Original Investigation

Association of Sickle Cell Trait With Chronic Kidney Disease and Albuminuria in African Americans

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IMPORTANCE The association between sickle cell trait (SCT) and chronic kidney disease (CKD) is uncertain.

OBJECTIVE To describe the relationship between SCT and CKD and albuminuria in self-identified African Americans.

DESIGN, SETTING, AND PARTICIPANTS Using 5 large, prospective, US population-based studies (the Atherosclerosis Risk in Communities Study [ARIC, 1987-2013; n = 3402], Jackson Heart Study [JHS, 2000-2012; n = 2105], Coronary Artery Risk Development in Young Adults [CARDIA, 1985-2006; n = 848], Multi-Ethnic Study of Atherosclerosis [MESA, 2000-2012; n = 1620], and Women's Health Initiative [WHI, 1993-2012; n = 8000]), we evaluated 15 975 self-identified African Americans (1248 participants with SCT [SCT carriers] and 14 727 participants without SCT [noncarriers]).

MAIN OUTCOMES AND MEASURES Primary outcomes were CKD (defined as an estimated glomerular filtration rate [eGFR] of <60 mL/min/1.73 m^2 at baseline or follow-up), incident CKD, albuminuria (defined as a spot urine albumin:creatinine ratio of >30 mg/g or albumin excretion rate >30 mg/24 hours), and decline in eGFR (defined as a decrease of >3 mL/min/1.73 m^2 per year). Effect sizes were calculated separately for each cohort and were subsequently meta-analyzed using a random-effects model.

RESULTS A total of 2233 individuals (239 of 1247 SCT carriers [19.2%] vs 1994 of 14 722 noncarriers [13.5%]) had CKD, 1298 (140 of 675 SCT carriers [20.7%] vs 1158 of 8481 noncarriers [13.7%]) experienced incident CKD, 1719 (150 of 665 SCT carriers [22.6%] vs 1569 of 8249 noncarriers [19.0%]) experienced decline in eGFR, and 1322 (154 of 485 SCT carriers [31.8%] vs 1168 of 5947 noncarriers [19.6%]) had albuminuria during the study period. Individuals with SCT had an increased risk of CKD (odds ratio [OR], 1.57 [95% CI, 1.34-1.84]; absolute risk difference [ARD], 7.6% [95% CI, 4.7%-10.8%]), incident CKD (OR, 1.79 [95% CI, 1.45-2.20]; ARD, 8.5% [95% CI, 5.1%-12.3%]), and decline in eGFR (OR, 1.32 [95% CI, 1.07-1.61]; ARD, 6.1% [95% CI, 1.4%-13.0%]) compared with noncarriers. Sickle cell trait was also associated with albuminuria (OR, 1.86 [95% CI, 1.49-2.31]; ARD, 12.6% [95% CI, 7.7%-17.7%]).

CONCLUSIONS AND RELEVANCE Among African Americans in these cohorts, the presence of SCT was associated with an increased risk of CKD, decline in eGFR, and albuminuria, compared with noncarriers. These findings suggest that SCT may be associated with the higher risk of kidney disease in African Americans.

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Sickle cell trait (SCT) is defined as inheritance of a single copy of the sickle mutation that results from a single base pair substitution in the gene encoding the β-globin chain of hemoglobin. It is estimated that SCT affects 1 in 12 African Americans and nearly 300 million people worldwide.[1,2]

Renal disease in individuals with 2 copies of the sickle hemoglobin mutation (sickle cell disease) has been well characterized and includes impaired urinary concentrating ability, hematuria, chronic kidney disease (CKD), albuminuria, and end-stage renal disease (ESRD).[3,4] Although SCT largely has been considered a benign condition, renal manifestations are the most commonly reported complications and include impaired urinary concentration, asymptomatic hematuria, and papillary necrosis.[1,2,5,6] Nonetheless, the relationship of SCT to long-term functional impairment of the kidney has not been firmly established. Prior studies demonstrated a higher than expected prevalence of SCT among participants with ESRD, leading a National Institutes of Health (NIH) consensus panel to identify kidney disease as an area of priority in SCT research.[1,7-9]

CKD *chronic kidney disease*

eGFR *estimated glomerular filtration rate*

ESRD *end-stage renal disease*

ln *natural logarithm*

SCT *sickle cell trait*

UACR *urinary albumin:creatinine ratio*

African Americans have a disproportionately higher risk of CKD and progression to ESRD compared with white or Asian American populations.[10-12] Sickle cell trait may be an important and unrecognized risk factor for renal disease in this population. We hypothesized that SCT is associated with CKD, decline in estimated glomerular filtration rate (eGFR), and albuminuria.

Methods

Study Population

All participants who were included in the analyses provided written informed consent for genetic studies, and institutional review board approval was obtained separately at each participating institution. The study population was derived from 5 population-based, prospective cohort studies from the United States: the Atherosclerosis Risk in Communities Study (ARIC), Jackson Heart Study (JHS), Coronary Artery Risk Development in Young Adults (CARDIA), Multi-Ethnic Study of Atherosclerosis (MESA), and Women's Health Initiative (WHI). The design and methods of each study have been previously described[13-17] and are summarized in **Table 1** and described in the eAppendix in the Supplement. Clinical information was collected by self-report and in-person examination. Data from years 1987-2013 were used for analysis in ARIC, 2000-2012 for JHS, 1985-2006 for CARDIA, 2000-2012 for MESA, and 1993-2012 for WHI.

Exposure Assessment

Genotype data for rs334encoding the sickle cell mutation (*HBB* p.Glu7Val) were obtained by custom genotyping or exome sequencing, or by imputation into the remaining sample of African Americans with genome-wide genotyping (eAppendix in the Supplement). We examined kidney function outcomes by the number of risk alleles (0 or 1).

Covariate Assessment

Baseline characteristics for each study participant were determined at the time of the first creatinine measurement. Hypertension was defined as a baseline systolic blood pressure measurement of 140 mm Hg or higher, a diastolic blood pressure measurement of 90 mm Hg or higher, or self-reported use of antihypertensive medication. Diabetes was defined as baseline fasting glucose measurement of 126 mg/dL or higher (to convert to mmol/L, multiply by 0.0555), self-reported physician diagnosis of diabetes, or self-reported use of oral hypoglycemic medication or insulin. To correct for any cryptic population structure, the global percentage of African ancestry for each participant was estimated based on high-density genome-wide genotyping data using population genetics software programs (Structure or Frappe), as previously described.[18,19] All participants included in this analysis had complete baseline data for age, sex, estimated African ancestry proportion, hypertension, and diabetes. The *APOL1* risk variants (G1 and G2), which are associated with CKD in African Americans,[20,21] were directly genotyped in all individuals in ARIC and a subset of participants in JHS.[22]

Kidney Function Outcome Assessment

Serum creatinine values were calibrated to the Cleveland Clinic or isotope dilution mass spectrometry reference standard. The eGFR was estimated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation.[23] The eGFR was also estimated using cystatin C measurements in available cohorts as described previously.[24] Chronic kidney disease was defined as an eGFR lower than 60 (stage G3 or higher in the Kidney Disease: Improving Global Outcomes [KDIGO] CKD definition)[25] at any time during the study, including baseline or any follow-up visit. Incident CKD was defined as development of an eGFR lower than 60 mL/min/1.73 m^2 during follow-up with a baseline eGFR of 60 mL/min/1.73 m^2 or higher. Albuminuria was defined as spot urinary albumin:creatinine ratio (UACR) higher than 30 mg/g or an albumin excretion rate of more than 30 mg/24 hours (stage A2 or higher per KDIGO).[25] Each cohort has been followed longitudinally; the number and frequency of repeated measures of serum creatinine, cystatin C, and UACR vary by cohort (Table 1). Participants with incident ESRD were identified in ARIC and WHI through linkage with the US Renal Data System, a national registry of all participants with ESRD.[10]

Statistical Methods

The association of SCT carrier status with CKD outcomes was assessed using linear regression for quantitative eGFR and log-transformed urinary albumin, logistic regression for CKD, incident CKD, albuminuria, and presence of decline in kidney function (defined as a decrease in eGFR of >3 mL/min/1.73 m^2

Table 1. Baseline Characteristics of Cohorts

	CARDIA	MESA	JHS	WHI	ARIC
Total participants enrolled, No.	5115	6814	3630	161 808	15 792
African American participants enrolled, No.	2637	1891	3630	14 348	4266
African American participants in our study, No.	848	1620	2105	8000	3402
Exclusions					
Lack of genetic data	1647	264	1410	6206	130
Homozygous for sickle cell variant	0	0	3	2	3
Missing kidney outcome measures	0	0	0	140	101
Missing covariate data	142	7	112	0	630
Location	Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA	Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; New York, NY; St. Paul, MN	Tri-county area of Mississippi: Hinds, Madison, and Rankin counties	40 sites across the United States	Forsyth County, NC; Jackson, MS; suburbs of Minneapolis, MN; Washington County, MD
Age range at baseline, y	18-30	45-84	21-94	50-79	45-64
Follow-up frequency	1985-1986 (baseline) 1987-1988 (year 2) 1990-1991 (year 5) 1992-1993 (year 7) 1995-1996 (year 10) 2000-2001 (year 15) 2005-2006 (year 20)	2000-2002 (baseline) 2002-2004 (examination 2) 2004-2005 (examination 3) 2005-2007 (examination 4) 2010-2012 (examination 5)	2000-2004 (examination 1) 2005-2008 (examination 2) 2009-2012 (examination 3)	From baseline (1993-1998) to 2005, medical history and examination follow-up occurred annually in the WHI-CT and at year 3 in WHI-OS; during 2005-2011, annual medical history updates; in 2012, a home-visit examination including blood collection	1987-1989 (baseline visit) 1990-1992 (2nd visit) 1993-1995 (3rd visit) 1996-1998 (4th visit) 2011-2013 (5th visit) annual phone updates
Kidney outcomes	Serum creatinine at baseline and at years 10, 15, and 20; cystatin C at examination years 10, 15, and 20; UACR at examination years 10, 15, and 20	Serum creatinine examinations 1, 3, 4, and 5; cystatin C at examination 5; UACR at visits 1, 3 and 5	Spot and 24-h urine collections at examination 1; spot urine samples at examinations 2 and 3; serum creatinine at examinations 1 and 3	Serum creatinine at baseline and again in about 25% of the original sample at 2012 follow-up examination; linkage to USRDS	Serum creatinine at visits 1, 2, 4, and 5; cystatin C at visits 2, 4, and 5; UACR at visit 4 and 5; linkage to USRDS

Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; CARDIA, Coronary Artery Risk Development in Young Adults; JHS, Jackson Heart Study; MESA, Multi-Ethnic Study of Atherosclerosis; NA, not available; UACR, urinary albumin:creatinine ratio; USRDS, United States Renal Data System; WHI, Women's Health Initiative; WHI-CT, Women's Health Initiative Clinical Trial; WHI-OS, WHI Observational Study.

per year), and Cox regression for incident ESRD. To evaluate the association between SCT and eGFR decline, we used linear mixed models with random intercepts and slopes to estimate and compare linear trends in mean eGFR. Linear mixed models account for the correlation of observations within individual participants. Annual decline was estimated using eGFR data from examinations 1, 2, 4, and 5 in ARIC; examinations 1, 4, 5, 6, and 7 in CARDIA; examinations 1, 3, 4, and 5 in MESA; examinations 1 and 3 in JHS; and examination 1 and a subsequent visit about 15 years later in a subsample of WHI (n = 2139).

All regression models were minimally adjusted for covariates of age, sex, clinic or region, and African genetic ancestry to account for population stratification (model 1). We additionally adjusted for 2 major clinical risk factors: baseline diabetes and hypertension (model 2). All tests were 2-sided and a *P* value of less than .05 was considered statistically significant. The following sensitivity analyses were performed: (1) confining to ARIC and JHS, the 2 cohorts with the highest percentage of direct genotyping for rs334 (100% in ARIC; 98% in JHS; n = 5507) (eTable 2 in the Supplement), (2) excluding hemoglobin C carriers in genotyped samples, and (3) adjusting for the presence of 2 copies of the *APOL1* risk variants (G1 and G2) in individuals with available genotypic data (n = 4490).

Effect modification of SCT on the development of incident CKD by baseline hypertension or diabetes status or by the presence of 2 *APOL1* risk variants was evaluated using 2 distinct methods: performing stratified analyses and including an interaction term in the original model. We defined the significance level for interaction as a *P* value of less than .05.

Because of the variability of risk across cohorts of various age ranges, we used ARIC prevalence and incidence rates as a fixed standard and calculated absolute risk differences from the meta-analyzed effect measures. Using ARIC as a standard allowed for the applicability of risk estimates to a middle-aged population.

Given the demographic heterogeneity of the cohorts included in this study, all data were analyzed separately within each cohort. Although the I^2 for heterogeneity for all analyzed outcomes was less than 50%, with the I^2 statistic

Table 2. Characteristics of African American Participants by Sickle Cell Trait Carrier Status[a]

	CARDIA		MESA		JHS		WHI		ARIC	
	Noncarriers	SCT Carriers	Noncarriers	SCT Carriers	Noncarriers	SCT Carriers	Noncarriers	SCT Carriers	Noncarriers	SCT Carriers
No. (%)	776 (91.5)	72 (8.5)	1469 (90.7)	151 (9.3)	1941 (92.2)	164 (7.8)	7356 (91.9)	644 (8.1)	3185 (93.6)	217 (6.4)
Age, mean (SD), y	24.3 (3.8)	24.9 (4.1)	62.3 (10.2)	61.6 (9.7)	50.3 (12.0)	50.8 (124)	61.6 (7.0)	61.5 (7.1)	54.0 (5.8)	54.1 (5.9)
Women, No. (%)	481 (62.0)	48 (66.7)	797 (54.3)	83 (55.0)	1189 (61.3)	92 (56.1)	7356 (100)	644 (100)	1972 (61.9)	132 (60.8)
Hypertension, No. (%)	34 (4.4)	1 (1.4)	870 (59.2)	88 (58.3)	1079 (55.6)	91 (55.5)	4347 (59.1)	370 (57.5)	1770 (55.6)	121 (55.8)
Blood pressure, mean (SD), mm Hg										
Systolic	111 (10)	110 (10)	131 (22)	131 (20)	125 (18)	123 (18)	132 (18)	132 (18)	129 (21)	130 (21)
Diastolic	69 (9)	70 (9)	75 (10)	74 (10)	80 (11)	79 (11)	78 (9)	78 (9)	80 (12)	79 (12)
Diabetes, No. (%)	5 (0.7)	0 (0.0)	250 (17.0)[b]	37 (24.5)[b]	358 (18.4)	27 (16.5)	1259 (17.1)	114 (17.7)	608 (19.1)	42 (19.4)
Fasting blood glucose, mean (SD), mg/dL	82 (12)	79 (8)	100 (33)	104 (36)	98 (32)	97 (33)	107 (41)	108 (44)	113 (46)	119 (56)
BMI, mean (SD)	25.6 (5.7)	24.9 (5.2)	30.1 (5.9)	30.6 (6.2)	32.4 (7.7)	31.5 (8.1)	30.9 (6.3)	30.6 (6.3)	29.6 (6.1)	30.0 (6.3)
African genetic ancestry, mean (SD), %	80.5 (11.2)	81.9 (10.1)	78.0 (14.0)	82.0 (12.0)	82.4 (8.6)	83.2 (6.5)	75.7 (15.5)	79.4 (12.4)	82.3 (10.1)	83.7 (9.2)
Presence of *APOL1* risk variants, No. (%)					157 (13.4)	11 (11.0)			399 (13.2)	22 (10.7)
Presence of hemoglobin C, No. (%)					7 (1.5)	1 (2.5)			78 (2.5)	2 (0.9)

Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CARDIA, Coronary Artery Risk Development in Young Adults; JHS, Jackson Heart Study; MESA, Multi-Ethnic Study of Atherosclerosis; SCT, sickle cell trait; WHI, Women's Health Initiative.

[a] Values listed based on available data; not all characteristics were available in all participants.

[b] Unadjusted *P* values for differences between SCT carriers and noncarriers within cohort were less than .05.

being 0% for the primary outcomes, the cohort-specific results were meta-analyzed using a random-effects model to provide a conservative pooled estimate given the inherent heterogeneity in design and population between cohorts. Forest plots were generated for the primary outcomes. All statistical analyses were performed using Stata (StataCorp), version 12.

Results

Baseline Characteristics

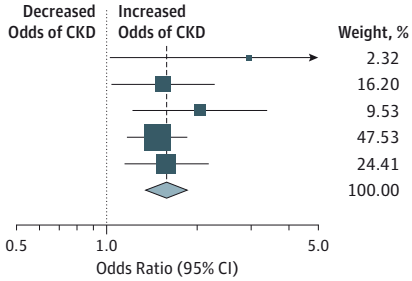
After excluding participants with missing data for SCT (n = 9657), kidney phenotypes (n = 241) or covariates (n = 891), and those with homozygous hemoglobin S (n = 8), the present analysis included 15 975 African Americans from 5 population-based, prospective cohort studies (ARIC, JHS, CARDIA, MESA, and WHI). Genotype data for rs334 encoding the SCT mutation (*HBB* p.Glu7Val) were obtained by custom genotyping (n = 3402), exome sequencing (n = 2791), or by imputation into the remaining sample of African Americans with genomewide genotyping (n = 9782). The *APOL1* risk variants (G1 and G2), which are associated with CKD in African Americans were directly genotyped in 3221 individuals in ARIC and a subset of 1269 participants in JHS. Baseline characteristics of African American participants by cohort and SCT carrier status are shown in **Table 2.** CARDIA participants were younger than participants of all other cohorts. A total of 1248 individuals in our study had SCT. The prevalence of SCT among the cohorts ranged from 6.4% to 9.3%, consistent with previous population prevalence estimates in African Americans.[5,26,27] There was little difference in age, sex, body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), hypertension, and diabetes between African American participants with SCT (SCT carriers) and without SCT (noncarriers) in each cohort.

Association of SCT With CKD and Incident CKD

Chronic kidney disease using creatinine values (eGFR <60 mL/min/1.73 m^2) was present in 2233 individuals (239 of 1247 SCT carriers [19.2%] vs 1994 of 14 722 noncarriers [13.5%]) in all 5 cohorts and in 1164 participants (113 of 516 SCT carriers [21.9%] vs 1051 of 6468 noncarriers [16.2%]) from 4 cohorts based on cystatin C measurements. In the meta-analysis, SCT carriers had an increased risk of CKD compared with noncarriers (odds ratio [OR], 1.57 [95% CI, 1.34-1.84]; absolute risk difference [ARD], 7.6% [95% CI,

Figure 1. Meta-analysis of Odds Ratios for CKD Using Creatinine Values Comparing Sickle Cell Trait Carriers With Noncarriers

Study	No. of Participants		No. (%) With CKD		Odds Ratio (95% CI)
	Noncarriers	SCT Carriers	Noncarriers	SCT Carriers	
CARDIA	776	72	21 (2.7)	5 (6.9)	2.95 (1.02-8.22)
MESA	1464	150	378 (25.8)	50 (33.3)	1.53 (1.03-2.27)
JHS	1941	164	180 (9.3)	26 (15.9)	2.03 (1.21-3.39)
WHI	7356	644	841 (11.4)	102 (15.8)	1.46 (1.16-1.84)
ARIC	3185	217	574 (18.0)	56 (25.8)	1.57 (1.14-2.17)
Overall (I^2 = 0.0%, P = .60)					1.57 (1.34-1.84)



CKD indicates chronic kidney disease; eGFR, estimated glomerular filtration rate; SCT, sickle cell trait. Chronic kidney disease was defined as an eGFR level lower than 60 mL/min/1.73 m^2 at baseline or follow-up. All models adjusted for age, sex, clinic or region, African genetic ancestry, hypertension, and diabetes. The size of data markers indicate the weight of study.

4.7%-10.8%]) (**Figure 1**). The meta-analyzed risk for CKD in the sensitivity analysis using ARIC and JHS alone was similar (82 of 381 SCT carriers [21.5%] vs 754 of 5126 noncarriers [14.7%]; OR, 1.69 [95% CI, 1.28-2.22]; ARD, 9.1% [95% CI, 3.9%-14.8%]) (eTable 2 in the Supplement). Similar results were also obtained using cystatin C–based eGFR (OR, 1.76 [95% CI, 1.37-2.27]; ARD, 12.8% [95% CI, 6.8%-19.0%]) in the meta-analysis of available values from ARIC, JHS, CARDIA, and MESA (**Table 3**, model 2).

A total of 1298 (140 of 675 SCT carriers [20.7%] vs 1158 of 8481 noncarriers [13.7%]) experienced incident CKD. Incident CKD was more common in SCT carriers compared with noncarriers in all cohorts. (OR, 1.79 [95% CI, 1.45-2.20]; ARD, 8.5% [95% CI, 5.1%-12.3%]) (**Figure 2**). Results were similar using data from ARIC and JHS alone (60 of 325 SCT carriers [18.5%] vs 525 of 4506 noncarriers [11.7%]; OR, 1.81 [95% CI, 1.33-2.45]; ARD, 8.7% [95% CI, 3.8%-14.4%]) (eTable 2 in the Supplement).

Association of SCT With Decline in eGFR and ESRD

Sickle cell trait was significantly associated with a faster decline in eGFR, with a pooled adjusted estimate of an increased rate of decline in eGFR of 0.218 mL/min/1.73 m^2 per year (95% CI, 0.062 to 0.374) compared with noncarriers (Table 3, model 2). The rate of decline was 0.254 mL/min/1.73 m^2 per year (95% CI, 0.089 to 0.418) faster for SCT carriers compared with noncarriers among the subgroup of 8923 individuals without baseline CKD. Sickle cell trait was not associated with faster decline in the subset of 361 participants with baseline eGFR lower than 60 mL/min/1.73 m^2 (β = 0.024 [95% CI, −0.484 to 0.533])

In our study, a total of 1719 individuals (150 of 665 SCT carriers [22.6%] vs 1569 of 8249 noncarriers [19.0%]) from the 5 cohorts experienced eGFR decline. Evaluation of decline in eGFR (>3 mL/min/1.73 m^2 decline per year) demonstrated that SCT carriers had an increased risk of decline compared with noncarriers in the meta-analysis (OR, 1.32 [95% CI, 1.07 to 1.61]; ARD, 6.1% [95% CI, 1.4% to 13.0%]) (**Figure 3**). Using ARIC and JHS only, the results were similar (81 of 305 SCT carriers [26.6%] vs 1040 of 4272 noncarriers [24.3%]; OR, 1.21 [95% CI, 0.92 to 1.59]; ARD, 4.1% [95% CI, −1.7% to 10.5%]) (eTable 2 in the Supplement). As with CKD and incident CKD, the direction of the association was consistent among all cohorts analyzed, though the relationship was not statistically significant in any individual cohort.

In the 2 cohorts with available US Renal Data System follow-up data on ESRD (ARIC and WHI), a total of 314 individuals (26 of 852 SCT carriers [3.1%] vs 288 of 10 411 noncarriers [2.8%]) developed incident ESRD. Incidence of ESRD did not differ significantly between SCT carriers and noncarriers either in the individual cohorts or in meta-analysis (hazard ratio [HR], 1.02 [95% CI, 0.59 to 1.76]; ARD, 0.1% [95% CI, −1.8% to 3.3%]) (Table 3, model 2).

Association of SCT and Albuminuria

Using both UACR and albumin excretion rate data, the mean baseline urinary albumin was 0.49 natural log units (95% CI, 0.351-0.628) of milligrams per gram or milligrams per 24 hours higher among SCT carriers compared with noncarriers (Table 3, model 2). A total of 1322 individuals (154 of 485 SCT carriers [31.8%] vs 1168 of 5947 noncarriers [19.6%]) from the 4 cohorts with available data had albuminuria. Similar to CKD, albuminuria (>30 mg/g or >30 mg/24 hours) was more common in SCT carriers compared with noncarriers (OR, 1.86 [95% CI, 1.49-2.31; ARD, 12.6% [95% CI, 7.7%-17.7%]) in the pooled analysis (**Figure 4**). Similar results for albuminuria were observed using ARIC and JHS cohorts only (88 of 283 SCT carriers [31.1%] vs 801 of 3880 noncarriers [20.6%]; OR, 1.75 [95% CI, 1.17-2.62]; ARD, 11.2% [95% CI, 2.9%-20.7%]) (eTable 2 in the Supplement).

Association of SCT and Incident CKD by Hypertension and Diabetes Status

There was no evidence that the association of SCT with incident CKD was modified by either baseline hypertension (P = .09) or diabetes status (P = .60) (**Table 4**).

Association of SCT and *APOL1* Risk Variants on CKD and Albuminuria

We assessed the association of SCT and *APOL1* on CKD and albuminuria in a subset of 3221 participants in ARIC and 1269 participants in JHS with genotypes available for the G1 and G2 alleles (eAppendix in the Supplement). Carrier status

for SCT and *APOL1* risk genotypes segregated independently, with 22 individuals (1%) carrying both genetic risk factors in ARIC and 11 individuals (1%) in JHS. There was no significant genetic interaction by *APOL1* status on the relationship of SCT and CKD (P = .17) or albuminuria (P = .18) (**Table 5**).

Table 3. Association of Sickle Cell Trait With Chronic Kidney Disease and Albuminuria by Cohort[a]

	CARDIA		MESA		JHS		WHI		ARIC		
	Non-carriers	SCT Carriers	Non-carriers	SCT Carriers	Non-carriers	SCT Carriers	Non-carriers	SCT Carriers	Non-carriers	SCT Carriers	Meta-analysis
Baseline eGFR											
Participants, No.	776	72	1469	151	1941	164	7356	644	3185	217	
Mean (SD), mL/min/1.73 m^2	131.81 (5.71)	131.14 (14.40)	80.64 (18.04)	79.06 (18.49)	98.67 (21.67)	94.92 (22.44)	92.44 (19.30)	88.75 (20.49)	111.32 (19.77)	106.77 (20.26)	
Difference (95% CI)[b]											
Model 1	0.106 (−3.56 to 3.77)		−1.52 (−4.28 to 1.24)		−3.00 (−5.87 to −0.131)		−3.433 (−4.84 to −1.96)		−4.205 (−6.74 to −1.67)		−2.809 (−4.052 to −1.566)
Model 2	0.102 (−3.57 to 3.78)		−1.83 (−4.58 to 0.918)		−3.035 (−5.89 to −0.178)		−3.492 (−4.90 to −2.03)		−4.231 (−6.75 to −1.71)		−2.978 (−4.109 to −1.847)
$CKD_{Cyst\text{-}C}$											
No./total (%)	12/769 (1.6)	2/72 (2.8)	162/927 (17.4)	27/95 (28.4)	63/1934 (3.3)	8/164 (4.9)			814/2838 (28.7)	76/185 (41.8)	
OR (95% CI)[b]											
Model 1	1.61 (0.35 to 7.51)		2.20 (1.29 to 3.76)		1.48 (0.67 to 3.29)				1.69 (1.24 to 2.29)		1.76 (1.38 to 2.26)
Model 2	2.08 (0.43 to 10.01)		2.10 (1.21 to 3.65)		1.49 (0.66 to 3.37)				1.70 (1.25 to 2.31)		1.76 (1.37 to 2.27)
eGFR Decline per Year											
Participants, No.	534	44	1469	151	1429	122	1974	165	2843	183	
Mean (SD), mL/min/1.73 m^2	−1.320 (3.216)	−1.961 (3.533)	−0.961 (2.33)	−1.369 (2.352)	−1.125 (1.956)	−1.080 (1.941)	−1.259 (1.160)	−1.530 (1.160)	−2.434 (3.136)	−2.522 (2.485)	
Difference (95% CI)[b]											
Model 1	−0.900 (−1.86 to 0.72)		−0.423 (−0.815 to −0.031)		0.0576 (−0.303 to 0.418)		−0.267 (−0.451 to −0.082)		−0.155 (−0.345 to 0.035)		−0.214 (−0.370 to −0.058)
Model 2	−0.899 (−1.87 to 0.072)		−0.367 (−0.757 to 0.022)		0.044 (−0.313 to 0.401)		−0.285 (−0.468 to −0.108)		−0.154 (−0.344 to 0.036)		−0.218 (−0.374 to −0.062)
Incident ESRD											
No./total (%)							144/7233 (2.0)	11/635 (1.7)	144/3178 (4.5)	15/217 (6.9)	
HR (95% CI)[b]											
Model 1							0.70 (0.31 to 1.33)		1.27 (0.74 to 2.16)		0.99 (0.56 to 1.77)
Model 2							0.75 (0.39 to 1.44)		1.31 (0.76 to 2.24)		1.02 (0.59 to 1.76)
Baseline ln Urinary Albumin											
Participants, No.	610	53	1458	149	1138	94			1935	130	
Mean (SD), mg/g or mg/24 h[c]	1.639 (0.994)	1.950 (1.266)	1.944 (1.225)	2.563 (1.365)	2.110 (1.237)	2.419 (1.437)			1.30 (1.84)	1.96 (1.73)	
Mean difference (95% CI)[b]											
Model 1	0.206 (−0.070 to 0.482)		0.628 (0.423 to 0.833)		0.325 (0.070 to 0.581)				0.673 (0.351 to 0.996)		0.503 (0.338 to 0.669)
Model 2	0.226 (−0.048 to 0.500)		0.561 (0.370 to 0.750)		0.334 (0.093 to 0.576)				0.681 (0.378 to 0.984)		0.490 (0.351 to 0.628)

Abbreviations: AOR, adjusted odds ratio; ARIC, Atherosclerosis Risk in Communities Study; CARDIA, Coronary Artery Risk Development in Young Adults, $CKD_{Cyst\text{-}C}$, chronic kidney disease defined at eGFR <60 (using Chronic Kidney Disease Epidemiology Collaboration cystatin C–based equation); eGFR, estimated glomerular filtration rate (mL/min/1.73 m^2); ESRD, end-stage renal disease; HR, hazards ratio (derived from Cox proportional hazards model); JHS, Jackson Heart Study; MESA, Multi-Ethnic Study of Atherosclerosis; OR, odds ratio (derived from logistic regression model); SCT, sickle cell trait; WHI, Women's Health Initiative.

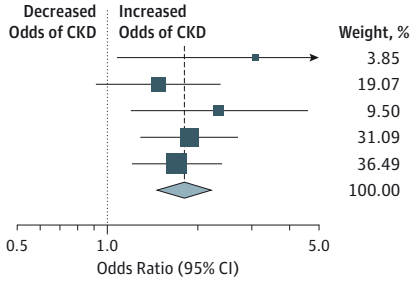
[a] Noncarriers are the reference category.

[b] Model 1 adjusted for age, sex, clinic or region, and African genetic ancestry. Model 2 additionally adjusted for diabetes and hypertension status.

[c] Albuminuria was defined as spot urine albumin:creatinine ratio higher than 30 mg/g or albumin excretion rate higher than 30 mg/24 hours.

Figure 2. Meta-analysis of Odds Ratios for Incident CKD Using Creatinine Values Comparing Sickle Cell Trait Carriers With Noncarriers

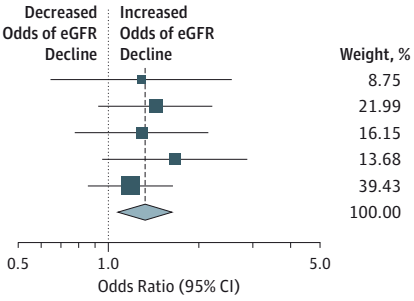
Study	No. of Participants		No. (%) With Incident CKD		Odds Ratio (95% CI)
	Noncarriers	SCT Carriers	Noncarriers	SCT Carriers	
CARDIA	775	72	20 (2.6)	5 (6.9)	3.09 (1.07-8.93)
MESA	1283	124	203 (15.8)	26 (21.0)	1.47 (0.91-2.36)
JHS	1388	114	91 (6.6)	14 (12.3)	2.33 (1.19-4.59)
WHI	1917	154	410 (21.4)	49 (31.8)	1.86 (1.28-2.70)
ARIC	3118	211	434 (13.9)	46 (21.8)	1.69 (1.20-2.39)
Overall (I^2 = 0.0%, P = .66)					1.79 (1.45-2.20)



CKD indicates chronic kidney disease; eGFR, estimated glomerular filtration rate; SCT, sickle cell trait. Incident CKD was defined as development of an eGFR level lower than 60 mL/min/1.73 m^2 during follow-up. All models adjusted for age, sex, clinic or region, African genetic ancestry, hypertension, and diabetes. The size of data markers indicate the weight of study.

Figure 3. Meta-analysis of Odds Ratios for Estimated Glomerular Filtration Rate Decline Comparing Sickle Cell Trait Carriers With Noncarriers

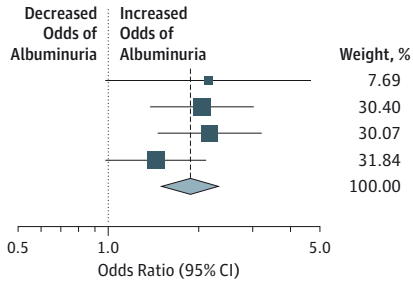
Study	No. of Participants		No. (%) With eGFR Decline		Odds Ratio (95% CI)
	Noncarriers	SCT Carriers	Noncarriers	SCT Carriers	
CARDIA	534	44	180 (33.7)	22 (50.0)	1.28 (0.64-2.55)
MESA	1469	151	210 (14.3)	30 (19.9)	1.43 (0.92-2.20)
JHS	1429	122	191 (13.4)	20 (16.4)	1.28 (0.77-2.13)
WHI	1974	165	139 (7.0)	17 (10.3)	1.65 (0.95-2.87)
ARIC	2843	183	849 (29.9)	61 (33.3)	1.18 (0.85-1.63)
Overall (I^2 = 0.0%, P = .87)					1.32 (1.07-1.61)



CKD indicates chronic kidney disease; eGFR, estimated glomerular filtration rate; SCT, sickle cell trait. Estimated glomerular filtration rate decline was defined as a decrease in eGFR level of more than 3 mL/min/1.73 m^2 per year. All models adjusted for age, sex, clinic or region, African genetic ancestry, hypertension, and diabetes. The size of data markers indicate the weight of study.

Figure 4. Meta-analysis of Odds Ratios for Albuminuria Comparing Sickle Cell Trait Carriers With Noncarriers

Study	No. of Participants		No. (%) With Albuminuria		Odds Ratio (95% CI)
	Noncarriers	SCT Carriers	Noncarriers	SCT Carriers	
CARDIA	609	53	75 (12.3)	15 (28.3)	2.13 (0.97-4.67)
MESA	1458	149	292 (20.0)	51 (34.2)	2.03 (1.37-3.02)
JHS	1790	153	327 (18.3)	46 (30.1)	2.16 (1.45-3.21)
ARIC	2090	130	474 (22.7)	42 (32.3)	1.43 (0.97-2.10)
Overall (I^2 = 0.0%, P = .45)					1.86 (1.49-2.31)



CKD indicates chronic kidney disease; SCT, sickle cell trait. Albuminuria was defined as spot urine albumin:creatinine ratio higher than 30 mg/g or albumin excretion rate higher than 30 mg/24 hours. All models adjusted for age, sex, clinic or region, African genetic ancestry, hypertension, and diabetes. The size of data markers indicate the weight of study.

Discussion

Although SCT is known to be associated with hematuria and renal papillary necrosis,[1,2,5] the relationship between SCT and CKD has not been clearly established. In this pooled analysis of more than 15 000 individuals from 5 population-based cohorts of African Americans, SCT was associated with an increased risk of CKD and incident CKD, decline in eGFR, and albuminuria. Our results were reproducible within each individual cohort. Our findings show an association of SCT with the development of CKD in African Americans.

Potential pathophysiological mechanisms for kidney injury in individuals with sickle cell disease have been described. Chronic reversible sickling induced by hypoxia in

Table 4. Association of Sickle Cell Trait With Incident Chronic Kidney Disease by Hypertension or Diabetes Status[a]

	CARDIA		MESA		JHS		WHI		ARIC		
	Non-carriers	SCT Carriers	Non-carriers	SCT Carriers	Non-carriers	SCT Carriers	Non-carriers	SCT Carriers	Non-carriers	SCT Carriers	Meta-analysis
Without Hypertension											
No./total (%)	17/741 (2.3)	4/74 (5.4)	55/558 (9.9)	7/59 (11.9)	17/660 (2.6)	4/56 (7.1)	124/925 (13.4)	25/82 (30.5)	178/1410 (12.6)	22/94 (23.4)	
OR (95% CI)[b]	2.19 (0.69-6.93)		1.36 (0.56-3.27)		3.22 (0.99-10.54)		2.98 (1.76-5.06)		1.95 (1.18-3.25)		2.26 (1.65-3.09)
With Hypertension											
No./total (%)	3/34 (8.8)	1/1 (100)	148/725 (20.4)	19/65 (29.2)	74/728 (10.2)	10/58 (17.2)	286/992 (28.8)	24/72 (33.3)	256/1708 (15.0)	24/117 (20.5)	
OR (95% CI)[b]	2.38 (0.04-33.6)		1.65 (0.93-2.91)		1.95 (0.88-4.32)		1.25 (0.74-2.10)		1.48 (0.93-2.37)		1.50 (1.14-1.98)
Without Diabetes											
No./total (%)	18/770 (2.3)	5/75 (6.7)	151/1073 (14.1)	15/99 (15.2)	55/1163 (4.7)	9/98 (9.2)	337 /1703 (19.8)	40/139 (28.8)	326/2540 (12.8)	36/173 (20.8)	
OR (95% CI)[b]	2.78 (0.98-7.93)		0.95 (0.45-2.00)		2.26 (0.99-5.11)		1.67 (1.12-2.49)		1.85 (1.27-2.70)		1.73 (1.36-2.20)
With Diabetes											
No./total (%)	2/5 (40.0)	0	52/210 (24.8)	11/25 (44.0)	35/224 (15.6)	5/16 (31.3)	73/214 (34.1)	9/15 (60.0)	101/578 (17.5)	6/38 (15.8)	
OR (95% CI)[b]			1.94 (0.67-5.59)		2.59 (0.77-8.67)		3.05 (1.01-9.18)		1.18 (0.52-2.66)		1.85 (1.12-3.08)

Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; CARDIA, Coronary Artery Risk Development in Young Adults; CKD, chronic kidney disease; inc CKD, incident CKD; JHS, Jackson Heart Study; MESA, Multi-Ethnic Study of Atherosclerosis; OR, odds ratio; SCT, sickle cell trait; WHI, Women's Health Initiative.

[a] Noncarriers are the reference category.

[b] Models adjusted for age, sex, clinic or region, and African genetic ancestry.

Table 5. Association of Sickle Cell Trait With Chronic Kidney Disease and Albuminuria by *APOL1* Carrier Status in ARIC and JHS[a]

	CKD					Albuminuria				
	ARIC		JHS			ARIC		JHS		
	Non-carriers	SCT Carriers	Non-carriers	SCT Carriers	Meta-analysis	Non-carriers	SCT Carriers	Non-carriers	SCT Carriers	Meta-analysis
Without *APOL1* Risk Variant										
No./total (%)	444/2617 (17.0)	49/183 (26.8)	96/1012 (9.5)	14/89 (15.7)		362/1724 (21.0)	30/120 (25.0)	192/929 (20.7)	24/83 (28.9)	
OR (95% CI)[b]	1.79 (1.27-2.53)		2.00 (1.04-3.87)		1.73 (1.27-2.36)	1.25 (0.81-1.92)		1.65 (0.99-2.76)		1.40 (1.01-1.95)
With *APOL1* Risk Variant										
No./total (%)	96/399 (24.1)	5/22 (22.7)	23/157 (14.6)	0/11		85/266 (32.0)	7/13 (53.8)	36/146 (24.7)	5/11 (45.5)	
OR (95% CI)[b]	0.87 (0.31-2.44)				0.87 (0.31-2.44)	2.17 (0.70-6.74)		3.56 (0.94-13.54)		2.67 (1.13-6.33)

Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; CKD, chronic kidney disease; JHS, Jackson Heart Study; OR, odds ratio; SCT, sickle cell trait.

[a] Noncarriers are the reference category.

[b] Models adjusted for age, sex, clinic or region, and African genetic ancestry.

the renal medulla results in ischemia and microinfarction of the renal tubules.[6] Local ischemia and hemolysis cause release of vasoactive factors,[28] which promotes glomerular hyperfiltration, ultimately resulting in glomerulosclerosis and proteinuria.[29] In SCT, injection radiographs demonstrate renal medullary vascular disruption, though to a lesser extent than seen in sickle cell disease, suggesting that sickle hemoglobin may have a dose-dependent relationship with kidney injury.[6] Our finding that SCT was related to both CKD and albuminuria is consistent with these proposed mechanisms.

In our study, the association of SCT with CKD appeared to be independent of *APOL1* risk variants, which have recently drawn attention as an explanation for the higher risk of CKD in African Americans.[20,21] Although *APOL1* risk variants are associated with CKD progression in African Americans, they do not fully explain the observed increased risk of CKD among African Americans compared with other populations.[20] Our findings suggest that SCT may additionally relate to the racial disparity in CKD, with a population attributable risk for incident CKD of approximately 6%. Although we observed no gene-gene interaction with *APOL1*

or gene-environment interaction with diabetes or hypertension, further studies with even larger sample sizes are needed to sufficiently address potential interactions between SCT and these other CKD risk factors.

In contrast to *APOL1*, genetic testing for SCT is performed widely in the United States. Universal newborn screening for sickle hemoglobin is mandated in all 50 states, and screening for SCT is also variably implemented in college athletics, pregnancy, and renal transplant donor evaluations.[1,7,30] As a result, SCT carriers are identified at a young age, and high-risk individuals may benefit from early intervention. Studies investigating angiotensin-converting enzyme inhibition to delay the progression of albuminuria in participants with sickle cell disease and sickle nephropathy have had promising results,[31] although the long-term benefits remain unknown. Angiotensin-converting enzyme inhibition in SCT-associated CKD may provide a similar potential benefit but has not been evaluated.

Our study has limitations. The clinical and pathological cause of CKD in each individual was not explicitly recorded. In addition, direct genotyping for SCT was not available on all individuals; however, sensitivity analysis using the cohorts with the highest percentage of direct genotyping yielded substantially similar results to the overall meta-analysis. We were also unable to evaluate the modifying effects of coexisting hemoglobin mutations, such as α-thalassemia.[32] Our ability to assess the potential for interaction of *APOL1* was limited because genotypic data were only available in 2 cohorts. The strengths of our study include the large prospective, population-based sample of African Americans with detailed genotypic and phenotypic information and the reproducibility of results across cohorts with differing geographic, age, and sex compositions. In addition, we were able to evaluate outcomes that have not been previously evaluated in SCT, including CKD, decline in eGFR, and albuminuria.

Sickle cell trait was not associated with ESRD in our analysis. Our study is, to our knowledge, the first prospective study of SCT and ESRD; however, the relatively small number of incident ESRD cases, which was available by US Renal Data System linkage in only 2 cohorts, may have resulted in insufficient power to detect an association with SCT. Two prior studies examining the relationship between SCT and ESRD have demonstrated discordant findings, which can be potentially explained by limitations and variation in design.[9,33] A single-center study demonstrated a higher prevalence of SCT compared with the population prevalence obtained from birth records.[9] Another study, a cross-sectional analysis of a preexisting genetic cohort, did not show a higher prevalence of SCT among participants with ESRD compared with nonnephropathy controls.[33] Although we were unable to demonstrate a clear association with ESRD, the observed relationship with eGFR decline suggests that SCT may be associated with severe renal phenotypes. Additional prospective studies are needed to resolve this question.

In this large multicohort study, SCT was associated with CKD and incident CKD, decline in eGFR, and albuminuria in African Americans. These associations were independent of *APOL1* risk variants and may offer an additional genetic explanation for the increased risk of CKD observed among African Americans compared with other racial groups. Our study also highlights the need for further research into the renal complications of SCT. Because screening for SCT is already being widely performed, accurate characterization of disease associations with SCT is critical to inform policy and treatment recommendations.

Conclusions

Among African Americans in these cohorts, the presence of SCT was associated with an increased risk of CKD, decline in eGFR, and albuminuria, compared with noncarriers. These findings suggest that SCT may be related to the higher risk of kidney disease in African Americans.

ARTICLE INFORMATION

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