**APOL1, Sickle Cell Trait, and CKD in the Jackson Heart Study**

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**Rationale & Objective:** Apolipoprotein L1 (APOL1) high-risk variants are associated with an increased risk for chronic kidney disease (CKD) among African Americans. Less is known regarding the risk for the development of CKD and kidney failure (end-stage kidney disease [ESKD]) among African Americans with only 1 APOL1 risk variant or whether the risk is modified by sickle cell trait.

**Study Design:** The Jackson Heart Study is a community-based longitudinal cohort study.

**Setting & Participants:** Self-reported African Americans in the Jackson Heart Study (n = 5,306).

**Exposures:** APOL1 G1 and G2 genotypes and sickle cell trait.

**Outcomes:** Incident CKD (estimated glomerular filtration rate < 60 mL/min/1.73 m²), albuminuria (urinary albumin-creatinine ratio ≥ 30 mg/g), continuous and rapid kidney function decline (≥230% decline), and incident ESKD.

**Analytical Approach:** Multivariable linear and logistic regression, and Cox proportional hazards models adjusted for age, sex, hypertension, diabetes, ancestry informative markers, and sickle cell trait.

**Results:** Of 2,300 participants, 41.3% had zero, 45.1% had 1, and 13.8% had 2 APOL1 risk variants. Sickle cell trait was present in 8.5%. Compared with participants with zero APOL1 risk variants, those with 2 alleles had an increased risk for incident albuminuria (adjusted HR [aHR], 1.88; 95% CI, 1.04 to 3.40), ESKD (aHR, 9.05; 95% CI, 1.79 to 45.85), incident CKD (aHR, 1.65; 95% CI, 1.06 to 2.57), continuous decline (β = −1.90; 95% CI, −3.35 to −0.45), and rapid kidney function decline (OR, 2.21; 95% CI, 1.22 to 4.00) after adjustment for sickle cell trait, with similar results after adjustment for ancestry informative markers. Having 1 APOL1 risk variant was not associated with CKD outcomes and there was no interaction of APOL1 with sickle cell trait.

**Limitations:** Single-site recruitment of African American individuals with APOL1 and sickle cell trait.

**Conclusions:** The presence of 1 APOL1 risk allele was not associated with increased risk for CKD outcomes, whereas 2 risk alleles were associated with incident albuminuria, CKD, ESKD, and rapid and continuous kidney function decline. Additional studies are needed to determine factors that might alter the risk for adverse kidney outcomes among individuals with high-risk APOL1 genotypes.

E nd-stage kidney disease (ESKD) currently affects more than 700,000 persons in the United States and disproportionately affects African Americans, who experience 2- to 4-fold greater risk for ESKD than Whites. Some of this excess risk is thought to be due in part to 2 variants of the apolipoprotein L1 (APOL1) gene, namely G1 and G2. The G1 variant incorporates 2 tightly linked single-nucleotide polymorphisms that replace amino acids at positions 342 (ser→gly) and 384 (ile→met), while the G2 variant is defined by a 6-base pair deletion that results in the in-frame removal of amino acids 388 and 389 (asp and tyr, respectively).6

The initial case-control studies in nondiabetic African Americans found that those with 2 risk variants (G1/G1, G2/G2, or G1/G2) were at 10.5-fold (95% CI, 6.0–18.4) greater risk for focal segmental glomerulosclerosis (FSGS)-associated ESKD, 7.3-fold (95% CI, 5.6–9.5) greater risk for hypertensive ESKD, and 29-fold (95% CI, 13–68) greater risk for HIV-associated nephropathy ESKD compared with African Americans with 1 or no copy of the APOL1 alleles.7 Subsequent cohort studies have shown that among those with chronic kidney disease (CKD), APOL1 high-risk variants were associated with increased risk for kidney disease progression,9,10 proteinuria,11 earlier and younger age of dialysis initiation, longer survival receiving dialysis,12,13 and increased risk for kidney transplant failure.14

Initial studies have suggested that >30% of the African American population carry at least 1 risk allele,15 and the prevalence of having 2 risk alleles among African Americans is ~13%.16 Whether increased ESKD risk is attributed to the G1 variant compared with the G2 variant remains unclear, and further research is needed to understand whether other comorbid conditions such as obesity, diabetes, and hypertension (HTN) or other genetic disorders such as sickle cell trait predispose those affected with APOL1 to the development of kidney disease and progression to ESKD.

Sickle cell trait affects 300 million people worldwide and 8% of African Americans in the United States. In screening programs of newborns, rates of sickle cell trait are highest in the Southern states such as Mississippi, Alabama, Tennessee, and Florida. We found recently that sickle cell trait was associated with increased prevalence of
CKD, albuminuria, incident CKD, and decline in kidney function, but not with the development of ESKD, in large meta-analyses of several US cohort studies. Little is known regarding the population-based association of sickle cell trait with 1 versus no APOL1 allele and the effect of sickle cell trait and APOL1 on the risk for incident albuminuria, CKD, and ESKD among African Americans.

Using data from the Jackson Heart Study (JHS), we evaluated the risk for developing kidney disease among African Americans in the Jackson Heart Study. We found that carriers of 2 high-risk genes had the highest risk for chronic kidney disease, kidney disease worsening over time, and kidney failure compared with those without the high-risk genetic variants in a population-based cohort. Sickle cell trait did not change the findings. More studies are needed to confirm results.

**METHODS**

**Study Population**

JHS is a prospective, community-based, longitudinal cohort study of African Americans recruited from the metropolitan tricounty region of Jackson, MS (Hinds, Madison, and Rankin counties) originally designed to evaluate risk factors for cardiovascular diseases exclusively in self-reported African Americans. Study participants underwent examinations at baseline (Exam 1, 2000-2004), and follow-up (Exam 2, 2005-2008, and Exam 3, 2009-2013), which included surveys of demographics, medications, and clinical comorbid conditions. Outcomes include adjudicated cardiovascular disease events, CKD, and mortality. Recruitment and data collection protocols and survey instruments have been described previously.

Serum creatinine level was obtained during Exams 1 and 3 only and validated to isotope-dilution mass spectrometry standards.

Participants without serum creatinine measured at Exam 1 (n = 91) or Exam 3 (n = 1,638), those receiving dialysis (self-report) at Exam 1 (n = 10), or those without APOL1 genetic data (n = 1,358) were excluded from analyses, leaving a baseline cohort of n = 2,300 for this analysis (Fig 1).

Included participants were similar to the overall JHS cohort, except more participants were insured (88% vs 65%) and had albuminuria (11% vs 14%, respectively).

**Human Participants/Ethics**

All analyses were performed using protocols approved by JHS and the Institutional Review Board of the University of Mississippi Medical Center and with informed consent from all participants through the JHS coordinating center. We also obtained human subjects’ approval through the University of Washington Institutional Review Board for analyses.

**Exposure/Risk Groups**

**APOL1**

APOL1 G1 variants were originally genotyped in 3,000 JHS participants on the Affymetrix Genome-Wide Human SNP
Array 6.0, as previously described. The G2 variant was assessed by targeted sequencing in approximately 2,000 JHS participants using a custom hybrid capture array specifically for JHS participants, as previously described, and was assessed by exome sequencing in a total of 3,400 (overlapping with the previous 2,000) participants. Duplicate genotypes obtained by different methods were compared for reproducibility, and genotype data were pooled after appropriate quality control. At-risk APOL1 variants, including (G1/G1), (G1/G2), (G2/G2), (G0/G1), and (G0/G2), were compared with the reference variant (G0/G0).

**Sickle Cell Trait**

Sickle cell trait was assessed as a potential modifier of APOL1 in the development of CKD and ESKD. Genotyped data for the sickle cell mutation rs334 were obtained by exome sequencing performed through the National Heart, Lung, and Blood Institute (NHLBI) Exome Sequencing Project (JHS=367), the NHLBI Minority Health Genomics and Translational Research Bio-Repository Database (N = 311 from JHS), and the National Institute of Diabetes and Digestive and Kidney Diseases Type 2 Diabetes Genetic Exploration by Next-Generation Sequencing in Multi-Ethnic Samples (T2D-GENES; N = 571 from JHS). Three JHS participants who were homozygous for rs334 were excluded from further analyses. We examined kidney function outcomes by the number of rs334 risk alleles (0 or 1).

**Primary Outcomes of Interest**

**Continuous and Rapid Kidney Function Decline**

Serum creatinine was measured using a multipoint enzymatic spectrophotometric assay at the baseline study visit using the Vitros Ortho-Clinical Diagnostics Analyzer. Serum creatinine was re-measured in 2006 for 206 participants using the enzymatic method on a Roche Chemistry analyzer (Roche Diagnostics Corp). To harmonize serum creatinine measurements across examinations, we calibrated all Exam 1 serum creatinine measurements to those at Exam 3 using the isotope-dilution mass spectrometry–traceable method. We then estimated glomerular filtration rate (GFR) from serum-calibrated creatinine level using the 4-variable CKD Epidemiology Collaboration (CKD-EPI) equation (with race included), which was derived from a series of pooled cohorts that used iothalamate clearance as the criterion standard.

Continuous decline in estimated GFR (eGFR) was defined as the continuous change in eGFR assessed by linear regression. Rapid kidney function decline was defined as ≥30% decline within the 10-year time frame of longitudinal follow-up. In prior studies, similar outcomes were obtained when rapid kidney function decline was defined as an annual loss of ≥3 mL/min/1.73 m². Therefore, only 30% decline results are presented. Because 30% rapid kidney function decline incorporates baseline eGFR in the definition of decline, baseline eGFR was not adjusted for in the primary analyses. Prior analyses in which eGFR is incorporated into the baseline have shown similar results.

**Incident Albuminuria, CKD, and ESKD**

Incident albuminuria was defined as the development of urinary albumin-creatinine ratio (UACR) ≥ 30 mg/g in those with UACRs < 30 mg/g at baseline. Urinary albumin excretion was measured using a nephelometric immunoassay (Dade-Behring; now Siemens) and urinary creatinine excretion was measured using an enzymatic assay Vitros Ortho-Clinical Diagnostics Analyzer. Incident CKD was defined as incident development of eGFR < 60 mL/min/1.73 m² among those with eGFRs > 60 mL/min/1.73 m² at baseline and >1 mL/min/1.73 m² annual decline. Incident ESKD was defined as those who self-reported initiating dialysis either at Exam 2 or 3, an outcome which has been validated by the JHS Coordinating Center using JHS Centers for Medicare & Medicaid Services linked data that are not available for these analyses (A. Correa, unpublished data, 2020).

**Covariates**

Potential covariates of interest included age (years); sex; income (low, lower-middle, upper-middle, and affluent); education (less than high school, high school graduate, General Educational Development test equivalent or higher [less than college], and college degree); body mass index in kg/m²; systolic and diastolic blood pressures as the average of 2 blood pressure readings (mm Hg); HTN defined as blood pressure ≥140/90 mm Hg or the use of hypertensive medications; and diabetes defined as having blood glucose level > 126 mg/dL and glycated hemoglobin level ≥6.5% or receiving insulin or other hypoglycemic agents 2 weeks before the baseline visit. Other potential confounders of interest included high-sensitivity C-reactive protein (mg/dL) level; fasting low-density lipoprotein cholesterol (mg/dL) level; fasting high-density lipoprotein cholesterol (mg/dL) level; prevalent cardiovascular disease (history of coronary artery disease, stroke, or angioplasty); and UACR. UACR from spot urine samples correlated highly with UACR from timed urine samples (r=0.965).

**All-Cause Mortality**

Deaths were identified either from a monthly printout of Mississippi deaths from the Mississippi State Department of Health, hospital chart review, use of obituary notices, or linkage to the National Death Index reviewed until the time of follow-up. Death certificates were reviewed and cause of death was defined based on definitions found in the death certificate.

**Statistical Analysis**

We compared the characteristics of those with zero, 1, or 2 APOL1 alleles at baseline (Exam 1). We
Table 1. Characteristics by APOL1 Risk Alleles and Sickle Cell Trait

| Characteristic                   | Overall Sample | APOL1 Risk Alleles | APOL1 Risk Alleles | APOL1 Risk Alleles | Sickle Cell Trait |
|----------------------------------|----------------|---------------------|---------------------|---------------------|-------------------|
|                                  |                | 0 or 1              | 2                   | 0                   | 1                | 2                | No     | Yes    |
| N                                | 2,300          | 1,987               | 313                 | 950                 | 1,037             | 313              | 2,103  | 196    |
| Age, y                           | 55 ± 12        | 55 ± 12             | 54 ± 12             | 55 ± 12             | 54 ± 12           | 54 ± 12          | 54 ± 12 | 56 ± 12 |
| Female sex                       | 1,431 (62%)    | 1,249 (63%)         | 182 (58%)           | 587 (62%)           | 662 (64%)         | 182 (58%)        | 1,320 (63%) | 110 (56%) |
| Education                        |                |                     |                     |                     |                  |                  |        |
| <High school                     | 355 (16%)      | 310 (16%)           | 45 (14%)            | 144 (15%)           | 166 (16%)         | 45 (14%)         | 320 (15%) | 35 (18%) |
| High school graduate             | 409 (18%)      | 364 (18%)           | 45 (14%)            | 169 (18%)           | 195 (19%)         | 45 (14%)         | 369 (18%) | 40 (20%) |
| ≥General Educational Development |                |                     |                     |                     |                  |                  |        |
| College                          | 541 (24%)      | 468 (24%)           | 73 (23%)            | 230 (24%)           | 238 (23%)         | 73 (23%)         | 493 (24%) | 48 (25%) |
| Income                           |                |                     |                     |                     |                  |                  |        |
| Poor                             | 214 (11%)      | 181 (11%)           | 33 (13%)            | 79 (10%)            | 102 (12%)         | 33 (13%)         | 196 (11%) | 18 (11%) |
| Lower-middle                     | 441 (23%)      | 395 (23%)           | 46 (17%)            | 176 (22%)           | 219 (25%)         | 46 (17%)         | 403 (23%) | 37 (23%) |
| Upper-middle                     | 628 (32%)      | 539 (32%)           | 89 (34%)            | 270 (34%)           | 269 (30%)         | 89 (34%)         | 571 (32%) | 57 (35%) |
| Affluent                         | 671 (34%)      | 574 (34%)           | 97 (37%)            | 279 (35%)           | 295 (33%)         | 97 (37%)         | 619 (35%) | 52 (32%) |
| Health insurance status          |                |                     |                     |                     |                  |                  |        |
| Uninsured                        | 286 (12%)      | 244 (12%)           | 42 (14%)            | 124 (13%)           | 120 (12%)         | 42 (14%)         | 264 (13%) | 22 (11%) |
| Insured                          | 2,004 (88%)    | 1,734 (88%)         | 270 (87%)           | 824 (87%)           | 910 (88%)         | 270 (87%)        | 1,830 (87%) | 173 (89%) |
| Systolic blood pressure, mm Hg   | 126 ± 17       | 126 ± 18            | 126 ± 16            | 126 ± 18            | 125 ± 17          | 126 ± 16         | 126 ± 17 | 125 ± 16 |
| Diastolic blood pressure, mm Hg  | 79 ± 10        | 79 ± 10             | 80 ± 10             | 79 ± 10             | 79 ± 10           | 80 ± 10          | 79 ± 10 | 78 ± 10 |
| Hypertension                     | 1,379 (60%)    | 1,201 (60%)         | 178 (57%)           | 582 (61%)           | 619 (60%)         | 178 (57%)        | 1,260 (60%) | 118 (60%) |
| Hypertension medication use      | 1,129 (49%)    | 986 (60%)           | 143 (46%)           | 472 (50%)           | 514 (50%)         | 143 (46%)        | 1,034 (49%) | 94 (48%) |
| β-Blockers                       | 236 (13%)      | 203 (13%)           | 33 (13%)            | 94 (12%)            | 109 (13%)         | 33 (13%)         | 217 (13%) | 19 (12%) |
| Calcium channel blockers         | 426 (23%)      | 370 (23%)           | 56 (22%)            | 181 (23%)           | 189 (23%)         | 56 (22%)         | 396 (23%) | 30 (19%) |
| Diuretics                        | 716 (38%)      | 623 (39%)           | 93 (37%)            | 303 (38%)           | 320 (39%)         | 93 (37%)         | 662 (39%) | 54 (34%) |
| ACEI                             | 366 (16%)      | 318 (16%)           | 48 (15%)            | 151 (16%)           | 167 (16%)         | 48 (15%)         | 337 (16%) | 28 (14%) |
| ARB                              | 188 (8%)       | 160 (8%)            | 28 (9%)             | 84 (9%)             | 76 (7%)           | 28 (9%)          | 169 (8%) | 19 (10%) |
| Diabetes                         | 461 (20%)      | 390 (20%)           | 71 (23%)            | 174 (18%)           | 216 (21%)         | 71 (23%)         | 429 (20%) | 32 (16%) |
| HbA1c, %                         | 5.9 ± 1.2      | 5.9 ± 1.2           | 6.1 ± 1.3           | 5.9 ± 1.2           | 5.9 ± 1.2         | 6.1 ± 1.3        | 5.9 ± 1.2 | 5.7 ± 1.2 |
| Body mass index, kg/m²           | 32.0 ± 7.3     | 32.0 ± 7.4          | 32.3 ± 6.5          | 31.6 ± 7.3          | 32.3 ± 7.4        | 32.3 ± 6.5       | 32.0 ± 7.2 | 31.5 ± 8.1 |

(Continued)
| Characteristic                          | Overall Sample | APOL1 Risk Alleles | Sickle Cell Trait |
|----------------------------------------|----------------|--------------------|------------------|
|                                       |                | 0 or 1             | 2                | No | Yes |
| Weight, Kg                            | 91.9 ± 21.6    | 91.7 ± 21.9        | 93.4 ± 19.4      | 92.1 ± 21.5 | 90.5 ± 22.5 |
| Height, cm                            | 169.5 ± 9.3    | 169.4 ± 9.3        | 170.1 ± 9.5      | 169.5 ± 9.3 | 169.8 ± 9.3 |
| Waist circumference, cm               | 101.2 ± 16.1   | 101.1 ± 16.2       | 101.7 ± 15.4     | 101.3 ± 16.1 | 100.4 ± 16.8 |
| Cholesterol, mg/dL                    | 198.8 ± 40.2   | 198.9 ± 40.4       | 198.1 ± 39.1     | 198.5 ± 40.0 | 203.0 ± 42.4 |
| HDL cholesterol, mg/dL                | 51.6 ± 14.4    | 51.9 ± 14.6        | 50.2 ± 13.6      | 51.7 ± 14.3 | 51.2 ± 15.7 |
| LDL cholesterol, mg/dL                | 126.4 ± 36.6   | 126.3 ± 36.5       | 127.1 ± 37.4     | 125.9 ± 36.4 | 131.1 ± 38.2 |
| Triglycerides, mg/dL                  | 90 [64-126]    | 89 [64-126]        | 91 [63-130]      | 89 [63-126] | 91 [68-124] |
| Statin medication use                 | 235 (13%)      | 201 (12%)          | 34 (13%)         | 218 (13%) | 17 (11%) |
| C-Reactive protein, mg/dL             | 2.62 [1.11-5.62]| 2.61 [1.10-5.60]  | 2.70 [1.15-5.91] | 2.60 [1.07-5.63] | 2.95 [1.34-5.60] |
| Prevalent CHD                         | 142 (6%)       | 112 (6%)           | 30 (10%)         | 129 (6%) | 13 (7%) |
| Prevalent stroke                      | 75 (3%)        | 61 (3%)            | 14 (5%)          | 69 (3%) | 6 (3%) |
| Prevalent CVD                         | 203 (9%)       | 162 (8%)           | 41 (13%)         | 186 (9%) | 17 (9%) |
| eGFR, mL/min/1.73 m²                  | 95.7 ± 20.2    | 95.9 ± 19.9        | 94.5 ± 21.9      | 96 ± 20 | 92 ± 22 |
| eGFR < 60 mL/min/1.73 m²              | 96 (4%)        | 72 (4%)            | 24 (8%)          | 24 (8%) | 14 (7%) |
| UACR, mg/g                            | 5.79 [3.86-10.97] | 5.74 [3.82-10.18] | 6.41 [4.08-17.60] | 6.41 [4.08-17.60] | 5.72 [3.84-10.37] | 8.02 [4.24-30.92] |
| UACR > 30 mg/g                        | 160 (7%)       | 124 (6%)           | 36 (12%)         | 123 (6%) | 37 (19%) |

Note: Values expressed as mean ± standard deviation, number (percent), or median (interquartile range).

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; APOL1, apolipoprotein L1; ARB, angiotensin receptor blocker; CHD, coronary heart disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; UACR, urinary albumin-creatinine ratio.
Table 2. Associations of APOL1 Risk Alleles With Kidney Function Decline and Mortality

| Outcome/Model | No. of APOL1 Risk Alleles | 0      | 1      | 2      |
|---------------|---------------------------|--------|--------|--------|
|               |                           |        |        |        |
| Incident UACR |                           |        |        |        |
| Events/no. at risk | 54/589 | 76/520 | 25/174 |
| Incidence rate (%/y) | 1.19  | 1.66  | 1.89  |
| HR (95% CI)     | 1.00 (ref)                | 1.32 (0.79 to 2.23) |
| Adjusted for age, sex | 1.00 (ref) | 1.49 (0.88 to 2.52) |
| Adjusted for HTN, DM   | 1.00 (ref) | 1.52 (0.89 to 2.60) |
| Adjusted for sickle cell trait | 1.00 (ref) | 1.52 (0.89 to 2.60) |
| Unadjusted          | 1.00 (ref)                | 1.47 (0.97 to 2.22) |
| Adjusted for age, sex | 1.00 (ref) | 1.49 (0.98 to 2.26) |
| Adjusted for HTN, DM   | 1.00 (ref) | 1.50 (0.98 to 2.30) |
| Adjusted for sickle cell trait | 1.00 (ref) | 1.50 (0.98 to 2.30) |
| Incident Dialysis (self-report) |        |        |        |
| Events/no. at risk | 2/950  | 6/1,037 | 6/313 |
| Proportion | 0.20% | 0.60% | 1.90% |
| HR (95% CI)     | 1.00 (ref)                | 4.90 (1.69 to 14.23) |
| Adjusted for age, sex | 1.00 (ref) | 5.16 (1.77 to 15.04) |
| Adjusted for HTN, DM   | 1.00 (ref) | 4.78 (1.62 to 14.06) |
| Adjusted for sickle cell trait | 1.00 (ref) | 5.02 (1.69 to 14.92) |
| Incident CKD     |                           |        |        |        |
| Events/no. at risk | 97/922 | 113/993 | 37/289 |
| Incidence rate (%/y) | 1.32  | 1.42  | 1.61  |
| HR (95% CI)     | 1.00 (ref)                | 1.21 (0.83 to 1.76) |
| Adjusted for age, sex | 1.00 (ref) | 1.50 (1.01 to 2.25) |
| Adjusted for HTN, DM   | 1.00 (ref) | 1.51 (1.00 to 2.27) |
| Adjusted for sickle cell trait | 1.00 (ref) | 1.55 (1.03 to 2.33) |
| Continuous Decline, mL/min/1.73 m²/y |        |        |        |
| N  | 950 | 1,037 | 313 |
| β (95% CI)     | 1.00 (ref)                | −1.70 (−3.11 to −0.29) |
| Adjusted for age, sex | 1.00 (ref) | −1.92 (−3.28 to −0.55) |
| Adjusted for HTN, DM   | 1.00 (ref) | −1.78 (−3.13 to −0.43) |
| Adjusted for sickle cell trait | 1.00 (ref) | −1.82 (−3.17 to −0.47) |
| Unadjusted          | 1.00 (ref)                | −0.19 (−1.06 to 1.02) |
| Adjusted for age, sex | 1.00 (ref) | −0.25 (−1.26 to 0.76) |
| Adjusted for HTN, DM   | 1.00 (ref) | −0.12 (−1.12 to 0.87) |
| Adjusted for sickle cell trait | 1.00 (ref) | −0.14 (−1.14 to 0.85) |
| Decline ≥ 30%     | Events/no. at risk | 32/950 | 31/1,037 | 21/313 |

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evaluated incident CKD, incident albuminuria, percent change in eGFR over time, and rapid kidney function decline over the approximate 10-year period of follow-up. The association of APOL1 with rapid kidney function decline adjusting for sickle cell trait was evaluated for the entire cohort for whom there were available data.

Because only 2 fixed time points were available for kidney function determination, univariate and multivariable associations of risk factors with ≥30% decline were conducted with logistic regression and presented as odds ratios. Incident albuminuria, incident CKD, incident dialysis (self-report), and mortality were all assessed using discrete time proportional hazards modeling, while continuous change in eGFR was assessed using multivariable simple linear regression due to only 2 time points available. Because time points for incident albuminuria, incident CKD, and incident dialysis (self-report) were discrete and only assessed at fixed time points, we used a discrete time proportional hazards model. Initial models, based on a priori risk factor inclusion and factors significant in univariate analyses, included adjustment for age, sex, and ancestry informative markers. Analyses were further adjusted for HTN, diabetes, and sickle cell trait. Secondary mortality analyses were performed using IBM SPSS 22 (IBM Corp) and STATA (StataCorp, College Station, TX).

**RESULTS**

**Baseline Characteristics**

Data were available for 2,300 participants at baseline, of whom 41.3% (n = 950) had zero, 45.1% (n = 1,037) had 1, and 13.6% (n = 313) had 2 APOL1 risk alleles. Sickle cell trait was present in 8.5% (n = 196/2,299) participants (Table 1). Participants with zero, 1, or 2 APOL1 risk alleles were similar in all baseline demographics except those with 2 risk alleles were more likely to be in the upper-middle income range; slightly less likely to have a diagnosis of HTN or be receiving hypertensive medications; had slightly lower cholesterol, high-density lipoprotein cholesterol, and triglyceride levels; were more likely to be receiving a statin; had a higher prevalence of coronary heart disease; and were slightly more likely to have evidence of underlying CKD (eGFR < 60 mL/min/1.73 m² or UACR > 30 mg/g) compared with those with zero or 1 APOL1 allele.

| Outcome/Model                  | No. of APOL1 Risk Alleles | Unadjusted                  | Adjusted for age, sex | Adjusted for HTN, DM | Adjusted for sickle cell trait |
|-------------------------------|---------------------------|-----------------------------|-----------------------|----------------------|-------------------------------|
| Proportion                    |                           | OR (95% CI)                 | OR (95% CI)          | OR (95% CI)          |
| 0                             | 3.40%                     | 1.00 (ref)                  | 1.00 (ref)           | 1.00 (ref)           |
| 1                             | 3.00%                     | 2.20 (1.32 to 3.66)         | 2.42 (1.44 to 4.06)  | 2.36 (1.39 to 4.01)  |
| 2                             | 6.70%                     | 2.42 (1.42 to 4.13)         | 2.42 (1.42 to 4.13)  | 2.42 (1.42 to 4.13)  |
| Mortality Rate                |                           | HR (95% CI)                 | HR (95% CI)          | HR (95% CI)          |
| Percent/y                     |                           | 1.27%                       | 1.47%                | 1.31%               |
| Unadjusted                    |                           | 1.00 (ref)                  | 0.95 (0.69 to 1.33)  | 0.92 (0.66 to 1.27)  |
| Adjusted for age, sex         |                           | 1.00 (ref)                  | 0.96 (0.69 to 1.33)  | 0.91 (0.66 to 1.27)  |
| Adjusted for HTN, DM          |                           | 1.00 (ref)                  | 0.91 (0.66 to 1.27)  | 0.91 (0.66 to 1.27)  |
| Adjusted for sickle cell trait|                           | 1.00 (ref)                  | 1.15 (0.90 to 1.46)  | 1.03 (0.72 to 1.46)  |
| Mortality events/no. at risk  |                           | 116/1,293                   | 152/1,479            | 41/444               |
| Unadjusted                    |                           | 1.00 (ref)                  | 1.03 (0.70 to 1.43)  | 1.00 (0.70 to 1.43)  |
| Adjusted for age, sex         |                           | 1.00 (ref)                  | 1.07 (0.75 to 1.53)  | 1.00 (0.70 to 1.43)  |
| Adjusted for HTN, DM          |                           | 1.00 (ref)                  | 1.00 (0.70 to 1.44)  | 1.00 (0.70 to 1.44)  |
| Adjusted for sickle cell trait|                           | 1.00 (ref)                  | 1.00 (0.70 to 1.44)  | 1.00 (0.70 to 1.44)  |

Abbreviations: APOL1, apolipoprotein L1; CKD, chronic kidney disease; DM, diabetes mellitus; HR, hazard ratio; HTN, hypertension; OR, odds ratio; ref, reference; UACR, urinary albumin-creatinine ratio.
## Table 3. Associations of APOL1 Risk Alleles With Kidney Function Decline and Mortality Adjusted for Ancestry Informative Markers

| Outcome/Model                  | No. of APOL1 Risk Alleles |          |          |
|--------------------------------|---------------------------|----------|----------|
|                                | 0                         | 1        | 2        |
| **Incident UACR**              |                           |          |          |
| Events/no. at risk             | 54/589                    | 76/520   | 25/174   |
|                               | HR (95% CI)               | HR (95% CI) | HR (95% CI) |
| Unadjusted                     | 1.00 (ref)                | 1.32 (0.79 to 2.23) |
| Adjusted for age, sex, AIMs    | 1.00 (ref)                | 1.29 (0.77 to 2.16) |
| Adjusted for HTN, DM           | 1.00 (ref)                | 1.33 (0.78 to 2.26) |
| Adjusted for sickle cell trait | 1.00 (ref)                | 1.33 (0.78 to 2.26) |
| Unadjusted                     | 1.00 (ref)                | 1.47 (0.97 to 2.22) |
| Adjusted for age, sex, AIMs    | 1.00 (ref)                | 1.47 (0.96 to 2.25) |
| Adjusted for HTN, DM           | 1.00 (ref)                | 1.48 (0.96 to 2.29) |
| Adjusted for sickle cell trait | 1.00 (ref)                | 1.48 (0.96 to 2.29) |
| **Incident Dialysis (self-report)** |                         |          |          |
| Events/no. at risk             | 2/950                     | 6/1,037  | 6/313    |
|                               | HR (95% CI)               | HR (95% CI) | HR (95% CI) |
| Unadjusted                     | 1.00 (ref)                | 4.90 (1.69 to 14.23) |
| Adjusted for age, sex, AIMs    | 1.00 (ref)                | 5.21 (1.74 to 15.62) |
| Adjusted for HTN, DM           | 1.00 (ref)                | 4.83 (1.58 to 14.75) |
| Adjusted for sickle cell trait | 1.00 (ref)                | 5.02 (1.62 to 15.54) |
| Unadjusted                     | 1.00 (ref)                | 2.72 (0.55 to 13.51) |
| Adjusted for age, sex, AIMs    | 1.00 (ref)                | 2.84 (0.55 to 14.68) |
| Adjusted for HTN, DM           | 1.00 (ref)                | 2.78 (0.53 to 14.75) |
| Adjusted for sickle cell trait | 1.00 (ref)                | 2.67 (0.50 to 14.26) |
| **Incident CKD**               |                           |          |          |
| Events/no. at risk             | 97/922                    | 113/993  | 37/289   |
|                               | HR (95% CI)               | HR (95% CI) | HR (95% CI) |
| Unadjusted                     | 1.00 (ref)                | 1.12 (0.83 to 1.76) |
| Adjusted for age, sex, AIMs    | 1.00 (ref)                | 1.46 (0.97 to 2.20) |
| Adjusted for HTN, DM           | 1.00 (ref)                | 1.47 (0.97 to 2.21) |
| Adjusted for sickle cell trait | 1.00 (ref)                | 1.51 (0.99 to 2.28) |
| Unadjusted                     | 1.00 (ref)                | 1.07 (0.80 to 1.43) |
| Adjusted for age, sex, AIMs    | 1.00 (ref)                | 1.14 (0.83 to 1.55) |
| Adjusted for HTN, DM           | 1.00 (ref)                | 1.14 (0.83 to 1.56) |
| Adjusted for sickle cell trait | 1.00 (ref)                | 1.14 (0.83 to 1.56) |
| **Continuous Decline in eGFR (mL/min/1.73 m² %/y)** |          |          |          |
| N                              | 950                       | 1,037    | 313      |
|                               | β (95% CI)                | β (95% CI) | β (95% CI) |
| Unadjusted                     | 1.00 (ref)                | −1.70 (−3.11 to −0.29) |
| Adjusted for age, sex, AIMs    | 1.00 (ref)                | −1.84 (−3.22 to −0.33) |
| Adjusted for HTN, DM           | 1.00 (ref)                | −1.73 (−3.10 to −0.37) |
| Adjusted for sickle cell trait | 1.00 (ref)                | −1.78 (−3.15 to −0.42) |
| Unadjusted                     | 1.00 (ref)                | −0.19 (−1.06 to 1.02) |
| Adjusted for age, sex, AIMs    | 1.00 (ref)                | −0.22 (−1.24 to 0.80) |
| Adjusted for HTN, DM           | 1.00 (ref)                | −0.12 (−1.13 to 0.89) |
| Adjusted for sickle cell trait | 1.00 (ref)                | −0.15 (−1.16 to 0.86) |
| **Decline ≥ 30%**              |                           |          |          |
| Events/no. at risk             | 32/950                    | 31/1037  | 21/313   |
|                               | OR (95% CI)               | OR (95% CI) | OR (95% CI) |
| Unadjusted                     | 1.00 (ref)                | 2.20 (1.32 to 3.66) |
| Adjusted for age, sex, AIMs    | 1.00 (ref)                | 2.42 (1.43 to 4.10) |

(Continued)
Incident Albuminuria

Those with 2 risk alleles were found to have a 1.88-fold (95% CI, 1.04-3.40) greater risk for incident albuminuria, defined as UACR > 30 mg/g adjusting for age, sex, HTN, diabetes mellitus, and sickle cell trait (Table 2), which remained significant after adjustment for ancestry informative markers (adjusted hazard ratio [aHR], 1.98; 95% CI, 1.07-3.64), compared with those with no risk alleles (Table 3). Those with 1 APOL1 risk allele showed a trend toward increased incident albuminuria (aHR, 1.50; 95% CI, 0.98-2.30) compared with those with no risk allele, which remained nonsignificant after adjustment for ancestry informative markers (aHR, 1.48; 95% CI, 0.96-2.29).

Incident ESKD

Those with 2 alleles had a 9.05-fold (95% CI, 1.79-45.85) adjusted greater risk for incident self-reported dialysis initiation compared with those with zero or 1 risk allele (Table 2), which remained significant after adjustment for ancestry informative markers (aHR, 1.50; 95% CI, 0.98-2.30) compared with those with no risk allele, which remained nonsignificant after adjustment for ancestry informative markers (aHR, 1.48; 95% CI, 0.96-2.29).

Incident CKD

There was an association of APOL1 with incident CKD defined as eGFR < 60 mL/min/1.73 m² at Exam 3 for those with 2 risk alleles compared with those with zero (aHR, 1.65; 95% CI, 1.06-2.57) that was similar after adjustment for ancestry informative markers (aHR, 1.62; 95% CI, 1.03-2.53), while it remained nonsignificant for those with 1 allele compared with those with zero risk allele with (aHR, 1.14; 95% CI, 0.83-1.56) and without adjustment for ancestry informative markers (aHR, 1.14; 95% CI, 0.83-1.56) after adjustment.

Continuous and Rapid Decline in eGFR

Continuous decline in eGFR was significant for those with 2 risk alleles compared with zero or 1 (β = −1.90; 95% CI, −3.35 to −0.45) that was similar after adjustment for ancestry informative markers (β = −1.86; 95% CI, −3.34 to −0.39), while those with 1 allele had a nonsignificant decrease in eGFR compared with those with no risk allele (β = −0.14; 95% CI, −1.14 to 0.85), which was similar after adjustment for ancestry informative markers (β = −0.15; 95% CI, −1.16 to 0.86). In addition, those with 2 risk alleles were found to have a 2.21-fold (95% CI, 1.22 to 4.00) greater risk for rapid decline in eGFR compared with those with zero allele, which was similar after adjustment for ancestry informative markers (Tables 2 and 3). Those with 1 risk allele did not have any increase in risk compared with zero allele, both with and without adjustment for ancestry informative markers.

Mortality

When comparing those with 2 alleles with those with zero or 1 APOL1 allele, there were no statistically significant
differences in all-cause mortality. When models were stratified by zero versus 1 or zero versus 2 risk alleles, there were no differences in mortality. Those with 2 risk alleles had no additional risk for mortality before or after adjustment (Tables 2 and 3).

**Sickle Cell Trait Interactions**

Sickle cell trait was present in 8.5% of the analysis cohort, of whom 13 (7%) had 1 or 2 risk alleles for APOL1 (Table 3). We confirmed that sickle cell trait was associated with incident CKD, decline in eGFR, and rapid kidney function decline in initial and adjusted models (Table S1) that were not modified by diabetes, HTN, or APOL1 genotype. Models were stratified by APOL1 status and sickle cell trait. There were no significant interactions between sickle cell trait and APOL1 in any model.

**DISCUSSION**

We found that study participants with 1 APOL1 allele had no significant increased odds of incident albuminuria or risk for incident CKD, rapid kidney function decline, ESKD, or continuous decline in eGFR. We also confirmed that in a population-based cohort, study participants with 2 high-risk APOL1 alleles had increased risk for albuminuria, ESKD, rapid kidney function decline, and continuous eGFR decline compared with those with 1 or no risk allele. There was no interaction with sickle cell trait for any of the outcomes.

Earlier case-control studies linking APOL1 genotypes to kidney disease showed the association of high-risk APOL1 alleles with greater risk for FSGS-associated ESKD compared with those 1 or no high-risk allele. The studies by Genoves, Pollak and colleagues and Tzur superseded the initial data that linked MYH9 with FSGS-associated ESKD, implicating APOL1. Subsequent cohort studies, particularly among individuals with CKD, have shown that having 2 of the APOL1 high-risk variants was associated with more rapid decline in kidney function and increased risk for proteinuria among African Americans with CKD.

Among participants in the Coronary Artery Risk Development in Young Adults (CARDIA) study, Peralta et al. found that younger African Americans with 2 risk alleles had greater incident albuminuria compared with Whites and those with 1 risk allele, and those with high-risk alleles had a 0.45% faster rate of decline in eGFR than Whites. African Americans with 1 or no risk allele had an intermediate risk for albuminuria and a faster rate of decline compared with Whites, which became insignificant after further adjustment.

In the Atherosclerosis Risk in Communities (ARIC) study (some of whom participated in JHS), Foster et al. found that participants with 2 APOL1 alleles had greater risk for CKD (1.49-fold increased risk for CKD [95% CI, 1.02 - 2.17] and 1.88-fold increased risk for ESKD [95% CI, 1.20-2.93]) compared with zero or 1 risk allele. Our findings confirm the increased risk for albuminuria and ESKD for carriers of APOL1 alleles, but differ from those of Peralta et al. and Foster et al., respectively, in that we assessed the risk for additional adverse kidney outcomes associated with 1 versus no risk allele and 2 versus no risk alleles.

APOL1 has been shown to protect against a virulent form of West African sleeping sickness by interfering with the secreted protein that blocks lysis of the trypanosome by normal APOL1-high-density lipoprotein variants. Review of the initial risk for FSGS-associated ESKD was consistent with an autosomal recessive penetrance of APOL1 in African Americans. More recent laboratory data show that kidney cells transformed to have either APOL1 allele mutations have cytotoxic phenotypes that appear to be mediated by stress-activated protein kinases, which are associated with loss of intracellular potassium channels and loss of potassium efflux. In addition, APOL1 is found in podocytes and may be linked with accelerating apoptosis, which may predispose affected individuals to certain renal disorders such as FSGS. Exact mechanisms of APOL1 variants and increased risk for kidney disease remain elusive; however, current research continues to investigate potential mechanisms of disease pathophysiology.

JHS is one of the largest prospective community-based cohort studies in African Americans with adjudicated data, which has information on APOL1, clinical parameters, ancestry informative markers, and sickle cell trait. Limitations include a relatively younger cohort and 10 years of follow-up, which may explain why fewer participants developed incident albuminuria, CKD, or ESKD compared with other cohorts in which older more high-risk patients or only patients with CKD were enrolled. Despite this limitation, our findings provide additional public health information regarding the absolute risk for the development of adverse kidney outcomes among African Americans in the general population with APOL1 risk variants. Longer follow-up and larger studies will help further elucidate APOL1 associations with kidney disease. Finally, the small sample size of individuals in JHS with both genotypes of interest limited the ability to assess effects by individual genotype.

The current study found that the presence of 1 APOL1 risk variant was not associated with increased risk for adverse CKD outcomes, but having 2 high-risk variants is associated with greater risk for some outcomes except mortality. This information has significant public health ramifications because it is estimated that >13.5% of the US African American population have 2 APOL1 risk alleles. Knowledge of APOL1 status will have important implications for counseling regarding kidney disease risk, particularly for those who are interested in living transplant donation among African Americans and other individuals with recent African heritage admixture. Further research is necessary to determine which additional factors may be important for those with 1 or 2 risk
alleles and whether modifiable behavioral factors are associated with greater risk for kidney disease.

**SUPPLEMENTARY MATERIAL**

**Supplementary File (PDF)**

**Table S1.** Associations of APOL1 with kidney function decline and mortality by the presence of sickle cell trait

**ARTICLE INFORMATION**

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Does the presence of one APOL1 risk allele and sickle cell trait influence kidney outcomes?

Demographics
- Jackson Heart Study
- Longitudinal Cohort Study
- N = 5306 African American

Exposures
- Sickle Cell Trait 8.5%
- APOL1 alleles
  - 0
  - 1
  - 2

Outcomes after adjusting for sickle cell trait

| Incident ACR | Incident Dialysis | Incident CKD (%)/yr | ≥ 30 % decline | Mortality |
|--------------|-------------------|--------------------|----------------|-----------|
| 1.19 %/yr    | 0.20 %/yr         | 1.32 %/yr          | 3.40 %/yr      | 1.27 %/yr |
| 1.66 %/yr    | 0.60 %/yr         | 1.42 %/yr          | 3.00 %/yr      | 1.47 %/yr |
| 1.89 %/yr    | 1.90 %/yr         | 1.62 %/yr          | 6.70 %/yr      | 1.31 %/yr |

Multivariable models compare 2 vs 0 or 1 risk alleles

| Incident ACR | Incident Dialysis | Incident CKD (%)/yr | ≥ 30 % decline | Mortality |
|--------------|-------------------|--------------------|----------------|-----------|
| aHR = 1.88   | aHR = 9.05        | aHR = 1.65         | aOR = 2.21     | aHR = 1.00 |
| [1.04, 3.40] | [1.79, 45.85]     | [1.06, 2.57]       | [1.22, 4.00]   | [0.70, 1.44] |

Conclusion: Compared to wild type APOL1, the presence of one APOL1 risk allele was not associated with increased risk of CKD outcomes, while two risk alleles were associated with incident albuminuria, CKD, kidney function decline, and incident dialysis after adjustment. There was no interaction between APOL1 and sickle cell trait on kidney or mortality outcomes.

Reference: Young B, Wilson J, Reiner A et al. APOL1, sickle cell trait, and CKD in the Jackson Heart Study. Kidney Medicine, 2021.

Visual Abstract by Sai Sudha Mannemuddhu, MD, FAAP