studies showed no differences in mortality[5-7] or paradoxically, longer survival in African Americans with high-risk versus low-risk nephropathy genotypes.[8-10]

The reasons for the inconsistencies in these findings are unclear, but may be related to the characteristics of the study populations being examined. Whereas CHS was a population-based cohort of older adults, the studies finding no or opposite associations of *APOL1* high-risk genotypes with mortality examined individuals who were younger on average and had established CKD or diabetes or both. Prior studies were also limited by having relatively few mortality events, reducing their statistical power to examine the association of *APOL1* nephropathy genotype with survival outcomes within key subgroups. Accordingly, in the current study, we examined the association of *APOL1* nephropathy genotypes with all-cause mortality in 10,380 African-American participants of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. In addition, we examined whether these associations differed by subgroups of baseline kidney disease, diabetes and age.

METHODS

Study Population

The REGARDS study is a population-based investigation of stroke incidence and cognitive function in African Americans and white Americans ≥45 years of age. The study design has been reported elsewhere.[11] Briefly, participants were recruited from the 48 contiguous US states and the District of Columbia. The study oversampled African Americans and persons residing in the stroke belt/buckle regions of the US. Between January 2003 and October 2007, 30,239 individuals were enrolled (42% African American, 55% women). Participants or their proxies were contacted every 6 months by telephone to assess outcomes including death. The REGARDS Study protocol was approved by the Institutional Review Boards governing research in human subjects at the participating centers and all participants provided informed consent.

Genotype Assessment/Primary Exposure

APOL1 alleles (G1 [rs73885319A>G, S342G] and G2 [Rs71785313 TTATAA/–N388Y389/–]) were genotyped in African-American participants using TaqMan SNP Genotyping Assays (Applied Biosystems/ThermoFisher Scientific).[1, 12] *APOL1* high-risk status was defined as the presence of 2 risk alleles (G1/G1, G2/G2, or G1/G2) versus the low-risk status, defined as having 1 or 0 risk alleles (G1/G0, G2/G0, G0/G0), representing a recessive model. A subset of participants had available genomic array data (Illumina exome chip) to estimate population substructure (n=6,714) via principal components generated using EIGENSOFT software.[13, 14]

Outcomes of interest

The primary outcome of interest was all-cause mortality and the secondary outcome of interest was cause-specific mortality. Participants or their proxies were queried every 6 months by telephone for hospitalizations or physician visits. Deaths were detected by report of the next-of-kin or through other sources (Social Security Death Index, National Death Index). All-cause mortality through March 30th, 2017 were available for the current analyses.

To adjudicate cause of death, death certificates, medical records and autopsy reports were obtained and reviewed by trained clinicians.[15] Deaths were reviewed by two adjudicators, and disagreements on the cause of death were decided by committee. For the current study, death was categorized as being related to cardiovascular (defined as death from definite, probable or possible myocardial infarction; stroke; sudden death; heart failure; other cardiac; not cardiac but other cardiovascular; or pulmonary embolism), cancer, or other causes. Adjudication for cause-specific mortality was available through December 31st, 2014.

Covariate data collection at baseline

Data on covariates of interest were collected during a baseline in-home visit (including the collection of a blood and spot urine sample) and a separate computer assisted telephone interview. Information on age, race, sex, smoking status, lipid-lowering drugs and antihypertensive medication use was collected by self-report and review of pill bottles during the in-home visit. Systolic and diastolic blood pressures were defined as the average of two seated blood pressure measures taken after a 5 minute rest. Diabetes was defined as fasting serum glucose ≥126 mg/dL, non-fasting serum glucose ≥200 mg/dL, or use of anti-diabetes medications. Serum creatinine was calibrated to an international isotope dilution mass spectroscopic-traceable standard, measured by colorimetric reflectance spectrophotometry. We calculated eGFR using the CKD-EPI equation.[16] Albumin and creatinine were measured using the random spot urine specimen by nephelometry (BN ProSpec Nephelometer, Dade Behring, Marburg, Germany) and Modular-P chemistry analyzer (Roche/Hitachi, Indianapolis, IN), respectively. Spot urinary albumin-creatinine ratio (UACR) was calculated in mg/g. Abnormal ACR was defined as ACR ≥30 mg/g. Individuals with an eGFR < 60 ml/min/1.73m^2 or an ACR ≥30 mg/g were classified as having CKD at baseline. Serum high sensitivity C-reactive protein (hsCRP) was measured using a high-sensitivity particle-enhanced immunonephelometric assay.

Statistical Analyses

We compared participant characteristics by *APOL1* risk allele count (0 or 1 vs. 2) in African-American participants using the χ^2 test for categorical variables and ANOVA for continuous variables. We calculated incidence rates and 95% confidence intervals of each outcome for each risk category (0 or 1 vs. 2). After confirming the proportionality assumption, Cox proportional hazards models were used to assess the association of *APOL1* high-risk vs. low-risk status (recessive model) with all-cause mortality in sequential models. Model 1 was unadjusted. Model 2 adjusted for age, sex, current smoking, income, diabetes, body mass index, blood pressure, history of coronary heart disease and lipid parameters total cholesterol and HDL-C). Since high-risk *APOL1* genotypes associate with kidney disease, in Model 3 we further adjusted for eGFR and log-transformed ACR to determine whether a potential association of *APOL1* genotype with mortality was in part mediated by kidney disease. Model 4 adjusted for principal components for ancestry in the subset of individuals with available data. Secondary analyses examined the association of *APOL1* risk alleles with all-cause mortality using dominant and additive models, and examined the association of *APOL1* with cause-specific mortality (cardiovascular, cancer or other). In addition, we examined the association of self-reported race with all-cause mortality, with race categorized as white American (reference group), African American with low-risk genotypes, and

African American with high-risk genotypes. In all models, we examined for effect modification by age (above or below the median), diabetes and CKD status on the association of *APOL1* genotypes with all-cause mortality by testing the statistical significance of interaction terms. All analyses were carried out using SAS v. 9.4.

RESULTS

Study population

A total of 10,605 African-American participants had *APOL1* genotype data. After excluding 225 with missing follow-up data, 10,380 African-American participants were available for analysis. Of these, 1,320 had 2 risk alleles (12.7% of the study population).

Association of APOL1 risk status with all-cause mortality

After a mean 8.4 +/− 3.7 (standard deviation) years of follow-up, a total of 2,563 African-American participants died. Table 1 shows baseline characteristics of the study population by *APOL1* genotype. As compared to participants with *APOL1* low-risk genotypes, participants with *APOL1* high-risk genotypes were younger, had a lower mean eGFR, higher median ACR, higher mean total cholesterol concentrations, and a higher incidence of end-stage kidney disease.

Crude incidence rates of all-cause mortality and hazard ratios (HR) of all-cause mortality by *APOL1* risk-status are shown in Table 2. The incidence of all-cause mortality was lower in *APOL1* high-risk as compared to low-risk participants. There was no statistically significant association of *APOL1* genotypes with all-cause mortality in the unadjusted model (HR, 0.90; 95% confidence interval [95%CI], 0.79-1.02); after adjustment for age, sex, current smoking, income, diabetes, body mass index, blood pressure, history of coronary heart disease, total cholesterol, and HDL-C (HR, 0.96; 95%CI, 0.84-1.09); or after further adjustment for eGFR and ACR (HR, 0.88; 95%CI, 0.77-1.01). A statistically significant association emerged after further adjustment for principal components of ancestry in the subset of participants with available data (HR, 0.81; 95%CI, 0.69-0.96). Results were qualitatively similar when analyses were repeated using additive or dominant models (Tables S1 & S2).

The association of *APOL1* genotype with all-cause mortality differed by the presence or absence of CKD ($P_{interaction}$=0.04) but not diabetes ($P_{interaction}$=0.37) or age ($P_{interaction}$=0.67). Baseline characteristics of study participants by *APOL1* genotype and CKD status are presented in Table S3. The risk of all-cause mortality was lower in CKD participants with high-risk vs. low-risk genotypes in the unadjusted analysis, and after adjustment for age, sex, current smoking, income, diabetes, body mass index, blood pressure, history of coronary heart disease, total cholesterol, HDL-C, eGFR, and ACR (HR, 0.78; 95%CI, 0.64-0.95; Table S4). Further adjustment for principal components of ancestry did not meaningfully change the results in the subset of CKD participants with available data (HR, 0.78; 95%CI, 0.62-0.99). The association of high-risk genotypes with mortality was in the same direction but did not reach statistical significance in the fully-adjusted model in

individuals without CKD (HR, 0.84; 95%CI, 0.66-1.05). Results were qualitatively similar when analyses were repeated using additive or dominant models (Tables S5 & S6)

Association of APOL1 genotype with cause-specific mortality

Table 3 presents the association of *APOL1* genotype with cause-specific mortality (cardiovascular vs. cancer vs. other death). There were no statistically significant associations of *APOL1* genotypes with deaths from cardiovascular disease events or cancer. As compared to African Americans with *APOL1* low-risk genotypes, African Americans with *APOL1* high-risk genotypes had a lower risk of death from other causes in the unadjusted model (HR, 0.78; 95%CI, 0.63-0.97), after adjustment for sociodemographic variables, co-morbidities, and kidney function (HR, 0.72; 95%CI, 0.55-0.93), and after further adjustment for principal components of ancestry (HR, 0.62; 95%CI, 0.45-0.86).

Association of race and APOL1 genotype with all-cause mortality

Table S7 depicts the association of race and *APOL1* risk status with all-cause mortality. As compared to white Americans, African Americans with low-risk genotypes had a higher risk of all-cause death in the unadjusted analysis (HR, 1.16; 95%CI, 1.10-1.22) in models adjusted for sociodemographic variables and comorbidities (HR, 1.08; 95%CI, 1.01-1.15), and in models further adjusted for kidney function (HR, 1.07; 95%CI, 1.00-1.14). In contrast, there was no statistically significant difference in mortality comparing African Americans with high-risk genotypes to white Americans in any model.

The association of race with all-cause mortality differed by CKD status ($P_{interaction}$=0.02). In individuals with CKD at baseline, African-American participants with *APOL1* high-risk genotypes had lower mortality than African-American participants with *APOL1* low-risk genotypes and white-American participants in the crude model (Table S8; HR, 0.73; 95%CI, 0.60-0.87) but this association was no longer statistically significant in the multivariable adjusted models. In individuals without CKD at baseline, there were no statistically significant differences in survival in white Americans as compared to African Americans irrespective of *APOL1* genotype status in any models.

Discussion

African Americans with two *APOL1* nephropathy risk alleles are at increased risk of the development and progression of CKD. Kidney disease is the 9th most common cause of death in the US, and likely contributes to many other deaths by increasing the risk of cardiovascular disease. As such, carriage of *APOL1* high-risk genotypes would logically be expected to be linked to an increased risk of death. The results of the current study, and others,[8-10] show opposite findings—African Americans with high-risk genotypes had a similar or lower risk of mortality than African Americans with low-risk genotypes and White Americans. Further, whereas African Americans with low-risk genotypes had a higher risk of mortality than white Americans, no such association was observed when comparing African Americans with high-risk genotypes to white Americans.

Multiple prior studies examined the association of *APOL1* nephropathy risk alleles with mortality, but the results have been inconsistent. A study of 798 African-American and 4964

white-American participants of CHS showed that African Americans with high-risk genotypes had higher risk of all-cause mortality than African Americans with low-risk genotypes or white Americans.[4] In contrast, no association was noted between *APOL1* genotype and survival in the African American Study of Kidney Disease and Hypertension (AASK),[5] the Atherosclerosis Risk in Communities (ARIC) study,[6] or in the Systolic Blood Pressure Intervention Trial (SPRINT).[7] More surprisingly, two separate reports from the African American-Diabetes Heart Study showed that carriage of greater numbers of *APOL1* nephropathy risk alleles was associated with reduced risk of all-cause mortality (whether examining additive, dominant or recessive models).[8, 9] In addition, in a study of African Americans initiating hemodialysis in the Southeastern US, carriage of two *APOL1* nephropathy risk alleles was associated with longer survival than carriage of zero or one risk alleles in those without diabetes, whereas no differences in survival were noted in those with diabetes.[10]

The current study both confirms and contradicts prior findings. Much like the African American-Diabetes Heart Study and the study of African Americans initiating hemodialysis, we found that *APOL1* high-risk genotypes were associated with better, not worse, survival in the fully adjusted models including genetic ancestry. We also found that African Americans with low-risk genotypes had higher risk of mortality than white Americans, whereas no differences in mortality were noted when comparing African Americans with high-risk genotypes to white Americans, opposite to what was reported in CHS. The reasons for these findings are unclear. There is some evidence that carriage of *APOL1* nephropathy risk variants may lower propensity for vascular calcification.[9, 17] In addition, we previously showed that individuals with *APOL1* high-risk genotypes have higher circulating concentrations of HDL subtypes that may protect against atherogenesis.[18] It is important to note, nonetheless, that the protective association of *APOL1* high-risk genotypes was most pronounced for causes of death other than cardiovascular disease or cancer in the current study. This suggests there may be non-traditional pathways by which *APOL1* high-risk alleles are protective, such as via effects on innate immunity that have been largely unexplored beyond known links with trypanosomiasis. It is also important to note that the association of *APOL1* high-risk genotypes with lower all-cause mortality became statistically significant only after adjustment for genetic ancestry in the subset of individuals with available data despite the drop in sample size. The associations of genetic ancestry with complex disease are varied, with some data suggesting that greater African ancestry is protective, whereas other data suggest the opposite.[19-21] It is known that *APOL1* high-risk genotype frequencies vary within African descent populations and adjustment for population substructure revealed confounding for the relationship between *APOL1* and survival in our data. Given heterogeneity in African descent populations in the US and the decrease in our sample size upon adjustment for ancestry, larger studies are needed to investigate this relationship. Finally, some studies have reported a protective relationship between African ancestry and atherosclerotic disease,[22] and although the reduction in all-cause mortality in REGARDS was not driven by cardiovascular disease, future studies are warranted to determine if *APOL1* could contribute to this protective phenomenon.

Unlike prior reports, we did not find that associations of *APOL1* genotypes with mortality differed by diabetes status. Instead, the association of *APOL1* nephropathy risk alleles and

mortality appeared to be stronger in individuals with CKD at baseline than in those without CKD at baseline. We interpret these latter results with caution given the possibility of collider bias—that is, individuals with CKD and high-risk genotypes may represent a healthier subset since their kidney disease is more likely related to carriage of *APOL1* risk alleles than individuals with CKD and low-risk genotypes, whose kidney disease may be more strongly related to a greater burden of comorbidities (diabetes, heart disease, etc.) linked to shortened survival. These findings need to be confirmed in other studies.

Our study had a number of strengths including the large sample size and prospective follow-up, allowing for the capture of a large number of death events and examination of associations within key subgroups. Our study also had limitations. We did not have ancestry informative markers on the entire cohort, which might have strengthened the *APOL1* associations. We could not completely exclude the possibility that our findings could be explained by survival bias (i.e., African Americans with high-risk genotypes who survived long enough to be enrolled in the REGARDS study represent a healthier subgroup than their low-risk genotype counterparts). While possible, there were no major differences in baseline characteristics of the two populations that would suggest that *APOL1* high-risk participants were a much healthier subgroup at the time of their enrollment into the REGARDS study. Another limitation was that we did not have sufficient data on follow-up measures of kidney function, precluding us from examining to what extent differences in the change in eGFR and albuminuria over time impacted the results. Finally, we were not able to determine which causes of death in the “other” category drove the association of *APOL1* genotype with mortality.

In summary, African Americans carrying *APOL1* high-risk genotypes had lower risk of death than African Americans with low-risk genotypes in fully adjusted models including genetic ancestry. Further, African Americans with low-risk genotypes had significantly higher risk of all-cause mortality than white Americans, whereas no such difference was observed when comparing African Americans with high-risk genotypes to white Americans, suggesting that carriage of high-risk genotypes may attenuate racial disparities in survival.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Baseline characteristics of African-American REGARDS participants by *APOL1* genotype.

	0/1 APOL1 risk allele (n=9060)	**2 APOL1 risk alleles (n= 1320)**	***P*-value**
Age, mean (SD)	64.2 (9.3)	63.4 (8.9)	0.003
Male sex, n (%)	3502 (39)	504 (38)	0.7
Region, n (%)			0.9
Stroke belt/buckle	4618 (51)	674 (51)	
Non-belt/buckle	4437 (49)	646 (49)	
Income <$20,000/year, n (%)	2398 (26)	366 (28)	0.3
Education < high school, n (%)	1776 (20)	254 (19)	0.5
Current smoking, n (%)	1597 (18)	210 (16)	0.1
Body mass index, mean (SD)	30.8 (6.7)	30.9 (6.6)	0.3
Blood pressure			
Systolic, mean (SD)	130.9 (17.4)	131.3 (17.3)	0.4
Diastolic, mean (SD)	78.4 (10.2)	78.9 (9.9)	0.1
Diabetes, n(%)	2663 (30)	394 (30)	0.8
History of heart disease, n(%)	1383 (16)	190 (15)	0.4
Hypertension, n(%)	6461 (71)	947 (72)	0.7
Medication use, n(%)			
Blood pressure medications	6205 (69)	926 (70)	0.2
Statins	2635 (29)	383 (29)	0.9
Aspirin	3439 (38)	536 (41)	0.07
eGFR, mean (SD)	88.6 (23.6)	86.1 (24.5)	<0.001
eGFR < 60 ml/min/1.73m^2, n(%)	1085 (12.1)	179 (13.6)	0.1
UACR, median [IQR]	7.8 [4.6,19.3]	9.2 [4.9,26.0]	<0.001
UACR ≥ 30 mg/g, n(%)	1634 (18.1)	293 (22.2)	<0.001
hsCRP, median [IQR]	2.9 [1.26.7]	2.9 [1.2,6.6]	0.6
Total cholesterol, mean (SD)	192.7 (41.4)	195.7 (39.6)	0.01
HDL-C, mean (SD)	53.3 (15.9)	54.2 (16.8)	0.08
Triglycerides, mean (SD)	113.9 (75.5)	114.0 (64.4)	0.9
Developed ESKD			0.001
No.	229	54	
Incidence, 95%CI*	299 (263-341)	486 (373-635)	

Unless otherwise indicated, values for continuous variables given as mean +/− SD or median [interquartile range]; for categorial variables, as count (percentage).

Abbreviations: HS, high school; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-creatinine ratio; hsCRP, high-sensitivity C-reactive protein; HDL-C, high-density lipoprotein cholesterol; ESKD, end-stage kidney disease; 95%CI, 95% confidence interval

* per 100,000 person-years of follow-up

Table 2.

All-cause mortality by *APOL1* risk status in African-American participants of REGARDS.

	0/1 *APOL1* risk alleles	**2 *APOL1* risk alleles**
n/N	2261/9060	302/1320
Incidence rate (95%CI) *	29.6 (28.4-30.9)	26.7 (23.9-29.9)
Hazard Ratio (95% CI)		
Model 1 †	1.00 (reference)	0.90 (0.79-1.02)
Model 2 †	1.00 (reference)	0.96 (0.84-1.09)
Model 3 †	1.00 (reference)	0.88 (0.77-1.01)
Model 4 †	1.00 (reference)	0.81 (0.69-0.96)

n/N: No. of events/ no. at risk

* Per 1000 person-years of follow-up

† Hazard ratio (95% confidence interval)

Model 1: Unadjusted. (n/N=2,563/10,380)

Model 2: adjusted for age, sex, current smoking, income, diabetes, body mass index, blood pressure, history of coronary heart disease, total cholesterol, and high-density lipoprotein-cholesterol. (events/N=2080/8680)

Model 3: adjusted for variables in model 1 and estimated glomerular filtration rate (eGFR) and log-transformed urinary albumin-creatinine ratio (UACR). (n/N=1936/8,397)

Model 4: adjusted for age, sex, total cholesterol, high-density lipoprotein-cholesterol, eGFR, log-transformed UACR and PCS for ancestry in the subset of participants with available ancestry data. (n/N=1399/5,895)

Table 3.

cause-specific mortality by *APOL1* risk status in African-American participants of REGARDS

	0/1 *APOL1* risk alleles	**2 *APOL1* risk alleles**
Cardiovascular		
n/N	677/9060	102/1320
Model 1	1.00 (reference)	1.02 (0.83,1.25)
Model 2	1.00 (reference)	1.15 (0.92,1.43)
Model 3	1.00 (reference)	1.04 (0.83,1.31)
Model 4	1.00 (reference)	0.98 (0.75,1.31)
Cancer		
n/N	488/9060	68/1320
Model 1	1.00 (reference)	0.94 (0.73,1.21)
Model 2	1.00 (reference)	1.00 (0.76,1.32)
Model 3	1.00 (reference)	0.99 (0.75,1.32)
Model 4	1.00 (reference)	0.89 (0.64,1.25)
Other		
n/N	789/9060	91/1320
Model 1	1.00 (reference)	0.78 (0.63,0.97)
Model 2	1.00 (reference)	0.84 (0.66,1.08)
Model 3	1.00 (reference)	0.72 (0.55,0.93)
Model 4	1.00 (reference)	0.62 (0.45,0.86)

n/N: No. of events/ no. at risk

Model 1: unadjusted (*Cardiovascular*: n/N=779/10,380; *Cancer:* n/N=556/10380; *Other:* n/N=880/10,380)

Model 2: adjusted for age, sex, current smoking, income, diabetes, body mass index, blood pressure, history of coronary heart disease, total cholesterol, high-density lipoprotein-cholesterol. (*Cardiovascular*— events/N=642/8680; *Cancer*—events/N=459/8680; *Other*—events/N=696/8680)

Model 3: adjusted for variables in model 1 and estimated glomerular filtration rate, and log-transformed urinary albumin-creatinine ratio. (*Cardiovascular: n*/N=595/8397; *Cancer: n*/N=437/8397; *Other: n*/N=633/8397)

Model 4: adjusted for for variables in model 2 and principal components for ancestry in the subset of participants with available ancestry data. (*Cardiovascular*: n/N=415/5895; *Cancer: n*/N=321/5895; *Other: n*/N=460/5895)