Explaining the Racial Difference in AKI Incidence

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ABSTRACT

African Americans face higher risk of AKI than Caucasians. The extent to which this increased risk is because of differences in clinical, socioeconomic, or genetic risk factors is unknown. We evaluated 10,588 African-American and Caucasian participants in the Atherosclerosis Risk in Communities study, a community-based prospective cohort of middle-aged individuals. Participants were followed from baseline study visit (1996–1999) to first hospitalization for AKI (defined by billing code), ESRD, death, or December 31, 2010. African-American participants were slightly younger (61.7 versus 63.1 years, $P<0.001$), were more often women (64.5% versus 53.2%, $P<0.001$), and had higher baseline eGFR compared with Caucasians. Annual family income, education level, and prevalence of health insurance were lower among African Americans than Caucasians. The unadjusted incidence of hospitalized AKI was 7.4 cases per 1000 person-years among African Americans and 5.8 cases per 1000 person-years among Caucasians ($P=0.002$). The elevated risk of AKI among African Americans persisted after adjustment for demographics, cardiovascular risk factors, kidney markers, and time-varying number of hospitalizations (adjusted hazard ratio, 1.20; 95% confidence interval [95% CI], 1.01 to 1.43; $P=0.04$); however, accounting for differences in income and/or insurance by race attenuated the association ($P>0.05$). High-risk *APOL1* variants did not associate with AKI among African Americans (demographic-adjusted hazard ratio, 1.07; 95% CI, 0.69 to 1.65; $P=0.77$). In summary, the higher risk of AKI among African Americans may be related to disparities in socioeconomic status.

J Am Soc Nephrol 25: 1834–1841, 2014. doi: 10.1681/ASN.2013080867

Racial disparities in kidney disease are pervasive. African Americans comprise 13.1% of the general United States population and 36.8% of the population on dialysis.[1,2] The lifetime risks of advanced CKD and ESRD are two to four times higher among African Americans than Caucasians.[2,3] Similar differences have been described in AKI. In 2010, the rate of AKI among Medicare patients was 44.2 per 1000 patient-years in African Americans and 24.3 per 1000 patient-years in Caucasians.[2] The extent to which racial disparity in AKI rates can be explained by differences in clinical, socioeconomic, or genetic risk factors has not been explored.

Many well described mediators of racial disparity in CKD may be relevant in AKI. The prevalence of diabetes, hypertension, and pathologic albuminuria—all strong risk factors for AKI—is much higher in African Americans than Caucasians.[4] Socioeconomic status, which is inversely associated with the development of CKD and explains some racial disparity in ESRD,[5,6] may correlate with poor quality care and iatrogenic AKI. Finally, recently discovered exonic variants of the gene *APOL1*, which are present almost exclusively in individuals of African descent,[7] are associated with a faster rate of GFR decline[8] as well as increased odds of HIV-associated nephropathy, systemic lupus erythematous-associated collapsing glomerulopathy, FSGS, and hypertensive nephrosclerosis.[9–14] Although the biology of the *APOL1*–CKD link remains uncertain, some hypothesize

Received August 16, 2013. Accepted December 23, 2013.

Published online ahead of print. Publication date available at www.jasn.org.

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that an *APOL1*-mediated arteriopathy contributes,[15] which may in turn predispose to alterations in renal hemodynamics and AKI.

Using the Atherosclerosis Risk in Communities (ARIC) study, a community-based prospective cohort, we sought to quantify AKI rates among Caucasian and African-American participants and evaluate the effect of both described and novel risk factors in explaining racial differences. Namely, we examined whether differences in demographic factors, baseline kidney function, comorbid conditions, socioeconomic status, and presence of high-risk *APOL1* genetic variants contribute to racial disparity in AKI.

RESULTS

Characteristics of ARIC Participants

Of 10,588 ARIC visit 4 participants with complete covariates, 2240 (21.2%) participants were African American (Table 1). African-American participants were slightly younger (61.7 versus 63.1 years, $P<0.001$), were more often women (64.5% versus 53.2%, $P<0.001$), and had higher mean eGFR and prevalence of moderate or severely increased albuminuria than Caucasian participants. African Americans were more likely to have diabetes and hypertension at baseline and less likely to have cardiovascular disease. Socioeconomic disparities were striking: 31.8% of African-American participants reported a total family annual income of <$12,000 compared with 5.0% of Caucasian participants. In addition, only 61.5% of African Americans reported having medical insurance at baseline compared with 92.7% of Caucasians, and 33.9% of African Americans versus 14.1% of Caucasians reported seeking medical care in an emergency department. Within the African-American population, 41.6% of participants carried no high-risk *APOL1* allele, 46.1% of participants carried one high-risk (G1 or G2) allele, and 12.3% of participants carried two high-risk alleles.

Table 1. Baseline characteristics of study participants by race

Variables	Caucasian Participants	African-American Participants	*P* Value
N	8348 (78.8%)	2240 (21.2%)	
Baseline variables			
Age, yr	63.1 (5.6)	61.7 (5.7)	<0.001
Women, %	53.2	64.5	<0.001
Income level, %			
<$12,000/yr	5.0	31.8	<0.001
$12,000–$24,999/yr	19.1	27.9	
$25,000–$49,999/yr	38.4	24.5	
≥$50,000/yr	37.5	15.9	
Health insurance, %	92.7	61.5	<0.001
Medicaid insurance, %	5.3	12.0	<0.001
Seeks medical care in an emergency department, %	14.1	33.9	<0.001
Education level, %			
Less than high school	14.1	33.9	<0.001
Some college	45.8	29.6	
Advanced degree	40.1	36.5	
Body mass index, kg/m^2	28.3 (5.2)	30.6 (6.3)	<0.001
Diabetes, %	13.8	26.3	<0.001
Hypertension, %	41.7	66.4	<0.001
Prior cardiovascular event, %	9.1	6.3	<0.001
Uric acid, mg/dl	5.6 (1.4)	5.9 (1.6)	<0.001
eGFR at visit 4, ml/min per 1.73 m^2	84.7 (14.2)	92.3 (19.7)	<0.001
Urine ACR, mg/g (median [IQR])	3.9 [2.0–7.7]	2.7 [0.9–8.5]	<0.001
Moderately increased albuminuria, %	5.4	10.2	<0.001
Severely increased albuminuria, %	1.2	3.2	<0.001
Number of *APOL1* high-risk alleles, %			<0.001
0	—	41.6	
1	—	46.1	
2	—	12.3	
Follow-up variables			
Hospitalizations (median [IQR])	1 [0–3]	1 [0–3]	0.50
Follow-up time on ACE inhibitor/ARB, %	1.5 (5.6)	2.0 (7.0)	<0.001
Death, %	20.5%	23.6%	<0.001

Values reflect mean (SD) unless otherwise noted. ACR, albumin-to-creatinine ratio; IQR, interquartile range; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

Unadjusted and Stratified Incidence of AKI by Race

There were 785 AKI events over a median follow-up time of 13.0 years; 196 events occurred in African-American participants. The unadjusted incidence rate ratio (IRR) of AKI comparing African Americans with Caucasians was 1.26 (95% confidence interval [95% CI], 1.07 to 1.49; P=0.003). Differences persisted by subgroups of sex and age ($\leq$ or $>$60 years); however, rates were not significantly different among those participants with obesity, diabetes, or hypertension, and they were not different in any category of income or presence of health insurance (Figure 1). For example, the IRRs of AKI comparing African Americans with Caucasians were 0.89 (95% CI, 0.62 to 1.30) for annual income$<$\$12,000, 1.04 (95% CI, 0.75 to 1.44) for income between \$12,000 and \$25,000, 0.88 (95% CI, 0.61 to 1.25) for income between \$25,000 and \$50,000, and 1.35 (95% CI, 0.85 to 2.07) for income$>$\$50,000.

Risk of AKI Associated with Race Adjusting for Potential Confounders

The relationship between race and AKI was evaluated in a series of nested models (Table 2). There was significant risk associated with African-American race in unadjusted analysis as well as analyses adjusted by demographics, baseline and time-varying clinical risk factors, and genetic risk factors (models 1–4). However, with adjustment for the presence of health insurance and total annual family income (model 6), associations between race and AKI were no longer significant (adjusted hazard ratio [HR], 1.09; 95% CI, 0.89 to 1.32; P=0.40). Education level, type of insurance at visit 4 (*e.g.*, Medicaid, Medicare, or private), use of the emergency department as a source of medical care, and time-varying angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use were evaluated but showed no significant association in multivariable analysis; thus, they were not included in the final model.

Patterns of Care by Income Level

Markers of socioeconomic status were highly correlated. In both African Americans and Caucasians, participants in the lowest category of income ($<$\$12,000) were much more likely to use the emergency room as a source of medical care than participants in the highest category of income ($\geq$\$50,000; 32.7% versus 13.6%, $P<0.001$). Low income was also

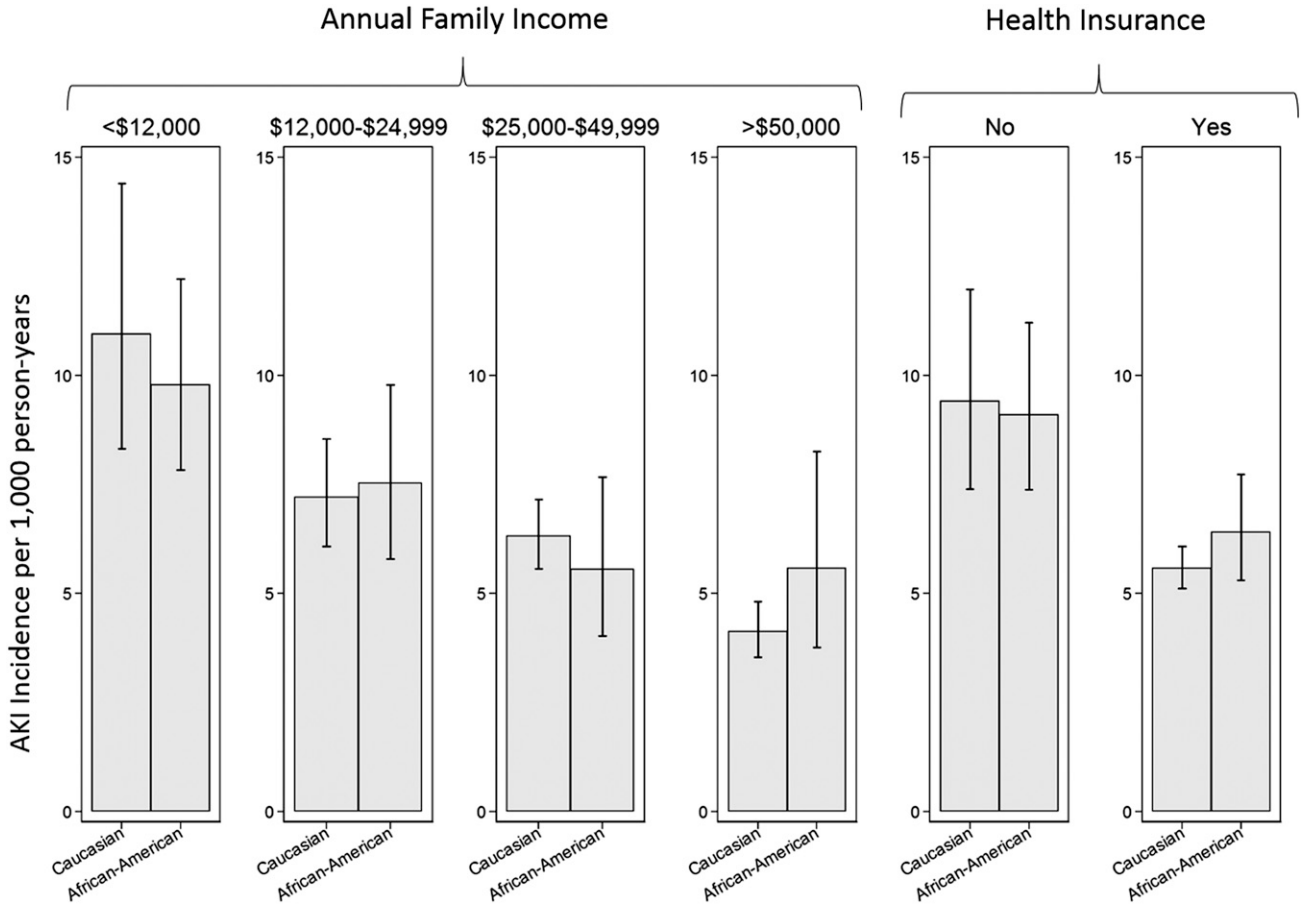

Figure 1. Rates of AKI by race, income level, and insurance status. There were no statistically significant differences in rates of AKI by race in any of the subgroups of income level and insurance.

Table 2. Association of African-American race with hospitalized AKI

	HR for African-American Race (95% CI)	*P* Value
Unadjusted	1.27 (1.08 to 1.49)	0.004
Model 1: adjusted for demographics	1.50 (1.27 to 1.77)	<0.001
Model 2: model 1+CV risk factors and kidney function	1.20 (1.01 to 1.43)	0.04
Model 3: model 2+*APOL1* risk alleles	1.28 (1.06 to 1.55)	0.01
Model 4: model 2+time-varying hospitalizations	1.19 (1.00 to 1.42)	0.04
Model 5: model 4+insurance	1.11 (0.91 to 1.34)	0.30
Model 6: model 5+income	1.09 (0.89 to 1.32)	0.40

Models include demographics (age and sex), cardiovascular (CV) risk factors (diabetes, hypertension, prevalent coronary heart disease, body mass index>30 kg/m^2, uric acid, current smoking, and former smoking), kidney function (ACR [log 8-fold] and eGFR (knot at 60 ml/min per 1.73 m^2), *APOL1* risk alleles (two high-risk variants [yes or no]), time-varying hospitalizations (number of hospitalizations since baseline), insurance (yes or no), and income (<$12,000, $12,000–$24,999, $25,000–$49,999, and >$50,000).

associated with lack of health insurance (57.4% of participants in the lowest category of income compared with 3.0% of participants in the highest category, $P<0.001$), less education (53.8% of participants in the lowest income category versus 4.1% of participants in the highest income category did not graduate from high school, $P<0.001$), higher number of total hospitalizations (relative risk, 2.38; 95% CI, 2.20 to 2.56; $P<0.001$), higher rate of AKI (unadjusted HR, 2.51; 95% CI, 2.00 to 3.15; $P<0.001$), and higher rate of death (31.4% versus 13.2%, $P<0.001$). Relationships were similar comparing participants with and without health insurance at baseline: participants without health insurance reported less education (48.1% versus 13.5% of participants did not graduate from high school, $P<0.001$), were more likely to use the emergency room as a source of care (29.9% versus 16.4%, $P<0.001$), and had higher numbers of hospitalizations (relative risk, 2.22; 95% CI, 2.07 to 2.38; $P<0.001$) and higher rates of AKI (unadjusted HR, 1.68; 95% CI, 1.41 to 2.01; $P<0.001$) and death (32.4% versus 19.3%, $P<0.001$). There was no modification by race in any of these associations.

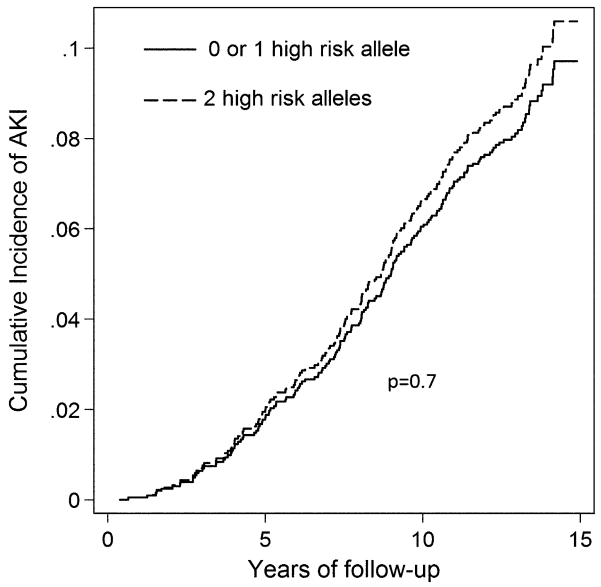

Figure 2. Cumulative incidence of AKI among African Americans by *APOL1* high-risk status. Analysis accounts for the competing risks of ESRD and death.

Risk of AKI among African Americans by *APOL1* Risk Alleles

Among African Americans, the presence of two risk alleles was not significantly associated with AKI risk in demographic-adjusted analyses (HR, 1.07; 95% CI, 0.69 to 1.65; $P=0.77$). There was no relationship between high-risk alleles and income or insurance status. Taking into account the competing risk of ESRD did not materially affect results ($P=0.67$) (Figure 2).

Sensitivity Analyses

To evaluate whether a differential loss to follow-up by race between ARIC visits 1 and 4 could have driven results, analyses were repeated using ARIC visit 1 (1987–1989) as a baseline. The results were very similar to those results using visit 4 as a baseline: in a model adjusted solely by demographic variables, African-American race conferred a 60% increase in AKI risk (HR, 1.60; 95% CI, 1.40 to 1.83; $P<0.001$) over a median follow-up time of 21.6 years. However, after adjustment for insurance status, income level, and prevalent diabetes, hypertension, and coronary heart disease, the association was significantly attenuated and no longer significant (HR, 1.06; 95% CI, 0.90 to 1.24; $P=0.50$). The presence of two high-risk *APOL1* alleles was not associated with AKI (demographic-adjusted HR, 0.84; 95% CI, 0.60 to 1.17; $P=0.30$).

DISCUSSION

This large, community-based study shows significant racial disparity in rates of AKI, with African Americans facing nearly 30% greater risk than Caucasians during 13 years of follow-up. Through careful accounting for potential confounders, we show that the disparity is not fully explained by the differences in the prevalence of diabetes, hypertension, albuminuria, or coronary heart disease—although all prove strong risk factors for AKI—or the presence of high-risk variants of the *APOL1* allele. Rather, we find that, after accounting for differences

in income and/or insurance, racial disparities in AKI are attenuated.

The importance of income in AKI incidence is a new finding and consistent with previous studies in CKD. In ARIC, low income conferred 2.4 times increased risk of 3-year kidney function decline.[16] In the US Renal Data System registry, neighborhood poverty—a community-level factor—was associated with ESRD incidence, with an effect stronger among African Americans than Caucasians.[17] Income might also affect outcomes of kidney disease, since the probability of anemia, phosphatemia, disability, depression, and cardiovascular disease was greater among those patients with low income.[18–24] Our study adds to this body of evidence by providing new data relating AKI (which itself is both a risk factor for and an outcome of CKD[25,26]) to low income.

The mechanism by which low income associates with kidney disease risk is uncertain; however, impaired access to health care may play a role.[27] In the Kidney Early Evaluation Program, persons without health insurance had a 72% greater risk of ESRD (and 82% greater risk of all-cause mortality) than persons with private health insurance.[28] In our study, participants without health insurance (as well as those participants with lower reported annual income) were more likely to list the emergency department as a usual source of medical care and had, on average, higher numbers of hospitalizations. Relevant to AKI, lack of quality outpatient care may result in increased use of over-the-counter medications (such as nonsteroidal anti-inflammatory drugs), mismanagement of prescription medications, and poor control of concurrent disease (such as diabetes and hypertension); in addition, more frequent use of the emergency department might increase the likelihood of intravenous contrast administration—all of which are suspected etiologies of AKI.[29] However, it is possible that AKI differentially represents true AKI in an underinsured population without regular blood work; in this scenario, events labeled as AKI might actually represent CKD progression. In our previous validation work, however, there was no difference in the sensitivity of diagnostic code-identified AKI by race.[30]

Insofar as health care use and implementation affect AKI risk, there have been documented racial differences in these factors, even among those patients with stable health insurance.[31,32] In Medicare beneficiaries, healthy African Americans reported diminished access to care compared with their Caucasian counterparts on several secondary measures, such as customer service and prescription drug information, as well as some tertiary measures, such as immunization for pneumonia.[33] African Americans also reported greater challenges in obtaining prescription medications through Medicare Part D.[34] In our study of a slightly younger, community-based population, there were no racial differences in rates of emergency department use after income level or insurance status was considered. However, we have no data on outpatient care use and, thus, cannot directly assess the association between health care use and AKI risk.

The lack of association between *APOL1* risk alleles and AKI is somewhat surprising. Given the inextricable role of AKI in CKD progression[25,35] and the substantial overlap of risk factors between AKI and CKD, a genetic predisposition for CKD seems apt to extend to AKI. In our study, there was a suggestion of increased AKI risk associated with the *APOL1* risk alleles in demographic-adjusted analyses; however, this finding was not statistically significant. This may be due to the poor sensitivity in outcome ascertainment (billing code identification of AKI may capture only a minority of the Kidney Disease: Improving Global Outcomes [KDIGO] creatinine-based criteria cases of AKI[30]), which, in turn, diminishes the power to detect associations. Alternatively, this finding may be because of distinct biologic pathways. Most APOL1-associated disease discovered thus far shows injury to the glomeruli,[7] whereas tubulointerstitial injury may be implicated in many cases of hospitalized AKI.

To our knowledge, this study is the first to comprehensively evaluate racial disparities in AKI, including genetic risk factors. Baseline risk factors were carefully and comprehensively measured, and hospitalizations—one of the stronger risk factors for AKI—were assessed longitudinally. Although the sensitivity of AKI hospitalizations identified by billing codes is low, we have previously undertaken extensive validation, determining that there is no difference in sensitivity or specificity of billing codes by race. The undercapture of true AKI events could result in effect sizes that are conservatively biased. Finally, the ARIC study did not collect neighborhood-level measures of income; however, individual-level measures are likely more important in the development of kidney disease.[36]

In summary, this study shows that African Americans face greater risk of AKI than Caucasians, similar to chronic forms of kidney disease. Although this observational study shows only associations and not cause and effect, the increased risk of AKI among African Americans seems to be driven largely by differences in socioeconomic status, particularly family income and the presence of health insurance. Global improvement in access to quality health care may lower rates of AKI and attenuate racial disparities.

CONCISE METHODS

Study Population

The ARIC study is a prospective, community-based cohort of 15,792 individuals ages 45–64 years. Designed to study risk factors in cardiovascular disease and atherosclerosis, original enrollment occurred from 1987 to 1989 in four United States communities: Washington County, Maryland; Minneapolis, Minnesota; Jackson, Mississippi; and Forsyth County, North Carolina. After initial enrollment, follow-up clinical examinations occurred at approximately 3-year intervals until visit 4 (1996–1999); visit 5 was recently completed (2011–2013). For the purposes of this analysis, visit 4 was selected as baseline, because it was the first visit in which urine albumin and urine creatinine were measured. Only self-identified African-American and

Caucasian participants with eGFR>15 ml/min per 1.73 m^2 and no previous episode of AKI were considered (n=11,575 of 11,656 participants attending visit 4). Analyses were performed on those participants with complete covariates (n=10,588). Of note, repeating analysis using multiple imputation for missing variables made no meaningful differences in results (data not shown).

Ascertainment of AKI Hospitalizations

ARIC participant vital status and intervening hospitalizations are determined annually for all participants (irrespective of visit attendance) by telephone follow-up (response rate=92% in year 20) as well as ongoing active surveillance of local newspaper obituaries, state death lists, death certificates from the Department of Vital Statistics, and community hospital discharge lists. For each hospitalization, 26 discrete International Classification of Diseases, 9th Revision, Clinical Modification discharge billing codes are abstracted. For the current study, billing codes for all hospitalizations occurring between visit 4 (February 1, 1996 to January 30, 1999) and December 31, 2010 were evaluated. Hospitalizations with an International Classification of Diseases, 9th Revision, Clinical Modification code 584.x in any position were classified as AKI. A validation study using the ARIC cohort determined that, compared with the KDIGO classification of AKI,[29] the sensitivity of this algorithm was low (17%), but the specificity was high (>99%).[30] Sensitivity was higher when only stages 2 and 3 AKI were considered (40.3%). Neither sensitivity nor specificity varied by race.

Risk Factors for AKI

Clinical risk factors for AKI were chosen based on previously shown associations and biologic plausibility. Diabetes was defined as self-reported disease, the use of hypoglycemic medication, a fasting glucose level≥126 mg/dl, or a random glucose≥200 mg/dl. Hypertension was defined as a systolic BP≥140 mmHg or a diastolic BP≥90 mmHg measured at the study visit or the use of antihypertensive medications. Prevalent coronary heart disease was defined as a history of definite or probable myocardial infarction or cardiac procedure. Body mass index was measured along with serum urate, creatinine, and urine albumin-to-creatinine ratio. All measurements were captured at baseline (study visit 4). The number of hospitalizations was defined as a time-varying count of hospital stays from baseline until AKI event, ESRD, death, or end of study. The use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers was ascertained during annual follow-up telephone calls and modeled as a time-varying binary variable.

The socioeconomic status variables education level, type of insurance, use of the emergency department as a source of medical care, and annual total family income (in predefined categories) were self-reported. All were captured at baseline (study visit 4). For genetic risk factors, the presence of *APOL1* risk alleles was determined by direct genotyping of three recently identified *APOL1* risk variants[37] (rs73885319, rs60910145, and rs71785313) using a combination of an Illumina panel and Taqman in African-American ARIC participants. The call rate was 99%–100%. Caucasian participants were not genotyped for *APOL1* alleles, because the minor allele frequency is thought to be exceedingly low (0.028%–0.057% in Framingham Heart Study).[38] For full population analysis, Caucasians were imputed as having less than two high-risk *APOL1* alleles.

Statistical Analyses

Differences in baseline characteristics by race were evaluated using t and chi-squared tests for continuous and categorical variables, respectively. For continuous variables deviating from normal distributions, differences were evaluated by a nonparametric equality of medians test. Associations with total numbers of hospitalizations were performed using Poisson regression to account for the number of days in follow-up. The relative hazard of AKI associated with African-American race was evaluated using Cox proportional hazards regression censored at the date of last contact, ESRD, death, or end of study (December 31, 2010), whichever came first. Models were sequentially adjusted for demographic factors (age and sex), clinical risk factors (diabetes, hypertension, prevalent coronary heart disease, eGFR [linear splines with a knot at 60 ml/min per 1.73 m^2], log albumin-to-creatinine ratio, current smoking status, former smoking status, uric acid level, and obesity [body mass index>30]), and genetic risk factors (the presence of two high-risk *APOL1* variants). Given that the presence of two high-risk *APOL1* variants was not significantly associated with AKI, the final three models excluded this variable but were sequentially adjusted for time-varying number of hospitalizations, the presence of health insurance, and income level (<$12,000, $12,000–$24,999, $25,000–$49,999, and >$50,000). Unadjusted incidence rates of AKI among African-American and Caucasian participants were compared as IRRs. The association of *APOL1* risk alleles with AKI was evaluated in a recessive model among African-American ARIC participants using Cox proportional hazards analysis.

To determine if the lack of association between *APOL1* risk alleles and AKI was because of the competing risks of death and ESRD, the analysis was repeated using competing risk regression in the work by Fine and Gray[39] to determine the cumulative incidence of AKI over time (Figure 2). Finally, because a smaller proportion of African-Americans than Caucasian participants attended visit 4, sensitivity analyses were performed using visit 1 as a baseline. These analyses were designed to address the possibility of bias induced by differential loss to follow-up by race and included the full population of self-identified African-American and Caucasian participants with eGFR>15 ml/min per 1.73 m^2 at visit 1 (n=15,574). All analyses were performed using Stata/SE 11.2 (StataCorp., LP, College Station, TX).

ACKNOWLEDGMENTS

The authors thank the staff and participants of the Atherosclerosis Risk in Communities study for their important contributions.

M.G. is supported by National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases Grant K08-DK092287. M.F. and A.T. received support from a National Heart, Lung, and Blood Institute T32-HL007024 Cardiovascular Epidemiology Training Grant. W.H.L.K. received support from National Institute of Diabetes and Digestive and Kidney Diseases Grant R01-DK076770. The

Atherosclerosis Risk in Communities study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute Contracts HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C.

This study was presented at the American Society of Nephrology Annual Kidney Week on November 7, 2013, in Atlanta, GA.

M.G. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

DISCLOSURES

J.C. has consulted for Amgen and Merck and has an investigator-initiated grant from Amgen. The other authors have no relevant financial relationships to disclose.

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See related editorial, "Race, Class, and AKI," on pages 1615–1617.