African Ancestry, Socioeconomic Status, and Kidney Function in Elderly African Americans: A Genetic Admixture Analysis

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Kidney disease is a major public health problem in the United States that affects African Americans disproportionately. The relative contribution of environmental and genetic factors to the increased burden of kidney disease among African Americans is unknown. The associations of genetic African ancestry and socioeconomic status with kidney function were studied cross-sectionally and longitudinally among 736 community-dwelling African Americans who were aged >65 yr and participating in the Cardiovascular Health Study. Genetic African ancestry was determined by genotyping 24 biallelic ancestry-informative markers and combining this information statistically to generate an estimate of ancestry for each individual. Kidney function was evaluated by cystatin C and estimated GFR (eGFR) using the Modification of Diet in Renal Disease equation. Longitudinal changes in serum creatinine and eGFR were estimated using baseline and follow-up values. In cross-sectional analyses, there was no association between genetic African ancestry and either measure of kidney function ($P = 0.36$ for cystatin C and 0.68 for eGFR). African ancestry was not associated with change in serum creatinine ≥0.05 mg/dl per yr (odds ratio [OR] 0.94; 95% confidence interval [CI] 0.83 to 1.06) or with change in eGFR ≥3 ml/min per 1.73 m^2 per yr (OR 1.02; 95% CI 0.92 to 1.13). In contrast, self reported African-American race was strongly associated with increased risk for kidney disease progression compared with white individuals for change in creatinine (OR 1.77; 95% CI 1.33 to 2.36) and for change in eGFR (OR 3.21; 95% CI 2.54 to 4.06). Among self-identified African Americans, low income (<$8000/yr) was strongly associated with prevalent kidney dysfunction by cystatin C >1.29 g/dl (adjusted OR 2.7; 95% CI 1.0 to 7.5) or by eGFR <60 ml/min per 1.73 m^2 (adjusted OR 3.2; 95% CI 1.1 to 9.4) compared with those with incomes >$35,000/yr. Alleles that are known to be present more frequently in the African ancestral group were not associated with kidney dysfunction or kidney disease progression. Rather, kidney dysfunction in elderly African Americans seems more attributable to differences in environmental and social factors.

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The burden of kidney disease in the United States affects African Americans disproportionately (1–3). Recent studies have shown that the disparity that is seen between self-identified African Americans and non-Hispanic white individuals may be most significant at more advanced stages of kidney disease, suggesting higher rates of progression in African Americans than in white individuals (3,4). The degree to which this increased burden among African Americans may be due to genetic predisposition to kidney disease or to environmental factors is unknown. Genetic admixture analysis is a method to investigate potential genetic factors that contribute to racial differences in complex phenotypes, such as kidney disease. The technique is based on the knowledge that individuals sampled worldwide can be classified, on the basis of genetic markers, into clusters that correspond to continental lines and to commonly identified racial groups (African, European/West Asian, East Asian, Pacific Islander, and Native American) (5). Genetic admixture analysis quantifies the proportion of an individual's genome that is of a given ancestral origin (*e.g.*, European, African) using ancestry-informative

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markers (those with large frequency differences between the ancestral populations) (6–10). Because African Americans in the United States are a heterogeneous group and they are known to be admixed with African, European, and Native American ancestry (7), genetic admixture analysis provides a more sensitive method of studying genetic ancestry, rather than the more crude categorization into racial groups. The finding of an association between genetic ancestry and a particular trait within an admixed group suggests that the trait's differential expression among racial groups may be genetic (11), although such an association also may be confounded by environmental factors within a group (12). In addition, an association of genetic ancestry with a particular phenotype can lead to further investigation to detect specific causal genetic loci by a technique called admixture mapping (8–10,13). We designed this study to evaluate whether genetic African ancestry is associated with kidney function and/or progression of kidney disease using cystatin C, serum creatinine, and estimated GFR (eGFR) among self-identified African Americans in the Cardiovascular Health Study (CHS).

Materials and Methods

Participants

Participants were self-identified, community-dwelling African American men and women who were aged ≥65 yr and participated in the Cardiovascular Health Study. Study design details were published previously (14). The initial cohort was enrolled from January 1989 to June 1990, and an additional 687 African American participants were enrolled by June 1993. Of the 862 African Americans, 736 participants were included in this study. Fifty-two participants either refused genetic testing or lacked available DNA samples and 74 had missing measures of renal function. All study protocols were approved by the appropriate institutional review boards.

Primary Predictor Variable: Selection of Ancestry-Informative Markers and Genotype Analysis

Twenty-four biallelic single-nucleotide peptide (SNP) markers were identified either from the National Center for Biotechnology Information SNP database (http://www.ncbi.nlm.nih.gov/SNP/) or from previously reported literature as being highly informative for ancestry (6,15). A detailed description of the source of markers and marker validation has been published (16). Briefly, the markers were chosen on the basis of the known allele frequency differences (δ values) among African, European, and Native American populations. δ is defined as the absolute value of allele frequency differences between two populations and is a measure of a marker's informativeness for admixture analysis. A δ of 1 suggests complete ancestry informativeness, and a δ of 0 suggests no informativeness. These markers are spaced sufficiently distant throughout the genome that they offer independent association about genetic background or ancestry (16). Detailed information on these markers can be found in the dbSNP Web site under submitter handle "PSU-ANTH" or "HapMap-UCSF-WU-FP-TDI." Genotyping was performed using the AcycloPrime-FP method under standard conditions (16).

Secondary Predictors

Using records from the 1992 to 1993 visit, we recorded age, gender, and race (self-reported), body-mass index, smoking (current smoker *versus* former smoker or never smoked), diagnosis of diabetes (history of diabetes, use of a hypoglycemic agent or insulin, or a fasting glucose level of ≥126 mg/dl), hypertension (systolic BP >140/90 mmHg or treated hypertension), LDL and HDL cholesterol levels, and C-reactive protein levels (14). Categorical variables were used for education, (less than ninth grade, high school, or more than high school), income (<$8000/yr, $8000 to $35,000, and >$35,000), and occupation white collar ([professional, technical, administrative, sales, or clerical), blue collar (craftsman, machine operator, laborer, farming, or forestry workers), and other (housewife or refusal to answer]).

Outcome: Measures of Kidney Function

All assays were performed in fasting serum specimens that were stored at −70°C. Cystatin C was measured by means of a particle-enhanced immunonephelometric assay (N Latex Cystatin C; Dade Behring, Deerfield, IL) with a nephelometer (BNII; Dade Behring). The range of detection of the assay is 0.195 to 7.330 mg/L. The reference range for young, healthy individuals was reported as 0.53 to 0.95 mg/L. The assay remained stable over five cycles of freezing and thawing. Serum creatinine was measured by a colorimetric method (Ektachem 700; Eastman Kodak, Rochester, NY). The mean coefficient of variation for monthly controls was 1.94% (range 1.16 to 3.90%). We used the Modification of Diet in Renal Disease (MDRD) equation (17) to estimate GFR.

Statistical Analyses

The proportion of African, European, and Native American ancestry for each individual was estimated by a maximum-likelihood method (18) with the program IAE3 (19). For each genotype, an expression for the probability of this genotype is derived on the basis of the allele frequency in each of the ancestral populations. Because the markers are independent, the probabilities for each of the genotypes can be multiplied to give an expression for the multilocus probability or likelihood of a certain ancestry. The log of the likelihood then is maximized for each individual. An individual's percentage of African ancestry was coded as a continuous variable.

We categorized the cohort by quartiles of African ancestry, and we estimated the mean value of kidney function (by cystatin C and eGFR separately) for each quartile of African ancestry in a cross-sectional manner from the 1992 or 1993 visit. We used multivariable linear regression with adjusted means to test whether African ancestry was independently associated with each measure of kidney function (in separate models) after adjustment for age, gender, smoking, diabetes, hypertension, education, income, and occupation. We used linear spline models to depict graphically the association between African ancestry and kidney function across the range of ancestry and kidney function, using spline knots at the quartiles of African ancestry.

A change in serum creatinine ≥0.05 mg/dl per yr or a change in eGFR ≥3 ml/min per 1.73 m^2 per year was considered progression of kidney disease, on the basis of a previous study from this cohort (20). We determined the change in serum creatinine from baseline to follow-up visits. Length of follow-up was 7 yr for the original cohort and 4 yr for the African American cohort that was recruited in 1992 to 1993. Because there was a different length of follow-up for the original and the African American cohorts, we used linear regression to determine the average annual change in creatinine as the slope of the change in creatinine for each individual. We used multivariable logistic regression to study the association of African ancestry as well as self-reported race with kidney disease progression. In addition, to study the association between sociodemographic variables and kidney function, we used linear and logistic regression adjusting for age, gender, hypertension, diabetes, and smoking. All analyses were performed using S-Plus

(release 6.1; Insightful, Seattle, WA) and SPSS statistical software (release 12.0.2; SPSS, Chicago, IL). Two-tailed $P < 0.05$ was considered significant.

Results

Demographic Characteristics by African Ancestry

Among the 736 participants in this analysis, the average age was 73 yr (SD 5.6), and 38% were male. Self-identified African Americans, on average, had a mean African ancestry of 76%, only 21% were derived from white ancestry, and <3% were derived from Native American populations. Across quartiles of African ancestry, participants were similar in age; gender; prevalence of diabetes; hypertension; smoking; and levels of LDL, HDL, triglycerides, and CRP (all $P > 0.05$). Those in the highest quartile of African ancestry (>90% African), however, had lower incomes and lower levels of education and were more likely to have blue collar occupations compared with the lowest quartile (<64% African; $P < 0.001$ for all three comparisons).

The prevalence of reduced kidney function was high, with 31% (225) having cystatin C levels between 1.0 and 1.28 mg/L, 13% (97) having levels >1.29 mg/L, and 18% (128) having an eGFR <60 ml/min per 1.73 m^2.

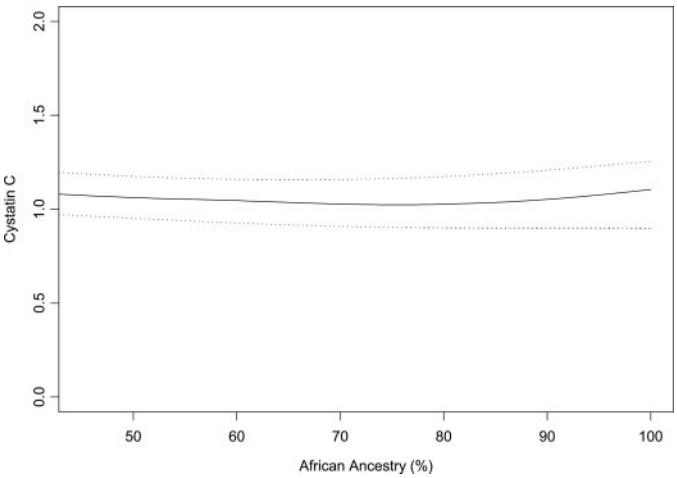

Figure 1. Association of genetic ancestry and renal function (by cystatin C) in elderly African Americans. Cubic smoothing splines depict the association between genetic African Ancestry and kidney function with knots placed at the quartiles of African ancestry. Dotted lines represent 95% confidence intervals.

Cross-Sectional Association of African Ancestry with Kidney Function

The mean level of kidney function (by cystatin C or eGFR) did not vary significantly across quartiles of African ancestry in unadjusted and adjusted analyses (Table 1). We also compared adjusted mean values of each kidney measure across the observed range of African ancestry using linear splines. There was no significant association between genetic African ancestry and renal function by either cystatin C or eGFR (Figures 1 and 2)

We used an alternative definition of kidney function by dividing the cohort into gender-specific serum creatinine quartiles. There was no association between African ancestry and serum creatinine for either men or women ($P > 0.20$ for linear trend).

Association of African Ancestry and Self-Reported Race with Kidney Disease Progression

Among 542 African American participants with repeated measures of serum creatinine, 11% had change in serum creatinine ≥0.05 mg/dl per yr and 20% had a change in eGFR ≥3 ml/min per 1.73 m^2 per yr. There was no significant association between genetic African ancestry and progression of kidney disease in this cohort either by change in serum creatinine or by change in eGFR. However, self-reported African American race was significantly associated with kidney disease progression when compared with white individuals (Table 2). We also conducted an analysis using change in creatinine and change in eGFR as continuous variables, and the results were unchanged.

Sociodemographic Factors and Kidney Function

In contrast to genetic ancestry, low income (<$8000/yr) was strongly associated with renal function among African Americans. In adjusted linear models, low income was associated with cystatin C levels that were 0.13 mg/L higher ($P = 0.038$ for linear trend) than in those with incomes >$35,000/yr. When adjusting for African ancestry, this difference was augmented to 0.16 mg/L ($P = 0.014$ for linear trend). Participants with lower incomes had eGFR that was 7.18 ml/min per 1.73 m^2

Table 1. Mean cystatin C and eGFR by quartile of African ancestry

Kidney Function Mean (95% CI)	African Ancestry				*P* for Linear Trend
	<64 (*n* = 189)	64 to 78 (*n* = 193)	79 to 89 (*n* = 183)	≥90 (*n* = 171)	
Cystatin C (mg/L)					
unadjusted	1.10 (1.04 to 1.17)	1.00 (0.94 to 1.07)	1.04 (0.98 to 1.11)	1.08 (1.02 to 1.15)	0.12
adjusted[b]	1.13 (1.07 to 1.20)	1.00 (0.94 to 1.07)	1.03 (0.96 to 1.10)	1.06 (0.99 to 1.14)	0.36
eGFR (ml/min per 1.73 m^2)					
unadjusted	79.5 (75.9 to 83.2)	82.1 (79.0 to 85.3)	79.1 (76.0 to 82.1)	78.4 (75.0 to 81.9)	0.43
adjusted[b]	79.9 (76.6 to 83.2)	81.6 (78.4 to 84.7)	79.8 (76.5 to 83.1)	78.7 (75.2 to 82.1)	0.68

[a]CI, confidence interval; eGFR, estimated GFR.
[b]Adjusted for age, gender, smoking, diabetes, hypertension, education, income, and occupation.

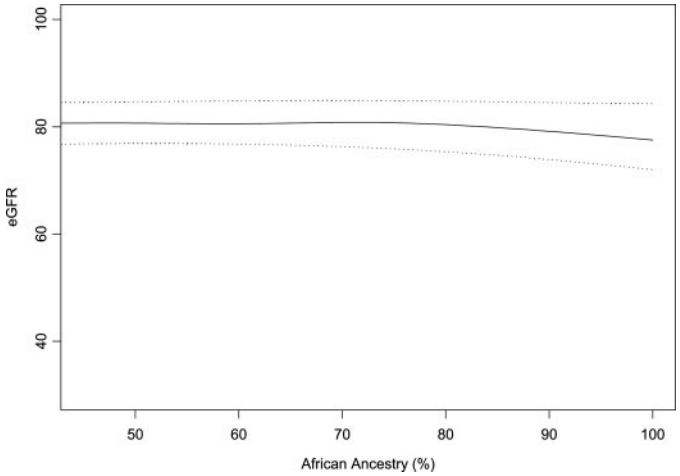

Figure 2. Association of genetic ancestry and renal function (by estimated GFR) in elderly African Americans. Cubic smoothing splines depict the association between genetic African Ancestry and kidney function with knots placed at the quartiles of African ancestry. Dotted lines represent 95% confidence intervals.

lower than those with higher incomes ($P = 0.017$), and this difference remained significant ($P = 0.02$) after adjustment for genetic ancestry. Low income was significantly associated with kidney dysfunction when using cystatin C >1.29 mg/L (or highest quartile) or eGFR <60 ml/min per 1.73 m^2, compared with those with highest incomes (>$35,000/yr; Table 3). Education and occupation were not significantly associated with kidney function in adjusted analyses ($P > 0.20$). In contrast, low income was not associated with kidney dysfunction among self-identified white individuals for cystatin C ≥1.29 mg/L (odds ratio 0.81; 95% confidence interval 0.56 to 1.17) and for eGFR <60 ml/min per 1.73 m^2 (odds ratio 0.78; 95% confidence interval 0.55 to 1.11).

We also evaluated the association of ancestry (as a continuous variable) with high cystatin C stratified by income category (as we previously defined) to test for interactions by income category among African Americans. There was no association between African ancestry and high cystatin C within any of the income categories in adjusted models ($P = 0.91$, 0.49, and 0.85, respectively).

Discussion

Our study found that genetic African ancestry was not associated with kidney function (by cystatin C or eGFR) or kidney disease progression (by changes in serum creatinine or eGFR) among elderly, self-identified African Americans using genetic admixture analysis. However, self-identified African American race was associated with kidney disease progression when compared with white individuals. Moreover, income was strongly associated with kidney function among African Americans. This suggests that the tremendous burden of kidney disease in African Americans may be more attributable to environmental factors than to their common genetic African ancestry.

Previous work has shown a greater burden of kidney disease in African Americans compared with white individuals (2,3). Our results are in accordance with previous data that suggest an association of self-identified African American race with faster progression of kidney disease (3,4), and these findings also were reported previously in the CHS Cohort (20). Many factors have been cited as potential explanations for these disparities, including sociodemographic factors, access to care, hypertension control, and genetics (3,21). In particular, the association between socioeconomic status (particularly income) and kidney disease has been described at the individual (22) and the area level (23). Because income but not African ancestry was associated with kidney dysfunction among African Americans, African Americans may be exposed and susceptible disproportionately to environmental, social, and health care access factors that affect the development and the progression of kidney disease (24).

The strength of our study is its novel method for addressing the association of genetic ancestry (rather than self-reported race) with kidney dysfunction and kidney disease progression.

Table 2. Association of African ancestry and self-reported race with kidney disease progression among elderly African Americans

Dichotomous Outcome	Δ Cr ≥0.05 mg/dl per yr (OR [95% CI])		Δ GFR ≥3 ml/min per 1.73 m^2 per yr (OR [95% CI])	
	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
Ancestry (per 10% increase)	0.94 (0.84 to 1.05)	0.94 (0.83 to 1.06)	1.02 (0.93 to 1.12)	1.02 (0.92 to 1.13)
Ancestry quartiles				
≤63	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
64 to 78	1.36 (0.73 to 2.53)	1.32 (0.637 to 2.60)	1.67 (0.99 to 2.82)	1.59 (0.92 to 2.76)
79 to 89	0.88 (0.44 to 1.76)	0.89 (0.42 to 1.89)	1.35 (0.78 to 2.34)	1.33 (0.74 to 2.39)
≥90	0.87 (0.42 to 1.18)	0.92 (0.42 to 2.02)	1.23 (0.70 to 2.19)	1.27 (0.69 to 2.34)
Race (self-reported)				
white ($n = 3997$)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
African American ($n = 598$)	2.05 (1.58 to 2.67)	1.77 (1.33 to 2.36)	3.78 (3.04 to 4.70)	3.21 (2.54 to 4.06)

[a]Adjusted for age, gender, smoking, diabetes, hypertension, education, occupation, and income.

Table 3. Association of income and African Ancestry with kidney dysfunction among elderly African Americans[a]

Dichotomous Outcome	Cystatin C ≥ 1.29 (OR [95% CI])	eGFR < 60 (OR [95% CI])
Model 1		
income		
≥$35,000 ($n$ = 250)	1.00 (reference)	1.00 (reference)
$8,000 to $34,999 ($n$ = 369)	1.74 (0.63 to 4.76)	3.16 (1.06 to 9.41)
<$8,000 ($n$ = 117)	3.37 (1.16 to 10.01)	3.07 (1.07 to 8.84)
Model 2		
African ancestry (per 10% increase)	0.96 (0.86 to 1.07)	1.00 (0.91 to 1.11)
Model 3		
income		
≥$35,000	1.00 (reference)	1.00 (reference)
$8,000 to $34,999	1.73 (0.64 to 4.68)	3.19 (1.10 to 9.24)
<$8,000	3.33 (1.16 to 9.54)	3.40 (1.12 to 10.32)
African ancestry (per 10% increase)	0.90 (0.80 to 1.01)	0.98 (0.88 to 1.09)

[a]All models adjusted for age, gender, smoking, diabetes, hypertension, education, and occupation.

In addition, we used two different measures of kidney function and thereby expanded the range of kidney function levels at which these associations could be tested. Although our study is negative, it does not rule out the possible genetic contribution to kidney disease. In fact, future analyses still may lead to admixture mapping of important loci (25). The higher burden of ESRD in African Americans still may be due, in part, to genetic reasons and environmental reasons or gene–environment interactions. Until these are elucidated, clinicians should continue to monitor for and treat early renal insufficiency aggressively according to accepted guidelines in this high-risk population. Future studies should be conducted in other populations that may lead to admixture mapping of important loci or elucidation of these possible gene–environment interactions.

Our study also has certain limitations. We used a relatively limited number of genetic markers, which may result in imprecise estimates for individual ancestry and may have biased our results toward the null (16,26). However, simulation studies indicate that even a limited number of highly informative markers (F_{ST} >0.5) may provide estimates of ancestry correlated to true ancestry (26). The African American population has approximately 80% African ancestry, and there are relatively few individuals with <50% African ancestry. Therefore, we are unable to test the full range of ancestry, which limits our capacity to detect nonlinear effects at the lower end of African ancestry. Other populations, such as certain Latino groups, may be useful to elucidate the effects of African ancestry across the lower ranges (27). Variation within the ancestral populations (*i.e.*, between African subgroups) cannot be captured by our method; therefore, information on African ancestry may be limited to informativeness from the ancestral populations genotyped. We did not include white individuals in our study, but previous analyses showed that non-Hispanic white individuals have <5% African ancestry (16,28); therefore, it is unlikely that there is sufficient African ancestry among Europeans to perform a similar analysis within that group (16). In addition, our study may have been biased by a survivor effect. That is, because our population is aged >65 yr, this cohort may not allow for the study of genetic differences in kidney function and progression in young African Americans, among whom disparities in kidney disease compared with white individuals are extreme. However, even among older individuals, African Americans also have a higher burden of kidney disease compared with white individuals (2). Further studies in younger cohorts and perhaps with larger numbers of makers may be required.

Conclusion

We found that genetic African ancestry may not be associated with kidney function or kidney disease progression but that low income was associated with kidney dysfunction in elderly African Americans. Although our study cannot completely rule out a genetic component to the disparities in kidney disease or progression to ESRD, our results suggest that nongenetic differences may play a more important role. In particular, the large burden of kidney disease in African Americans may be more attributable to differences in environmental and social factors.

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A full list of participating CHS investigators and institutions can be found at http://www.chs-nhlbi.org. M.S. and R.K. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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