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Apolipoprotein L1 gene variants associate with prevalent kidney but not prevalent cardiovascular disease in the Systolic Blood Pressure Intervention Trial

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Abstract

Apolipoprotein L1 gene (*APOL1*) G1 and G2 coding variants are strongly associated with chronic kidney disease (CKD) in African Americans. Here *APOL1* association was tested with baseline estimated glomerular filtration rate (eGFR), urine albumin:creatinine ratio (UACR), and prevalent cardiovascular disease (CVD) in 2,571 African Americans from the Systolic Blood Pressure Intervention Trial (SPRINT), a trial assessing effects of systolic blood pressure reduction on renal and CVD outcomes. Logistic regression models that adjusted for potentially important confounders tested for association between *APOL1* risk variants and baseline clinical CVD (myocardial infarction, coronary or carotid artery revascularization) and CKD (eGFR under 60 ml/min/1.73m^2 and/or UACR over 30 mg/g). African American SPRINT participants were 45.3%

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female with mean (median) age of 64.3 (63) years, mean arterial pressure 100.7 (100) mmHg, eGFR 76.3 (77.1) ml/min/1.73m^2, UACR 49.9 (9.2) mg/g, and 8.2% had clinical CVD. *APOL1* (recessive inheritance) was positively associated with CKD (odds ratio 1.37, 95% confidence interval 1.08–1.73) and log UACR estimated slope [β] 0.33) and negatively associated with eGFR (β −3.58), all significant. *APOL1* risk variants were not significantly associated with prevalent CVD (1.02, 0.82–1.27). Thus, SPRINT data show that *APOL1* risk variants are associated with mild CKD but not prevalent CVD in African American with a UACR under 1000 mg/g.

Keywords

African Americans; albuminuria; *APOL1*; cardiovascular disease; chronic kidney disease; SPRINT

Introduction

There has been significant progress in the delineation of the spectrum of non-diabetic chronic kidney disease (CKD) in African Americans (AAs) that are associated with the apolipoprotein L1 gene (*APOL1*) G1 and G2 coding variants. Patients with *APOL1*-associated primary glomerulosclerosis often have proteinuria, secondary hypertension, and focal segmental glomerulosclerosis (FSGS), HIV-associated nephropathy (HIVAN; FSGS, collapsing variant), focal global glomerulosclerosis accompanied by interstitial and vascular changes (often labeled “hypertension-attributed” nephropathy), sickle cell nephropathy, or severe lupus nephritis on kidney biopsy.[1–6] Patients inheriting two *APOL1* risk variants have high rates of progression to end-stage kidney disease (ESKD), explaining a large fraction of the differential risk of ESKD in AAs.[6–8] However, the specific disease mechanisms remain unclear. Modifying genetic (*APOL1* by second gene) and environmental factors (*APOL1* by environmental exposure) are likely present and may account for the variable glomerular histologic lesions.[3;9–12]Weaker *APOL1* association is observed with albuminuria and reduced kidney function in population-based studies of AAs.[13–15]

Recent results from the Jackson Heart Study (JHS) and Women’s Health Initiative (WHI) reported an association between *APOL1* nephropathy variants and incident cardiovascular disease (CVD).[16] This finding warrants additional consideration, since the African American Study of Kidney Disease and Hypertension (AASK) did not detect a significant relationship between *APOL1* and participant survival.[8] AASK extended *APOL1* association to AAs with putative hypertension-attributed nephropathy and urine protein:creatinine ratios (UPCR) less than 2,500 mg/g,[7] but did not appear to support *APOL1* association with CVD.[8] AASK also demonstrated that although aggressive blood pressure control slowed nephropathy progression in participants who had proteinuria exceeding 300 mg/day, the overall response to renin-angiotensin system (RAS) blockade was poor and nearly 60% of AASK participants met a primary study end-point (mainly nephropathy progression, not death) within 10 years.[17] *APOL1* was significantly associated with CKD in AASK cases and only *APOL1* genotype predicted nephropathy progression, blood pressure treatment arm and medication class did not.[7] Therefore, AASK suggested that *APOL1* is primarily involved in progression of non-diabetic nephropathy, without independent effects on CVD. As such, it is

unclear why JHS and WHI results differed from those in AASK. Approximately one quarter of JHS and WHI participants had diabetes mellitus, a known CVD risk factor, and their CVD definition differed from those employed in the National Institutes of Health (NIH)-sponsored AASK and Systolic Blood Pressure Intervention Trial (SPRINT).[16] AASK also excluded subjects with diabetes mellitus, congestive heart failure (CHF), or heart block greater than first degree.[18] Thus, analysis of other large cohorts is important to define potential relationships between *APOL1* and CVD.

The present analyses assessed *APOL1* G1 and G2 risk variant association with prevalent CVD and baseline CKD, eGFR, and albuminuria in AAs at high risk for CVD from SPRINT.[19] SPRINT enrolled large numbers of non-diabetic individuals with hypertension; participants were enriched for CVD and associated risk factors, the elderly, and those with nephropathy having low levels of albuminuria.

Results

Among all 2,802 AAs enrolled in SPRINT, 2,571 (91.8%) consented to participate in genetic research studies and had baseline clinical and *APOL1* G1 and G2 genotype data that passed quality control analyses. In the multivariate analysis, 342 of 2,802 participants were excluded due to failure to provide consent for genetic analyses, lack of DNA, or missing covariates. Compared with those in the multivariate analysis, no significant differences were observed for excluded participants regarding age, sex, body mass index (BMI), number of BP medications, or CVD events; although higher mean ± standard deviation (SD) (median) eGFR 79.0 ± 21.0 (78.6) ml/min/1.73 m^2 (p=0.03) and a trend toward lower urine albumin:creatinine ratio (UACR) 25.5±56.9 (8.1) mg/g (p=0.0501) were present (Supplementary Table 1 contains characteristics of participants included and excluded from the multivariate analysis).

Individuals in this analysis were 45.3% female with mean±SD (median) age 64.3±9.3 (63) years, mean arterial pressure 100.7±12.2 (100) mmHg, CKD-Epidemiology (EPI) estimated glomerular filtration rate (eGFR) 76.3±22.9 (77.1) ml/min/1.73m^2, UACR 49.9±188.6 (9.2) mg/g and 16.2% had CVD defined by the SPRINT Manual Of Operations (MOO; see Methods), while 8.2% had clinical CVD defined as prior coronary or carotid artery revascularization (surgical or percutaneous) or myocardial infarction (MI). Table 1 summarizes the demographic and clinical differences between those individuals with zero or one copies versus two copies of the *APOL1* G1/G2 risk alleles. Briefly, those with two risk variants were one year younger, but otherwise these two groups had similar proportions of women and similar BMI, tobacco use, and fasting glucose levels. Individuals with two copies of the *APOL1* risk variants had higher African ancestry (82% vs. 78%, $p=4.2\times10^{-9}$) and albuminuria ($p=3.8\times10^{-6}$) and more kidney disease (serum creatinine concentration p=0.0091; eGFR p=0.0249; CKD prevalence p=0.0129), even after adjusting for multiple comparisons.[20] In contrast to CKD, Table 1 reveals the general absence of *APOL1* association with baseline measures of CVD, whether defined as in the SPRINT MOO or clinical CVD (MI, coronary or carotid artery revascularization).

In order to account for the potentially confounding effects of age, gender, RAS blockade and African ancestral proportion on risk for kidney disease, multiple regression models that adjusted for these *a priori* factors as covariates were computed (Table 2). In the multiple logistic model, individuals with two copies of the G1/G2 risk variants had a higher prevalence of CKD (odds ratio (OR) = 1.37, p=0.0095), had lower eGFR (slope $(\hat{\beta}) = -3.57$, p=0.0029), and higher levels of albuminuria (log(UACR); slope $(\hat{\beta}) = 0.33$, $p=7.67\times10^{-6}$), compared to those with zero or one risk variants. Comparable effect sizes were observed if the sample was restricted to >0.40 and >0.80 African ancestry (data not shown).

A similar multiple logistic regression approach was computed to test for an association between *APOL1* risk variants and clinical CVD (Table 3). Specifically, a logistic regression model was computed with prevalent CVD as the response and adjusting for an *a priori* list of CVD risk factors (i.e., age, gender, BMI, number of blood pressure medications, statin use, eGFR, ACR, and smoking) and African ancestral proportion as covariates. As with the univariate analysis in Table 1, the adjusted analyses in Table 3 show no evidence of an association between the number of *APOL1* risk variants (additive genetic model) and clinical CVD (p=0.86, OR 1.02, 95% confidence interval [CI] 0.82–1.27). Adjusting for the same list of covariates but testing for an *APOL1* association under a recessive model yielded comparable results (p=0.54). The number of blood pressure medications, use of statins and smoking were significantly associated with clinical CVD. Given the lack of association with *APOL1*, it is important to consider whether the study had sufficient power to detect the effect size (OR=2.0) reported in the JHS/WHI study.[16] Thus, a power analysis was computed to estimate the power to detect the *APOL1* G1/G2 variant association with CVD assuming an additive genetic model, G1/G2 risk allele frequency of 0.36, a clinical CVD rate of 8.5% and a type 1 error rate of α=0.05. The 2,571 individuals analyzed have ~0.80 power for an OR=1.26, ~0.90 power for OR=1.31 and >0.99 power for OR=1.43. A similar analysis assuming a recessive model yields power estimates of 0.80 for OR=1.53, 0.90 for OR=1.63 and >0.99 for OR=1.87. Thus, SPRINT has excellent power to detect the effect sizes of OR=2.0 reported in the JHS/WHI study[16] and the difference in results are likely attributable to ascertainment (e.g., diabetes mellitus) and other study-specific design features and not sampling variation.

Discussion

Impressive genetic association exists between the G1 and G2 coding variants in *APOL1* and a spectrum of non-diabetic, often proteinuric nephropathies in populations with recent African ancestry.[21–23] The extent of this association has been less clear in individuals with mild CKD and lower levels of proteinuria as in SPRINT, as well as for CVD. The present analyses demonstrate significant association between *APOL1* and mild CKD in hypertensive AAs with a UACR below 1,000 mg/g, but not with CVD. As such, it is inconclusive whether *APOL1* independently associates with CVD beyond its known effect on renal blood vessels (glomeruli and the renal microvasculature). APOL1 protein is detectable in the media of medium-sized arteries and arterioles in subjects with kidney disease (FSGS or HIVAN).[24] Therefore, APOL1 could potentially play roles in susceptibility to large vessel disease including MI and stroke. However, CKD uniformly associates with increasing rates of CVD and CVD-associated mortality.

Because of the close relationship between CKD and CVD, it may be difficult to assess the direct effect of *APOL1* on CVD, independent of CKD and albuminuria, on the basis of statistical adjustment. Ito and colleagues reported an excess of adjudicated and verified CVD events among *APOL1* two risk variant carriers in the JHS and WHI, including after adjustment for CKD.[16] However, they also noted that JHS participants with two *APOL1* risk variants had paradoxically lower levels of coronary artery calcified atherosclerotic plaque (CAC) than did those with less than two risk variants. CAC is a powerful predictor of subsequent risk for MI, stroke, CVD, and mortality.[25;26] The protective effect of *APOL1* risk variants on CAC might not be expected if *APOL1* risk variants underlie CVD. To explain this finding, the authors suggested that novel CVD pathways may be present.[16]

The mean ± SD (median) UACR among SPRINT AAs included in these analyses were 49.9±188.6 (9.2) mg/g; in those with two *APOL1* risk variants it was 65.9±175.2 (12.1) mg/g. Although the relationships between albuminuria and proteinuria are not entirely consistent across different etiologies of CKD, the levels of proteinuria in SPRINT appear to be lower than those in AAs enrolled in AASK and CRIC. *APOL1* was associated with progression of CKD in both AASK and CRIC, and with presence of baseline CKD in AASK.[7;8] AASK enrolled hypertensive non-diabetic AAs with a UPCR <2,500 mg/g. The median (95% CI) UPCR in AASK participants was 74.2 (27.4–307.4) mg/g; among those with two *APOL1* risk variants UPCR was 203.0 (43.2–723.4) mg/g. AASK included the following cardiovascular (CV) end-points, adjudicated CV death and hospitalization for MI, stroke, CHF, revascularization procedures, and other hospitalized CV events.[18] In AA CRIC participants lacking diabetes, the mean ± SD (median) 24 hour urine protein excretion was 600±1,300 (100) mg; among those with two *APOL1* risk variants the 24 hour urine protein excretion was 900±1,600 (400) mg. Proteinuria impacts CKD progression independently from *APOL1*;[8] however, SPRINT demonstrates that CKD in non-diabetic hypertensive AAs without heavy proteinuria is significantly related to *APOL1*. The strength of the SPRINT *APOL1* association with CKD likely resides between those reported in population-based samples of AAs (and family members of AAs with non-diabetic forms of ESKD) where participants were not enrolled based on presence of hypertension or CKD, and those in samples with ESKD, AASK, and CRIC where participants were highly enriched for advanced CKD or ESKD. [7;8;13–15] Approximately 14% of AAs in SPRINT possess two *APOL1* G1 or G2 risk variants, similar to the 12–13% frequencies observed in the general AA population.[1] This likely reflects that SPRINT recruited hypertensive AAs without advanced CKD; only 33% had reduced eGFR (the majority mildly reduced) and/or low level proteinuria.

In SPRINT, we note the lack of *APOL1* association with baseline (prevalent) CVD including MI and coronary or carotid artery revascularization in a high-risk non-diabetic sample. Absence of *APOL1* association with CVD in SPRINT was observed despite significant association between *APOL1* and kidney disease in a population recruited to be at heightened risk for CVD. It is unlikely that this report contained a biased SPRINT sample; 91.8% (2,571/2,802) of all randomized AAs provided DNA and were included in the study. If *APOL1* is associated with death from CVD, the baseline SPRINT sample might not reflect this and longer term follow-up would be required to demonstrate an association with CVD.

Further, statistical power does not explain the lack of an association. The lack of *APOL1* association with CVD is supported by AASK.[8] The AASK primary outcome included a composite of progression of CKD to ESKD, doubling of serum creatinine concentration, or death.[27] Despite strong *APOL1* association with the primary AASK composite outcome, significant association between *APOL1* and death was not detected after nearly ten year follow-up.[8] The vast majority of AASK participants reaching a primary outcome had a renal event.[28] We add that there were only 59 CVD deaths in AASK after ten years and approximately 70% of participants underwent *APOL1* genotyping. Hence, AASK was not focused on CVD deaths and could have been underpowered.

Many differences exist between the JHS, WHI, AASK, and SPRINT studies and these likely contributed to differences in observed effect of *APOL1* nephropathy variants on risk for CVD. SPRINT enrolled hypertensive participants with high risk for subsequent CVD events, but excluded participants with stroke, diabetes, proteinuria >1 gram per day, eGFR <20 ml/min/1.73m^2, moderate to severe CHF, or non-adherence. Although AASK and SPRINT enrolled only hypertensive individuals without diabetes, approximately 25% of JHS and WHI participants had diabetes and those who had prior strokes were included. As such, it is conceivable that presence of diabetes underlies the disparate association results between JHS/WHI and AASK/SPRINT. In the report by Ito et al. there appears to be a positive correlation between diabetes and the number of *APOL1* risk alleles (JHS: p-value=0.0012; WHI: p-value=0.0428); these p-values are based on the frequencies and counts in their Table 1.[16] In addition, the events included in the CVD category in WHI included cerebrovascular disease and stroke and in JHS included stroke. Thus, given the strong relationship between diabetes and CVD, it would be interesting to examine the relationship between *APOL1* and CVD in the JHS and WHI, stratified by diabetes status. Finally, AASK, JHS, and WHI also benefitted from longitudinal follow-up and adjudicated event reporting. Longer-term follow-up in SPRINT will be necessary to firmly determine whether potential associations exist between *APOL1* and adjudicated MI, stroke, CHF, coronary revascularization, PVD, and death, as well as determine effects of blood pressure treatment on these CVD outcomes based on genotype.

We conclude that *APOL1* G1 and G2 coding variants are significantly associated with the presence of CKD, degree of albuminuria, and eGFR in AA SPRINT participants. In contrast to prior NIH cohort studies enrolling AAs with non-diabetic forms of advanced nephropathy, SPRINT participants have far lower levels of albuminuria and higher eGFRs at baseline. Baseline SPRINT results suggest that *APOL1* association may be limited to (or stronger with) nephropathy, with no effect seen for prevalent CVD. Long term follow-up will be required to determine whether *APOL1* associates with risk of incident CVD in SPRINT. Several studies reveal that AAs who possess two *APOL1* risk variants are at higher risk for progression of nephropathy, this despite RAS blockade and intensive blood pressure reduction. Although treating hypertension and attempting to reduce proteinuria remain paramount, it is imperative that we identify the pathogenetic mechanisms involved in *APOL1*-associated nephropathy. This will lead to novel treatments for this refractory spectrum of kidney diseases that are limited to those with recent African ancestry.

Materials and Methods

Study Participants

SPRINT is a two-armed NIH-sponsored randomized multicenter trial designed to test whether a treatment protocol aimed at reducing systolic blood pressure beyond current treatment guidelines will reduce CVD and renal outcomes in a high-risk multi-ethnic sample with hypertension. SPRINT is enriched for the elderly, ethnic minorities, subjects with CKD, and/or at high risk for CVD based on presence of hypertension in those aged 50 years or older, plus at least one of the following: clinical or subclinical CVD (excluding stroke), CKD, Framingham risk score for ten year CVD event ≥15%, or age greater than 75 years. Subjects with CKD had a baseline UACR less than 1,000 mg/g and CKD-EPI equation computed (serum creatinine-based) estimated glomerular filtration rate (eGFR) between 20 and 59 ml/min/1.73m^2.[29] Inclusion and exclusion criteria have been reported.[19]

All self-described AAs of non-Hispanic ethnicity in SPRINT who provided DNA and consented to molecular genetics analyses were evaluated in this report. Herein, CKD was defined as an individual having a UACR >30 mg/g and/or CKD-EPI eGFR <60 ml/min/1.73m^2. We focused on a clinical CVD definition that was limited to prior coronary or carotid artery revascularization or MI. In addition, we report prevalent CVD events as defined in the SPRINT MOO recorded at baseline; including myocardial infarction; acute coronary syndrome with or without resting electrocardiographic (ECG) changes, ECG changes on graded exercise test, or positive cardiac imaging study; coronary revascularization (coronary artery bypass grafting or percutaneous coronary intervention); carotid endarterectomy or carotid stenting; peripheral arterial disease with revascularization; 50% stenosis of a coronary, carotid, or lower extremity artery; abdominal aortic aneurysm ≥5 cm with or without repair; coronary artery calcium score ≥400 Agatston units; ankle-brachial index ≤0.90; and left ventricular hypertrophy by computer ECG reading, echocardiogram report, or other cardiac imaging procedure. The frequencies of CVD using both definitions are included in Table 1. All participants were evaluated for CVD history at the screening visit during an interview by clinic staff. The evaluation of inclusion and exclusion criteria became part of the participant's chart as source documentation, but this documentation is not part of the study database. Documentation included medical records, test and procedure reports, hospital discharge summaries, and ECG tracings. No tests or procedures were performed by the study for the purpose of determining eligibility related to CVD history. Participants with stroke, diabetes, proteinuria >1 gram/day, eGFR <20 ml/min/1.73m^2, symptomatic CHF or ejection fraction <35%, or with non-adherence were excluded. Incident strokes are being captured prospectively during the trial. CVD events recorded at enrollment included history of MI, angina, CHF, TIA, revascularization of coronary or carotid arteries, and PVD.

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 all subjects using a custom assay designed in the Wake Forest School of Medicine Center of Genomics and Personalized Medicine Research on the

Sequenom platform (San Diego, California). The G1 and G2 genotype calls were visually inspected for quality control. In addition, 106 biallelic ancestry informative markers were genotyped to provide African ancestry proportion estimates. The maximum likelihood approach of Tang *et al*. as coded in the package FRAPPE (frequentist estimation of individual ancestry proportion) was used to obtain the proportion of African and European ancestry for each individual.[30] Genotype data at these markers were obtained from 44 HapMap Yoruba individuals (YRI) and 39 European American controls as anchors and provided starting values for the Expectation-Maximization algorithm used in FRAPPE.

Statistical Analyses

Quality control analyses were completed on both the clinical and genotype data. Clinical data were examined for implausible and aberrant observations, outliers that might have undue influence on the analyses and consistency across related variables. The *APOL1* SNPs were examined for the quality of the genotyping calls, departures from Hardy-Weinberg Equilibrium expectations and differential missingness by CKD versus controls. To test for differences between the clinical and demographic characteristics and the APOL1 risk variants, individuals with two copies of the G1/G2 risk variants (recessive model as in prior reports)[1–6] were contrasted with those with zero or one copies (i.e., recessive model) using a generalized linear models (i.e., logistic regression for CKD and CVD and linear regression for UACR and eGFR). Model assumptions of conditional normality, homogeneity of variance and overly influential observations were examined, resulting in UACR being modeled using a natural logarithm transformation; CKD-EPI eGFR did not require a transformation in these data. To account for the three hypotheses tested, the sharper Bonferroni multiple comparisons adjustment was used.[20]

To account for the potential confounding effects of the demographic and clinical characteristics on the associations between *APOL1* G1/G2 risk variants and CVD and CKD-related traits, multiple linear or logistic regression analyses were computed. Associations for CKD (logistic regression), log(UACR) (linear regression) and CKD-EPI eGFR (linear regression) adjusted for age, gender, African ancestry proportion, and RAS blockade (either ACEi or angiotensin receptor blockers) as covariates. Similarly, the association of *APOL1* G1/G2 risk variants and CVD (logistic regression) adjusted for age, gender, BMI number of blood pressure medications, statin use, eGFR, ACR, smoking and African ancestry proportion. Here, the *APOL1* G1/G2 risk was modeled under an additive genetic model (0, 1, or 2 copies of the risk alleles) and a recessive genetic model (0 or 1 versus 2 copies of risk alleles). ORs and 95% CI are computed for a change of one unit on the predictor variable scale (*e.g.*, increase of one in the number of *APOL1* risk variants, increase of one on the BMI scale, increase of one in the number of blood pressure medications). A power analysis was computed for CVD and *APOL1* risk variants using Quanto.[31]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline demographic and laboratory data in African American SPRINT participants*

Variable	*APOL1* 2 risk variants (N=361)	*APOL1* 0/1 risk variants (N=2210)	P-value (2 vs. 0/1 risk variants)
Sex, % Female	46.8	45.1	0.5472
Age, years	63.4±9.0 (61)	64.4±9.0 (63)	0.0325
Body Mass Index, kg/m^2	31.5±6.7 (30.4)	30.8±6.3 (30.1)	0.1107
Number of BP meds	2.06±1.08 (2)	1.95±1.04 (2)	0.0801
% African ancestry	0.82±0.09 (0.84)	0.78±0.12 (0.80)	4.23×10^{-9}
Systolic BP, mmHg	139.4±15.8 (137)	139.8±16.4 (138)	0.6035
Diastolic BP, mmHg	82.3±12.6 (82)	81.1±12.4 (81)	0.0816
UACR, mg/g	65.9±175.2 (12.1)	47.2±190.6 (8.7)	3.75×10^{-6}
% UACR >30 mg/g	26.3	19.0	0.0013
% UACR >300 mg/g	6.7	3.0	0.0004
Serum creatinine, mg/dL	1.21±0.50 (1.08)	1.13±0.37 (1.05)	0.0091
Chronic Kidney Disease$^+$,%	41.0	34.3	0.0129
eGFR, ml/min/1.73m^2	73.4±24.7 (74.9)	76.8±22.6 (77.4)	0.0249
% eGFR <60 ml/min/1.73m^2	28.2	23.7	0.0652
ACEi/ARB use,%	56.2	52.1	0.1474
% Tobacco			0.1801
Current	24.1	22.7	
Former	28.5	33.2	
Never	47.7	44.1	
Pack years in smokers	7.8±12.7 (0.9)	9.1±15.4 (1.5)	0.1718
CVD, % (defined in Methods)	16.6	16.2	0.8576
Clinical CVD, % (defined below)	8.9	8.1	0.6230
Angina, %	7.0	7.9	0.5615
Carotid Endarterectomy,%	3.1	1.7	0.0872
Congestive Heart Failure,%	3.9	4.4	0.6828
Coronary Revascularization,%	4.7	4.0	0.5175

Variable	*APOL1* 2 risk variants (N=361)	*APOL1* 0/1 risk variants (N=2210)	P-value (2 vs. 0/1 risk variants)
Myocardial Infarction, %	6.4	5.3	0.4247
Peripheral Vascular Disease,%	6.1	4.8	0.2722
Transient Ischemic Attack,%	0.2	2.4	0.2464
Statin use,%	34.1	33.7	0.8928
Fasting glucose, mg/dL	96.8±13.9 (95)	97.9±16.0 (96)	0.1237

*Mean + standard (median);

+CKD defined as UACR >30 mg/g and/or eGFR <60 ml/min/1,73m^2;

BP – blood pressure; UACR – urine albumin:creatinine ratio; eGFR – CKD-EPI equation estimated glomerular filtration rate; ACEi/ARB – angiotensin converting enzyme inhibitor/angiotensin receptor blocker; CVD – cardiovascular disease; Clinical CVD includes myocardial infarction and coronary or carotid artery revascularization

Table 2

Differences in risk for chronic kidney disease and related parameters as a function of the number of *APOL1* G1/G2 risk variants (0/1 versus 2).

CKD modeled using logistic regression	**Odds Ratio**	**95% Confidence Interval**	**P-value**
Intercept	-	-	-
Age (five year change)	1.32	1.26–1.38	<0.0001
Female	1.27	1.08–1.51	0.0049
ACEi/ARB	1.23	1.04–1.45	0.0162
Admixture	2.63	1.30–5.33	0.0075
APOL1 G1/G2 compound risk	1.37	1.08–1.73	0.0095
eGFR modeled using linear regression			
	$\hat{\beta}$	se(β)	P-value
Intercept	153.90	4.23	<0.0001
Age	−0.97	0.05	<0.0001
Female	−2.28	0.83	0.0064
ACEi/ARB	−4.94	0.83	<0.0001
Admixture	−14.11	3.45	<0.0001
APOL1 G1/G2 compound risk	−3.57	1.20	0.0029
Log(UACR) modeled using linear regression			
	$\hat{\beta}$	se(β)	P-value
Intercept	1.16	0.26	0.2621
Age	0.016	0.003	<0.0001
Female	0.066	0.052	0.2027
ACEi/ARB	0.058	0.051	0.2540
Admixture	0.33	0.21	0.1171
APOL1 G1/G2 compound risk	0.33	0.07	7.67×10^{-6}

ACEi/ARB – angiotensin converting enzyme inhibitor/angiotensin receptor blocker

eGFR – estimated glomerular filtration rate based on CKD-EPI equation;

UACR – urine albumin:creatinine ratio

Table 3

Multivariable model for prior history of clinical CVD[1]

Variable	Slope (β)	SE (β)	P-value	Odds Ratio[2]	95% CI
Intercept	−4.3623	1.1139	9.0×10^{-5}		
Age[2]	0.0048	0.0096	0.6224	1.02	0.93–1.13
Female	0.0254	0.1599	0.8736	1.03	0.75–1.40
BMI	−0.0101	0.0132	0.4429	0.99	0.97–1.02
Number of blood pressure meds	0.3274	0.0804	4.7×10^{-5}	1.39	1.19–1.62
Statin use	1.5583	0.1644	2.6×10^{-21}	4.75	3.44–6.56
eGFR[2]	0.0002	0.0037	0.9667	1.00	0.93–1.08
Log(UACR)	0.0857	0.0573	0.1347	1.09	0.97–1.22
African ancestry proportion[2]	−0.2437	0.6340	0.7007	0.98	0.86–1.11
Smoking status			0.0019		
Former smoker	0.5423	0.1841		1.72	1.20–2.47
Current smoker	0.8078	0.2116		2.24	1.48–3.40
Number of *APOL1* risk variants[3]	0.0201	0.1099	0.8551	1.02	0.82–1.27

[1] CVD defined as prior coronary or carotid artery revascularization or myocardial infarction

[2] Odds ratios (OR) and 95% confidence intervals (CI) are computed for a change of one unit on the predictor variable scale (*e.g.*, increase of one in the number of *APOL1* risk variants) except as follows: increase in age of 5 years, increase in eGFR of 10 ml/min/1.73m^2, and increase in African ancestry proportion of 0.10

[3] Test of association of the number of *APOL1* risk variants (0, 1 or 2) with CVD

SE – standard error; CI – confidence interval; BMI – body mass index; eGFR – estimated GFR; UACR – urine albumin:creatinine ratio