Albuminuric and Racial Disparities in the Risk for ESRD

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ABSTRACT
The causes of the increased risk for ESRD among African Americans are not completely understood. Here, we examined whether higher levels of urinary albumin excretion among African Americans contributes to this disparity. We analyzed data from 27,911 participants in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study who had urinary albumin-to-creatinine ratio (ACR) and estimated GFR (eGFR) measured at baseline. We identified incident cases of ESRD through linkage with the United States Renal Data System. At baseline, African Americans were less likely to have an eGFR <60 ml/min per 1.73 m² but more likely to have an ACR ≥30 mg/g. The incidence rates of ESRD among African Americans and whites were 204 and 58.6 cases per 100,000 person-years, respectively. After adjustment for age and gender, African Americans had a fourfold greater risk for developing ESRD (HR 4.0; 95% CI 2.8 to 5.9) compared with whites. Additional adjustment for either eGFR or ACR reduced the risk associated with African-American race to 2.3-fold (95% CI 1.5 to 3.3) or 1.8-fold (95% CI 1.2 to 2.7), respectively. Adjustment for both ACR and eGFR reduced the race-associated risk to 1.6-fold (95% CI 1.1 to 2.4). Finally, in a model that further adjusted for both eGFR and ACR, hypertension, diabetes, family income, and educational status, African-American race associated with a nonsignificant 1.4-fold (95% CI 0.9 to 2.3) higher risk for ESRD. In conclusion, the increased prevalence of albuminuria may be an important contributor to the higher risk for ESRD experienced by African Americans.


African Americans have a three- to fourfold increased risk of ESRD compared with whites.1 This increased risk contrasts with the comparable or higher prevalence of earlier chronic kidney disease (CKD), defined by GFRs between 15 to 60 ml/min per 1.73 m², reported for whites in the National Health and Nutrition Survey (NHANES)1,2, the Multi-Ethnic Study of Atherosclerosis (MESA), study3 and the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study.4 The reasons for this discrepancy have not been fully explained.3–7

Albuminuria, defined as an albumin-to-creatinine ratio (ACR) of 30 mg/g or greater is an important risk factor for progression of CKD to ESRD.8–12 The prevalence of albuminuria is higher among African Americans compared with whites in NHANES and other studies even at higher levels of GFR.13–15 However, we are unaware of studies

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that have examined the degree to which racial disparities in the prevalence of albuminuria contribute to black-white differences in ESRD, and the present study examined this possibility.

**RESULTS**

The mean (SD) age of participants was 64.8 (9.4) years, 45.6% were men, and 40.5% were African American. Less than high school education was reported by 12.3% of participants, and 17.6% lived in low-income households (reported as below $20,000 annually). Hypertension (59.9%) and diabetes (20.9%) were common. At baseline, African Americans were younger than whites. African Americans were less likely to be men, had a greater waist circumference, were more likely to report a low income, to not have completed high school, and to have hypertension and diabetes (Table 1). In contrast, African Americans were more likely than whites to be treated with a renin-angiotensin system blocking agent.

The mean estimated GFR (eGFR) for African Americans was 88.8 (23.1) ml/min per 1.73 m² and 82.6 (17.1) ml/min per 1.73 m² in whites. The median ACR for African Americans was 8.0 mg/g and the 25th to 75th percentiles were 4.7 to 19.9 mg/g, respectively, and 7.1 mg/g (25th to 75th percentiles: 4.6 to 14.0 mg/g) for whites. Across levels of eGFR at baseline, the median ACR in African Americans increased from 7.4 mg/g at eGFR/H11350 90 ml/min per 1.73 m² to 91.2 mg/g at eGFR levels of 15 to 29 ml/min per 1.73 m². In contrast, among whites there was an increase from 6.8 to 20.6 mg/g in the median ACR level by level of GFR (Table 2). It should be noted that a large AA:W difference in ACR levels was present at eGFR below 30 ml/min per 1.73 m². The eGFR among African Americans and whites at higher levels of baseline ACR had a comparable pattern. Among African Americans the eGFR difference was 31.8 ml/min per 1.73 m² at ACR levels of /H11021 10 mg/g to /H11350 300 mg/g, whereas among whites it was 22.3 ml/min per 1.73 m².

**Table 1.** Baseline characteristics of REGARDS study participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total</th>
<th>African American</th>
<th>White</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>27,911</td>
<td>40.5%</td>
<td>59.5%</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>64.8 (9.4)</td>
<td>63.9 (9.2)</td>
<td>65.4 (9.5)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>45.6</td>
<td>38.5</td>
<td>50.5</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>59.9</td>
<td>71.1</td>
<td>50.5</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>20.9</td>
<td>29.3</td>
<td>15.2</td>
</tr>
<tr>
<td>Renin-angiotensin agent (%)</td>
<td>35.9</td>
<td>41.7</td>
<td>32.0</td>
</tr>
<tr>
<td>Low income (%)</td>
<td>17.6</td>
<td>26.4</td>
<td>11.6</td>
</tr>
<tr>
<td>Education &lt; HS (%)</td>
<td>12.3</td>
<td>19.7</td>
<td>7.2</td>
</tr>
<tr>
<td>eGFR (ml/min per 1.73 m²)*</td>
<td>85.1 (20.0)</td>
<td>88.8 (23.1)</td>
<td>82.6 (17.1)</td>
</tr>
<tr>
<td>Median ACR (mg/g)*</td>
<td>7.4</td>
<td>8.0</td>
<td>7.1</td>
</tr>
<tr>
<td>Waist circumference (cm)*</td>
<td>96.1 (15.0)</td>
<td>98.1 (15.3)</td>
<td>94.7 (15.5)</td>
</tr>
<tr>
<td>Albuminuria (%)**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 to 299 mg/g</td>
<td>12.2</td>
<td>14.6</td>
<td>10.5</td>
</tr>
<tr>
<td>≥300 mg/g</td>
<td>2.8</td>
<td>4.7</td>
<td>1.7</td>
</tr>
<tr>
<td>CKD (%)***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 to 59 ml/min per 1.73 m²</td>
<td>10.0</td>
<td>9.9</td>
<td>10.0</td>
</tr>
<tr>
<td>15 to 29 ml/min per 1.73 m²</td>
<td>1.09</td>
<td>1.1</td>
<td>0.6</td>
</tr>
</tbody>
</table>

REGARDS, Reasons for Geographic and Racial Differences in Stroke; eGFR, estimated GFR; ACR, albumin-to-creatinine ratio; CKD, chronic kidney disease.

*D Values are mean with SD in parentheses.

Differences between African-Americans and white subjects: *P < 0.0001; **Wilcoxon rank sum test, P < 0.0001; ***P = 0.0007.

**Table 2.** Levels of estimated glomerular filtration rate and elevated albumin-to-creatinine ratio at baseline by race and the African-American-to-white odds ratio for reduced estimated glomerular filtration rate and elevated albumin-to-creatinine ratio

<table>
<thead>
<tr>
<th>GFR (ml/min per 1.73 m²)*</th>
<th>African American</th>
<th>White</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥90</td>
<td>53.1</td>
<td>40.0</td>
</tr>
<tr>
<td>45 to 89</td>
<td>36.0</td>
<td>49.6</td>
</tr>
<tr>
<td>30 to 44</td>
<td>7.0</td>
<td>7.4</td>
</tr>
<tr>
<td>15 to 29</td>
<td>3.5</td>
<td>3.0</td>
</tr>
<tr>
<td>ACR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>58.8</td>
<td>64.8</td>
</tr>
<tr>
<td>10 to 29</td>
<td>22.9</td>
<td>23.2</td>
</tr>
<tr>
<td>30 to 299</td>
<td>14.5</td>
<td>10.4</td>
</tr>
<tr>
<td>≥300</td>
<td>3.8</td>
<td>1.6</td>
</tr>
</tbody>
</table>

| ACR                       | 62.3 (27.0)      | 64.4  |

GFR, glomerular filtration rate; ACR, albumin-to-creatinine ratio; AA:W, African American:white; OR, odds ratio; CI, confidence interval.

a Values are mean with SD in parentheses.

b Values are OR adjusted for age and gender, with 95% CI in parentheses.
The age and gender adjusted prevalence of African Americans compared with whites, expressed as the AA:W odds ratio (OR) with 95% confidence interval (CI), increased as both ACR increased and GFR decreased (Table 2).

Over a median of 3.6 years of follow-up, 133 participants developed incident ESRD and an incidence rate of 142 persons per 100,000 person-years of follow-up. There were 96 incident cases of ESRD among African Americans and 37 among white participants with respective incidence rates (95% CI) of 204 and 58.6 ESRD cases per 100,000 person-years. The crude African American-to-white hazard ratio (95% CI) for ESRD was 3.80 (2.60, 5.56). After adjustment for age and gender, the AA:W hazard ratio (HR) was 4.01 (2.73, 5.89).

ESRD incidence in both races increased as level of baseline eGFR declined, and baseline ACR increased (Table 3). The ESRD incidence rate increased among African Americans from 34.8 persons/100,000 person-years for a baseline eGFR of 90 ml/min per 1.73 m² or greater to 4242.2 persons/100,000 person-years for participants with baseline GFR <29 ml/min per 1.73 m². Analogous values for whites were 13.6 to 1506.4 persons/100,000 person-years (Table 3).

The ESRD rate for African Americans increased from 31.1 to 3763 persons/100,000 person-years and in whites from 16.5 to 1860 persons/100,000 person-years as baseline ACR increased from <10 mg/g to ≥300 mg/g.

The age-gender adjusted cumulative hazard during follow-up is shown for blacks and whites in Figure 1.

Multivariable models, which control for ACR, attenuated the AA:W HR (95% CI) for ESRD (Figure 2). The AA:W HR (95% CI) for incident ESRD controlling for age, gender, and waist circumference was 3.87 (2.63, 5.70). When log of ACR was added to this model the AA:W HR (95% CI) was substantially reduced to 1.81 (1.21, 2.72). In comparison, when eGFR was substituted for log of ACR the AA:W HR (95% CI) was reduced to 2.23 (1.49, 3.34). Inclusion of both eGFR and log ACR in the model, resulted in a modest reduction over that of ACR alone [AA:W HR (95% CI) = 1.60 (1.05, 2.43)].

When we sequentially adjusted the model with age, gender, waist circumference, eGFR, and ACR for diabetes, hypertension, and use of renin-angiotensin system blocking agents as well as for education and household income, the AA:W HR (95% CI) decreased to 1.44 (0.92, 2.56) (Figure 2). We tested for interaction between race, ACR, and GFR in the final model. The three-way interaction term was not significant ($P = 0.232$). In a model containing only two-way interaction terms neither that for race and ACR ($P = 0.824$) nor for race and eGFR ($P = 0.086$) was statistically significant.

**DISCUSSION**

African Americans have a comparable or lower prevalence of more advanced CKD, measured either by serum creatinine$^{16}$ or GFR$^{1,17,18}$ than whites, a finding we have previously reported for REGARDS participants$^4$ that was observed as well in the present study. Lower baseline eGFR was associated with increased risk of ESRD for African Americans compared with...
whites, although the AA:W HR was attenuated as the severity of CKD increased. These observations are similar to those reported by Choi et al. for a sample of more than two million patients in the Veterans Administration health system, where the AA:W HR for ESRD, adjusted for demographic characteristics, comorbid conditions, and socioeconomic status, declined from 2.14 (1.72 to 2.65) to 1.86 (1.75 to 1.98), for baseline GFR strata ≤90 and 15 to 29 ml/min per 1.73 m², respectively.¹⁹

These observations stand in contrast to three- to fourfold higher ESRD incidence rates among African Americans than whites and suggest that race-specific factors that influence progression of kidney disease may account for the discrepancy.²⁰ One potential risk factor for progressive CKD is the increased albumin excretion among African Americans. Increased urinary albumin excretion is a risk factor for progression of CKD, and our study suggests that racial differences in the prevalence and magnitude of increased ACR may account for a substantial proportion of this excess risk, at least among the covariates examined in the present study.

Racial differences in ACR have been reported in several studies. For example, the prevalence ACR ≥30 mg/g in the NHANES III population was 12% among African Americans and 8% among whites, AA:W OR (95% CI) of 1.41 (1.12 to 1.77) among individuals without diabetes, and 1.85 (1.18 to 2.91) among those with diabetes, racial differences of comparable magnitude to those we observed.¹⁴ In the Kidney Early Evaluation Program study ACR ≥30 mg/g was prevalent in 8% of whites and 11% of African Americans, an OR (95% CI) 1.38, (1.29 to 1.47).²⁴

Increased urinary albumin excretion among African Americans has been noted early in life. During early adulthood (age 20 to 37 years), African American participants in the Bogalusa Heart Study were observed to have higher ACR. ACR levels were associated with higher BP between ages 5 and 17 years in African-American, but not in whites participants.¹⁵ Hanevoid et al. reported that healthy, normotensive African-American adolescents were more likely to have an increased albumin excretion that was associated with impaired stress-induced pressure natriuresis and, in African-American men, with higher BP.²⁵ African-American participants in the Coronary Artery Risk Development in Young Adults (CARDIA) study, aged 50 years and younger, had a geometric mean ACR, adjusted for gender and race differences in creatinine excretion, which was higher among African Americans.²⁶ Of interest, higher geometric mean ACR in both races in the CARDIA study was independently associated with higher BP.

Despite the higher prevalence of elevated ACR in both hypertension¹⁹ and diabetes²⁷ and the strong association with risk of ESRD,²⁸ the role of ACR as a factor contributing to the racial disparities in progressive CKD has not been well studied. At baseline, African Americans in REGARDS had an increased prevalence of albumin excretion evident at levels of ACR currently regarded as within the normal range, and the racial disparity in ESRD incidence increased with increasing level of ACR. African Americans and whites with either high (ACR 30 to 299.9 mg/g) or very high (≥300 mg/g) levels of albuminuria had increased risk of ESRD.

The fourfold increased risk of ESRD among African Americans in our study is consistent with data from the United States Renal Data System (USRDS) for the US population and this excess risk was substantially attenuated after controlling for ACR. The reduction in the AA:W HR for ESRD controlling for ACR was greater than that observed when controlling for eGFR alone. Furthermore, the reduction in AA:W HR for ESRD in models controlling for both ACR and eGFR was comparable to that controlling for ACR alone. These results suggest that the increased prevalence of ACR ≥30 mg/g among African Americans may contribute importantly to the increased risk for ESRD experienced by this population.

These observations raise the question as to what factors might mediate racial differences in the prevalence of albumin-
In summary, differences in albumin excretion among individuals with CKD and incident ESRD were more pronounced among blacks in our study. This may be an important risk factor for racial disparities in albuminuria among individuals with CKD and suggest that interventions to reduce albuminuria in preventing or delaying the progression of chronic kidney disease. The strong and consistent evidence that reduction of proteinuria may delay and even prevent ESRD.

**CONCISE METHODS**

**Study Design.** The REGARDS study is a population-based ongoing cohort study of adults aged 45 years and older in the United States designed so that residents of the southeastern United States and African Americans were oversampled. The overall goal of REGARDS is to understand increased stroke mortality by African Americans and residents of the southeastern United States. Overall, 30,239 participants were enrolled. We excluded individuals missing either eGFR or ACR, with ESRD by self-report or based on data from the USRDS indicating the incidence of ESRD that occurred before enrollment in the REGARDS study. After these exclusions, data from 27,911 participants were available for analysis. This study was approved by the institutional review boards of the participating institutions.

**Data.** The data collection procedures have been described in detail previously. Briefly, data were obtained by a telephone interview and a subsequent in-home examination that included two sitting BP measurements using a standard technique, assessment of waist circumference, and ascertainment of medication use reported for the 2 weeks preceding the in-home visit. Renin-angiotensin system blocking agent use was defined as reported use of either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker. Serum creatinine, fasting blood glucose, and a random morning urine sample for measurement of creatinine and albumin were collected during the in-home visit. eGFR was calculated by the CKD-EPI equation using isotope dilution mass spectrometry-calibrated creatinine. The equation has been validated in African Americans and whites, adults with ages ranging from less than 40 to 80 years, both genders, and individuals with diabetes. We measured urinary albumin at the Department of Laboratory Medicine and Pathology at the University of Minnesota, using the BN ProSpec Nephelometer from Dade Behring (Marburg, Germany). Low annual household income was defined as below $20,000, and low educational attainment was defined as not having completed high school. Hypertension was defined as either self-reported use of antihypertensive medications or a mean SBP ≥140 mmHg or mean DBP ≥90 mmHg. Diabetes was defined as (1) self-reported use of insulin or oral hypoglycemics, (2) a fasting blood glucose greater than or equal to 126 mg/dl, or (3) a nonfasting blood glucose greater than or equal to 200 mg/dl.

Incident cases of ESRD were identified through linkage of REGARDS study participants with the USRDS, which records more than 90% of incident ESRD cases in the United States. A finder file containing unique individual identifiers (social security number, date of birth, and last and first name) was submitted for linkage with the USRDS Database. Sequential matching was accomplished using different configurations of full and partial individual identifiers. Individual records that did not produce a match candidate were again processed in subsequent rounds. For individuals with a match, but who
did not match on all identifiers, visual inspection of nonmatching variables was performed in the following rounds to confirm valid matches. Data from the USRDS included all incident ESRD cases, regardless of treatment modality, through August 2008. Thus, person-time was censored at death, date of ESRD incidence, or September 1, 2008, whichever occurred first.

**Analysis.**
Baseline characteristics were calculated as means or percentages for the overall population and for whites and African Americans. We used *t* tests, ANOVA, and χ² tests to test differences between races as appropriate. Log-transformed ACR was used, and we report the geometric means. We calculated incidence rates as the number of incident ESRD cases divided by the person-years of follow-up multiplied by 100,000. Incident rate ratios for African Americans compared with whites were computed as the ratios of each group’s incidence rates.

We used logistic regression models to examine the independent association between race and baseline kidney function controlling for other participant characteristics. Cox proportional hazards models were fitted to examine the association between the African-American and the white race and ESRD. In these analyses we accounted for the small numbers of participants in some cells by categorizing GFR as ≥60 and <60 ml/min per 1.73 m² and ACR as <30 and ≥30 mg/g.

First, we controlled the association between race and ESRD for age and gender. Next, models adjusting for either albuminuria (log transformed) or for GFR, and then with both were conducted to assess the degree to which the individual and combined measures of kidney function could attenuate the association between race and ESRD. Next, we determined if further adjustment for other risk factors for ESRD would modify the attenuation of the association between race and ESRD by measures of kidney function. We proceeded by adding as covariates to successive models: (1) hypertension and diabetes and (2) income and education.

We note that the sequence of covariate entry into our models may influence the interpretation of our results. Any reduction in the AA:W HR seen after first adding albuminuria to the age- and gender-adjusted model might not be as profound had we had entered socioeconomic and comorbid covariates. We chose this sequence a priori based on the underlying biologic models for progressive kidney disease that place increased ACR and reduced GFR as proximate risk factors in the etiology of ESRD.

We assessed potential interaction between race and albuminuria or eGFR, separately, on ESRD risk, using interaction terms for race and albuminuria, race and eGFR, and a three-way interaction term for race, albuminuria, and eGFR. All analyses were conducted using SAS 9.2 (SAS Institute, Cary, NC).

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**DISCLOSURES**
None.

**REFERENCES**


21. Jolly SE, Burrows NR, Chen SC, Li SY, Jurkovicz CT, Narva AS, Norris KC, Shlipak MG: Racial and ethnic differences in albuminuria in individuals with estimated GFR greater than 60 mL/min/1.73 m(2): Results from the Kidney Early Evaluation Program (KEEP). Am J Kidney Dis 55: S15–S22, 2010


34. Freedman BI, Kopp JB, Langefeld CD, Genovesi G, Friedman DJ,


