Kidney Medicine Original Research

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 m^2), albuminuria (urinary albumin-creatinine ratio ≥ 30 mg/g), continuous and rapid kidney function decline (≥30% 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 13.6% 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.

Visual Abstract included

Complete author and article information provided before references.

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End-stage kidney disease (ESKD) currently affects more than 700,000 persons in the United States[1] 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.[2-5] 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.[7,8] 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,[7] 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.[17] 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

PLAIN-LANGUAGE SUMMARY

Kidney failure is increased in African Americans compared with Whites. Alterations of the apolipoprotein L1 (*APOL1*) gene are associated with an increased risk for kidney disease among African Americans. People who carry 2 copies of the high-risk variants in this gene are at risk for kidney disease. 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.

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.[17] 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 incidence of CKD, CKD progression, and development of ESKD associated with *APOL1* alleles after adjusting for age, sex, ancestry informative markers, clinical factors, and sickle cell trait.

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.[18,19] 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.[20] Serum creatinine level was obtained during Exams 1 and 3 only and validated to isotope-dilution mass spectrometry standards.[21]

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

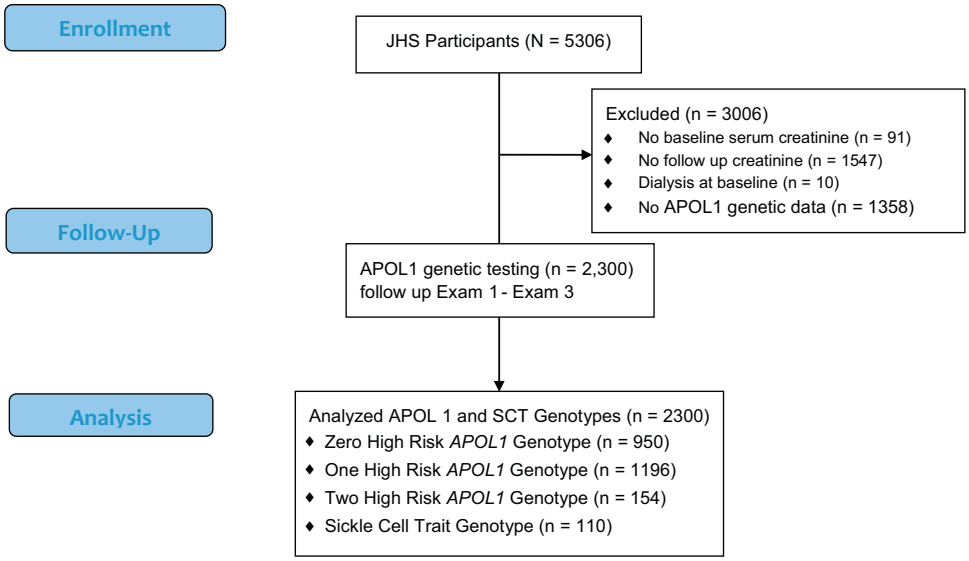

Figure 1. Jackson Heart Study (JHS) apolipoprotein L1 (*APOL1*) flow diagram.

Array 6.0, as previously described.[22] 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,[23] 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).[17] 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).[17]

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.[24] 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.[21] 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),[25] 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.[26,27] In prior studies, similar outcomes were obtained when rapid kidney function decline was defined as an annual loss of ≥3 mL/min/1.73 m^2.[28] 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.[28]

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 m^2 among those with eGFRs > 60 mL/min/1.73 m^2 at baseline and >1 mL/min/1.73 m^2 annual decline. Incident ESKD was defined as those who self-reported initialing 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/m^2; systolic and diastolic blood pressures are 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).[28]

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			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	541 (24%)	468 (24%)	73 (23%)	230 (24%)	238 (23%)	73 (23%)	493 (24%)	48 (25%)
College	990 (43%)	840 (42%)	150 (48%)	404 (43%)	436 (42%)	150 (48%)	916 (44%)	73 (37%)
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 (50%)	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%)
HbA_{1c}, %	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/m^2	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)

Table 1 (Cont'd). Characteristics by *APOL1* Risk Alleles and Sickle Cell Trait

		APOL1 Risk Alleles		*APOL1* Risk Alleles			Sickle Cell Trait	
Characteristic	**Overall Sample**	**0 or 1**	**2**	**0**	**1**	**2**	**No**	**Yes**
Weight, Kg	91.9 ± 21.6	91.7 ± 21.9	93.4 ± 19.4	90.8 ± 21.5	92.5 ± 22.3	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	169.6 ± 9.1	169.2 ± 9.4	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	100.3 ± 16.2	101.9 ± 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	198.8 ± 41.5	199.1 ± 39.4	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	51.6 ± 14.7	52.1 ± 14.4	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	126.3 ± 36.1	126.2 ± 36.9	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 [63-121]	89 [65-129]	91 [63-130]	89 [63-126]	91 [68-124]
Statin medication use	235 (13%)	201 (12%)	34 (13%)	88 (11%)	113 (14%)	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]	2.49 [1.03-5.42]	2.75 [1.15-5.81]	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%)	46 (5%)	66 (6%)	30 (10%)	129 (6%)	13 (7%)
Prevalent stroke	75 (3%)	61 (3%)	14 (5%)	23 (2%)	38 (4%)	14 (5%)	69 (3%)	6 (3%)
Prevalent CVD	203 (9%)	162 (8%)	41 (13%)	65 (7%)	97 (9%)	41 (13%)	186 (9%)	17 (9%)
eGFR, mL/min/ 1.73 m^2	95.7 ± 20.2	95.9 ± 19.9	94.5 ± 21.9	95.7 ± 19.2	96.1 ± 20.5	94.5 ± 21.9	96 ± 20	92 ± 22
eGFR < 60 mL/ min/1.73 m^2	96 (4%)	72 (4%)	24 (8%)	28 (3%)	44 (4%)	24 (8%)	82 (4%)	14 (7%)
UACR, mg/g	5.79 [3.86-10.97]	5.74 [3.82-10.18]	6.41 [4.08-17.60]	5.74 [3.85-10.00]	5.78 [3.80-10.81]	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%)	57 (6%)	67 (7%)	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, cardiovasculardisease; 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

	No. of *APOL1* Risk Alleles		
Outcome/Model	**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)	**HR (95% CI)**	**HR (95% CI)**
Unadjusted		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)	1.63 (0.92 to 2.88)
Adjusted for age, sex	1.00 (ref)	1.49 (0.98 to 2.26)	1.84 (1.03 to 3.28)
Adjusted for HTN, DM	1.00 (ref)	1.50 (0.98 to 2.30)	1.88 (1.04 to 3.40)
Adjusted for sickle cell trait	1.00 (ref)	1.50 (0.98 to 2.30)	1.88 (1.04 to 3.40)
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)	**HR (95% CI)**	**HR (95% CI)**
Unadjusted		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)
Unadjusted	1.00 (ref)	2.72 (0.55 to 13.51)	9.30 (1.87 to 46.34)
Adjusted for age, sex	1.00 (ref)	2.79 (0.56 to 13.89)	9.94 (1.99 to 46.69)
Adjusted for HTN, DM	1.00 (ref)	2.60 (0.52 to 13.02)	8.90 (1.76 to 44.88)
Adjusted for sickle cell trait	1.00 (ref)	2.47 (0.49 to 12.42)	9.05 (1.79 to 45.85)
Incident CKD			
Events/no. at risk	97/922	113/993	37/289
Incidence rate (%/y)	1.32	1.42	1.61
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**
Unadjusted		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)
Unadjusted	1.00 (ref)	1.07 (0.80 to 1.43)	1.26 (0.84 to 1.88)
Adjusted for age, sex	1.00 (ref)	1.15 (0.84 to 1.56)	1.62 (1.05 to 2.50)
Adjusted for HTN, DM	1.00 (ref)	1.14 (0.84 to 1.56)	1.62 (1.04 to 2.51)
Adjusted for sickle cell trait	1.00 (ref)	1.14 (0.83 to 1.56)	1.65 (1.06 to 2.57)
Continuous Decline, 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		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)	−1.71 (−3.22 to −0.20)
Adjusted for age, sex	1.00 (ref)	−0.25 (−1.26 to 0.76)	−2.05 (−3.51 to −0.58)
Adjusted for HTN, DM	1.00 (ref)	−0.12 (−1.12 to 0.87)	−1.85 (−3.29 to −0.40)
Adjusted for sickle cell trait	1.00 (ref)	−0.14 (−1.14 to 0.85)	−1.90 (−3.35 to −0.45)
Decline ≥ 30%			
Events/no. at risk	32/950	31/1,037	21/313

(Continued)

Table 2 (Cont'd). Associations of *APOL1* Risk Alleles With Kidney Function Decline and Mortality

	No. of *APOL1* Risk Alleles		
Outcome/Model	**0**	**1**	**2**
Proportion	3.40%	3.00%	6.70%
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**
Unadjusted	1.00 (ref)		2.20 (1.32 to 3.66)
Adjusted for age, sex	1.00 (ref)		2.42 (1.44 to 4.06)
Adjusted for HTN, DM	1.00 (ref)		2.36 (1.39 to 4.01)
Adjusted for sickle cell trait	1.00 (ref)		2.42 (1.42 to 4.13)
Unadjusted	1.00 (ref)	0.89 (0.54 to 1.46)	2.07 (1.18 to 3.65)
Adjusted for age, sex	1.00 (ref)	0.91 (0.55 to 1.51)	2.31 (1.30 to 4.10)
Adjusted for HTN, DM	1.00 (ref)	0.85 (0.51 to 1.43)	2.17 (1.21 to 3.92)
Adjusted for sickle cell trait	1.00 (ref)	0.84 (0.50 to 1.40)	2.21 (1.22 to 4.00)
Mortality events/no. at risk	116/1,293	152/1,479	41/444
Mortality Rate			
Percent/y	1.27%	1.47%	1.31%
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**
Unadjusted	1.00 (ref)		0.95 (0.69 to 1.33)
Adjusted for age, sex	1.00 (ref)		0.96 (0.69 to 1.33)
Adjusted for HTN, DM	1.00 (ref)		0.91 (0.66 to 1.27)
Adjusted for sickle cell trait	1.00 (ref)		0.91 (0.66 to 1.27)
Unadjusted	1.00 (ref)	1.15 (0.90 to 1.46)	1.03 (0.72 to 1.46)
Adjusted for age, sex	1.00 (ref)	1.23 (0.96 to 1.56)	1.07 (0.75 to 1.53)
Adjusted for HTN, DM	1.00 (ref)	1.18 (0.93 to 1.51)	1.00 (0.70 to 1.43)
Adjusted for sickle cell trait	1.00 (ref)	1.18 (0.93 to 1.51)	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.

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 m^2 or UACR > 30 mg/g) compared with those with zero or 1 *APOL1* allele.

Table 3. Associations of *APOL1* Risk Alleles With Kidney Function Decline and Mortality Adjusted for Ancestry Informative Markers

	No. of *APOL1* Risk Alleles		
Outcome/Model	**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)	1.63 (0.92 to 2.88)
Adjusted for age, sex, AIMs	1.00 (ref)	1.47 (0.96 to 2.25)	1.88 (1.04 to 3.41)
Adjusted for HTN, DM	1.00 (ref)	1.48 (0.96 to 2.29)	1.98 (1.07 to 3.64)
Adjusted for sickle cell trait	1.00 (ref)	1.48 (0.96 to 2.29)	1.98 (1.07 to 3.64)
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)	9.30 (1.87 to 46.34)
Adjusted for age, sex, AIMs	1.00 (ref)	2.84 (0.55 to 14.68)	10.32 (1.95 to 54.71)
Adjusted for HTN, DM	1.00 (ref)	2.78 (0.53 to 14.75)	9.56 (1.74 to 52.50)
Adjusted for sickle cell trait	1.00 (ref)	2.67 (0.50 to 14.26)	9.70 (1.75 to 53.93)
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)	1.21 (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)	1.26 (0.84 to 1.88)
Adjusted for age, sex, AIMs	1.00 (ref)	1.14 (0.83 to 1.55)	1.57 (1.01 to 2.43)
Adjusted for HTN, DM	1.00 (ref)	1.14 (0.83 to 1.56)	1.57 (1.01 to 2.45)
Adjusted for sickle cell trait	1.00 (ref)	1.14 (0.83 to 1.56)	1.62 (1.03 to 2.53)
Continuous Decline in eGFR (mL/min/1.73 m^2 %/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)	−1.71 (−3.22 to −0.20)
Adjusted for age, sex, AIMs	1.00 (ref)	−0.22 (−1.24 to 0.80)	−1.96 (−3.45 to −0.47)
Adjusted for HTN, DM	1.00 (ref)	−0.12 (−1.13 to 0.89)	−1.80 (−3.28 to −0.32)
Adjusted for sickle cell trait	1.00 (ref)	−0.15 (−1.16 to 0.86)	−1.86 (−3.34 to −0.39)
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)

Table 3 (Cont'd). Associations of *APOL1* Risk Alleles With Kidney Function Decline and Mortality Adjusted for Ancestry Informative Markers

	No. of *APOL1* Risk Alleles		
Outcome/Model	**0**	**1**	**2**
Adjusted for HTN, DM		1.00 (ref)	2.37 (1.37 to 4.08)
Adjusted for sickle cell trait		1.00 (ref)	2.45 (1.41 to 4.24)
Unadjusted	1.00 (ref)	0.89 (0.54 to 1.46)	2.07 (1.18 to 3.65)
Adjusted for age, sex, AIMs	1.00 (ref)	0.90 (0.54 to 1.51)	2.29 (1.27 to 4.13)
Adjusted for HTN, DM	1.00 (ref)	0.86 (0.51 to 1.45)	2.18 (1.19 to 4.01)
Adjusted for sickle cell trait	1.00 (ref)	0.84 (0.50 to 1.43)	2.24 (1.21 to 4.13)
Mortality			
Events/no. at risk	116/1293	152/1479	41/444
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**
Unadjusted		1.00 (ref)	0.95 (0.69 to 1.33)
Adjusted for age, sex, AIMs		1.00 (ref)	0.93 (0.67 to 1.30)
Adjusted for HTN, DM		1.00 (ref)	0.89 (0.64 to 1.23)
Adjusted for sickle cell trait		1.00 (ref)	0.89 (0.64 to 1.23)
Unadjusted	1.00 (ref)	1.15 (0.90 to 1.46)	1.03 (0.72 to 1.46)
Adjusted for age, sex, AIMs	1.00 (ref)	1.12 (0.96 to 1.57)	1.05 (0.73 to 1.50)
Adjusted for HTN, DM	1.00 (ref)	1.18 (0.92 to 1.51)	0.97 (0.68 to 1.40)
Adjusted for sickle cell trait	1.00 (ref)	1.18 (0.92 to 1.51)	0.98 (0.68 to 1.40)

Abbreviations: AIMs, ancestry informative markers; *APOL1,* apolipoprotein L1; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HR,hazard ratio; HTN, hypertension; OR, odds ratio; ref, reference; UACR, urinary albumin-creatinine ratio.

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, 9.70; 95% CI, 1.75-53.93), while those with 1 allele had a nonsignificant increase in HR (aHR, 2.47; 95% CI, 0.49-12.42) even after adjustment for ancestry informative markers (aHR, 2.67; 95% CI, 0.50-14.26).

Incident CKD

There was an association of *APOL1* with incident CKD defined as eGFR < 60 mL/min/1.73 m^2 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 ($\beta = -1.90$; 95% CI, −3.35 to −0.45) that was similar after adjustment for ancestry informative markers ($\beta = -1.86$; 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 ($\beta = -0.14$; 95% CI, −1.14 to 0.85), which was similar after adjustment for ancestry informative markers ($\beta = -0.15$; 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[7] and Tzur[29] superseded the initial data that linked MYH9 with FSGS-associated ESKD, implicating *APOL1*.[8] 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[30,31] and increased risk for proteinuria among African Americans with CKD.[10,30,32]

Among participants in the Coronary Artery Risk Development in Young Adults (CARDIA) study, Peralta et al[33] 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[9] 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[33] and Foster et al,[9] 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 APOL-high-density lipoprotein variants.[6] Review of the initial risk for FSGS-associated ESKD was consistent with an autosomal recessive penetrance of *APOL1* in African Americans.[6] 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.[34] 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.[11] Exact mechanisms of *APOL1* variants and increased risk for kidney disease remain elusive; however, current research continues to investigate potential mechanism of disease pathophysiology.[35,36]

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.[11] 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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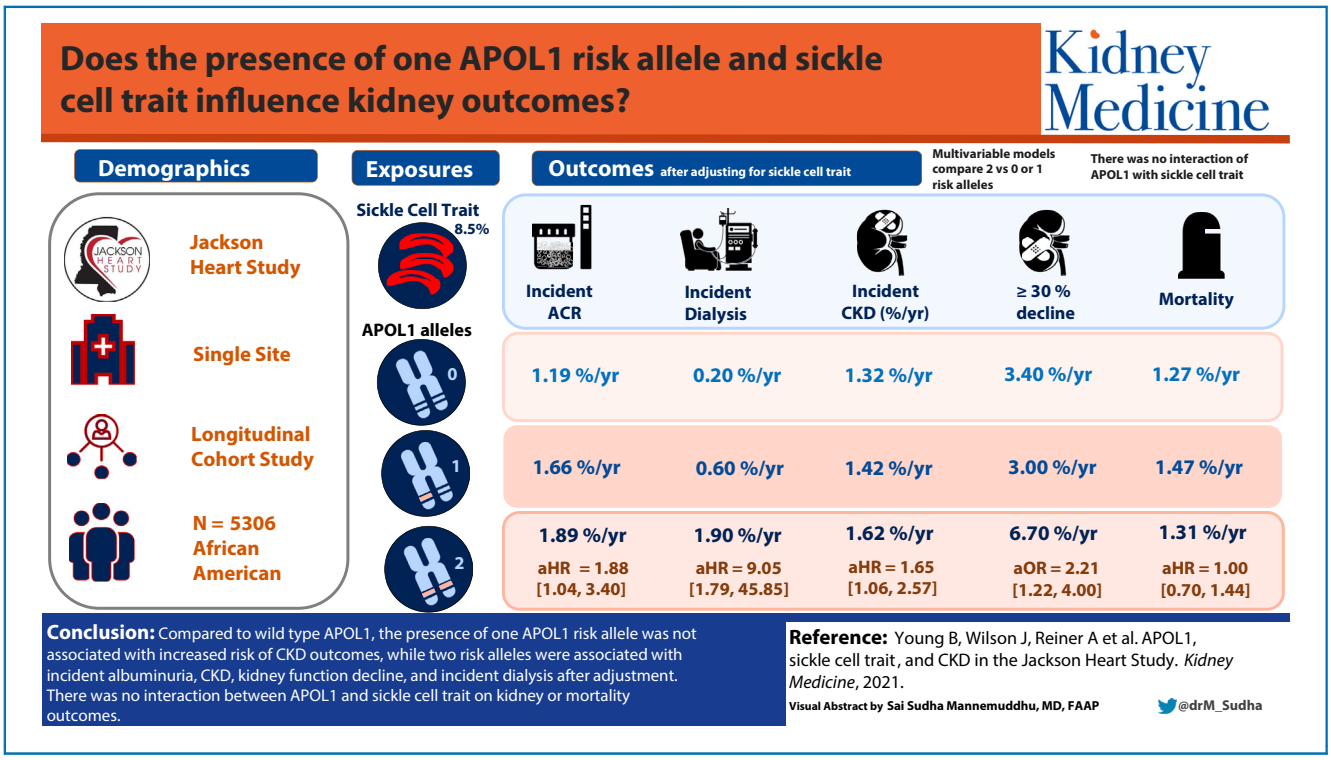
Does the presence of one APOL1 risk allele and sickle cell trait influence kidney outcomes?
Kidney Medicine
Demographics
Exposures
Outcomes after adjusting for sickle cell trait
Multivariable models compare 2 vs 0 or 1 risk alleles
There was no interaction of APOL1 with sickle cell trait
Jackson Heart Study
Single Site
Longitudinal Cohort Study
N = 5306 African American
Sickle Cell Trait 8.5%
APOL1 alleles
0
1
2
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
aHR = 1.88 [1.04, 3.40]
1.90 %/yr
aHR = 9.05 [1.79, 45.85]
1.62 %/yr
aHR = 1.65 [1.06, 2.57]
6.70 %/yr
aOR = 2.21 [1.22, 4.00]
1.31 %/yr
aHR = 1.00 [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.
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