

# Racial Differences in the Progression from Chronic Renal Insufficiency to End-Stage Renal Disease in the United States

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**Abstract.** Black Americans experience a disproportionate burden of ESRD compared with whites. Whether this is caused by the increased prevalence of chronic renal insufficiency (CRI) among blacks or by their increased progression from CRI to ESRD was investigated. A birth cohort analysis was performed using data from the Third National Health and Nutrition Examination Survey and the United States Renal Data System. It was assumed that those who developed ESRD in 1996 aged 25 to 79 yr came from the source population with CRI aged 20 to 74 yr that was sampled in the Third National Health and Nutrition Examination Survey (midpoint 1991). GFR was estimated using the Modification of Diet in Renal Disease study equation. The prevalence of CRI (GFR 15 to 59 ml/min per 1.73 m<sup>2</sup>) was not different among black compared with white

adults (2060 versus 2520 per 100,000;  $P = 0.14$ ). For each 100 blacks with CRI in 1991, five new cases of ESRD developed in 1996, whereas only one case of ESRD developed per 100 whites with CRI (risk ratio, 4.8; 95% confidence interval, 2.9 to 8.4). The increased risk for blacks compared with whites was only modestly affected by adjustment for age, gender, and diabetes. Blacks with CRI had higher systolic (147 versus 136 mmHg;  $P = 0.001$ ) and diastolic (82 versus 77 mmHg;  $P = 0.02$ ) BP and greater albuminuria (422 versus 158  $\mu$ g urine albumin/mg urine creatinine;  $P = 0.01$ ). The higher incidence of ESRD among blacks is not due to a greater prevalence of CRI among blacks. The key to understanding black–white differences in ESRD incidence lies in understanding the extreme differences in their progression from CRI to ESRD.

The prevalence of treated ESRD in the United States has more than doubled in the past decade. The population living with ESRD is projected to increase to 650,000 by the year 2010 with associated Medicare expenditures of \$28 billion (1).

It has long been known that black Americans experience a disproportionate burden of ESRD in the United States compared with whites (2,3), but the exact reasons for this remain unclear. Previous studies have shown that racial differences in age, the prevalence of diabetes and hypertension, socioeconomic status, and access to health care explain only part of the excess incidence of ESRD among blacks (4–9).

An important factor not addressed in previous studies is whether the population prevalence of chronic renal insufficiency (CRI) is higher among blacks. One hypothesis is that blacks on average have lower GFR than whites, perhaps as a result of their greater incidence of low birth weight, thereby leading to impaired renal development and fewer overall nephrons (10–12). Blacks may also have greater prevalence of CRI as a result of their increased prevalence of hypertension

and diabetes. If blacks have a substantially greater prevalence of CRI, then their increased incidence of ESRD compared with whites could occur even with a similar rate of renal disease progression. Alternatively, if the prevalence of CRI is similar in blacks and whites, then the high incidence of ESRD in blacks is presumably due to a faster rate of progression from CRI to ESRD.

We sought to test the above two hypotheses using a birth cohort analysis with data from the nationally representative National Health and Nutrition Examination Surveys (NHANES) and the United States Renal Data System (USRDS). This birth cohort analysis took advantage of the fact that both NHANES and USRDS are applicable to the entire United States population. We compared the proportion of blacks and whites in the “at-risk” population with CRI from NHANES with the incidence of ESRD cases in subsequent years.

## Materials and Methods

### Study Population: NHANES and USRDS

These analyses linked data on the prevalence of CRI from the nationally representative NHANES surveys with incident ESRD cases captured in USRDS. NHANES III was conducted by the National Center for Health Statistics to provide data on the health and nutritional status of the noninstitutionalized U.S. population from 1988 to 1994 (13). Before that, a smaller NHANES II was conducted from 1976 to 1980 (14). The USRDS is a comprehensive national registry of ESRD incidence and treatment in the United States (15).

We included only adults who were classified as being black or white in NHANES and USRDS. The prevalence of diabetes among

Received May 12, 2003. Accepted July 27, 2003.

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1046-6673/1411-2902

Journal of the American Society of Nephrology

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DOI: 10.1097/01.ASN.0000091586.46532.B4

NHANES examinees was defined by patient report of physician diagnosis (16) and among new ESRD patients from the USRDS Medical Evidence Form completed by nephrologists (15).

### Definition of CRI

CRI was defined as GFR 15 to 59 ml/min per 1.73 m<sup>2</sup>, corresponding to stages 3 and 4 of the recently proposed National Kidney Foundation Chronic Kidney Disease classification (17). GFR was estimated using the Modification of Diet in Renal Disease (MDRD) study equation, which has been separately validated among blacks (17–19):  $\text{GFR (ml/min per 1.73 m}^2\text{)} = 186 \times [\text{serum creatinine (mg/dl)}]^{-1.154} \times [\text{age}]^{-0.203} \times [0.742 \text{ if female}] \times [1.212 \text{ if black}]$

Previous studies found that the creatinine assay used in the NHANES III survey was systematically different from that used to derive the MDRD equation (20,21). We therefore adjusted the NHANES creatinine values in all subjects by subtracting the recommended 0.23 mg/dl (20). We did not find any calibration differences between NHANES II and III creatinine values. Specifically, the mean and median serum creatinine levels for whites aged 20 to 39 yr without diabetes or hypertension in both NHANES II and NHANES III were 1.1 mg/dl in men and 0.9 mg/dl in women.

In alternative analyses, CRI was defined using the Cockcroft-Gault equation (22) estimated creatinine clearance 15 to 59 ml/min normalized to 1.73 m<sup>2</sup> body surface area (23). We also confirmed our estimation of the prevalence of CRI among blacks using the recently published African-American Study of Hypertension and Kidney Disease (AASK) equation (19).

### Ascertainment of New ESRD Cases

Our birth cohort analysis assumed that adults who were aged 25 to 79 yr and developed ESRD in 1996 came from the source population with CRI aged 20 to 74 yr in the United States sampled in NHANES III (midpoint 1991). We also examined the number of new ESRD cases among black and white adults who were aged 23 to 77 yr in 1994, aged 24 to 78 yr in 1995, aged 26 to 80 yr in 1997, aged 27 to 81 yr in 1998, and aged 28 to 82 yr in 1999. In sum, these represented the new cases of ESRD from the same birth cohort spanning years 3 to 8 after the midpoint of NHANES III.

### Risk Factors for Progression from CRI to ESRD

We compared risk factor profiles among black and white individuals with CRI using data from NHANES III. BP was defined as the mean of six sitting readings (24), angiotensin-converting enzyme inhibitor use by self-report (25), proteinuria by random urine albumin ( $\mu\text{g}$ )/creatinine (mg) ratio, and glycemic control among those with diabetes by glycosylated hemoglobin levels (13).

### Statistical Analyses

The complex survey sampling design was taken into account in estimating confidence intervals (CI) and *P* values for weighted population totals and proportions using the *svy*means and *svy*tab functions in STATA Version 7 (Stata Corp, College Station, TX).

NHANES sampling weights were inflated so that the sums of the weights for respondents with nonmissing creatinine values within subgroups defined by NHANES stratum, age, gender, and race was equal to the sum for all respondents in the subgroup. This reweighting procedure provides approximately unbiased estimates of population parameters under the assumption that creatinine values were missing at random within each subgroup (25,26).

Incidence of ESRD within subgroups of interest was estimated by the ratio of new ESRD cases reported in the USRDS, divided by the

number of CRI cases in the population estimated from NHANES. CI for ratios of these proportions in blacks and whites were estimated using Poisson models for the number of ESRD cases. A Bonferroni procedure was used to account for uncertainty in the estimated number of people at risk in each category (27). We adjusted for individual-level demographic and clinical variables that were defined in both NHANES and USRDS. Three bivariate Poisson models were used to adjust the estimated black/white ratio for age, gender, and diabetes, again with Bonferroni confidence intervals taking account of uncertainty in the size of the subgroups at risk. Further multivariate adjustment was not possible because of the small number of NHANES examinees in subgroups defined by all three covariates as well as race.

### Results

In 1991 (midpoint of NHANES III), the prevalence of CRI was not significantly different among blacks compared with whites (2060 *versus* 2520 per 100,000; *P* = 0.14; Table 1). We obtained a similar estimate of the prevalence of CRI among blacks when we used the AASK equation instead of the MDRD (1970 per 100,000). The mean age and GFR among whites with CRI was 62 yr and 50 ml/min per 1.73 m<sup>2</sup> compared with 61 yr and 47 ml/min per 1.73 m<sup>2</sup> among blacks. The prevalence of CRI did not differ substantially by gender but was much higher among the elderly and those with diabetes (Table 1).

For each 100 black and white people with CRI in the United States in 1991, we found there to be five incident cases of ESRD in 1996 in blacks but only one case in whites. Specifically, in 1991, there were 394,000 blacks and 3,500,000 whites aged 20 to 74 with CRI (Table 1). By 1996, this birth cohort, now aged 25 to 79, produced 21,307 and 39,016 new cases of ESRD among blacks and whites. The unadjusted risk ratio (RR) for new ESRD cases from the source population with CRI was therefore  $([21,307/394,000]/[39,016/3,500,000]) = (0.054/0.011) = 4.8$  (95% CI, 2.9 to 8.4) for blacks compared with whites (Table 1, Figure 1).

The increased risk for blacks was seen in all analyses stratified by age, gender, or diabetes (*P* > 0.05 for all interactions; Figure 1). The increased risk also persisted after adjusting individually for age (RR, 4.6; 95% CI, 2.3 to 10.1), gender (RR, 4.9; 95% CI, 2.5 to 10.5), and diabetes (RR, 3.9; 95% CI, 1.8 to 9.6).

Similar temporal trends were observed when we varied the time period between ascertainment of CRI prevalence and incident ESRD cases from 1994 to 1999 (Figure 2). We also found similar increased risk for blacks compared with whites when we repeated the analysis using NHANES II (midpoint 1978) as the source population for ESRD cases in 1983 (RR, 5.9; 95% CI, 2.7 to 19.4). Using the Cockcroft-Gault equation, a relatively greater proportion of blacks were defined as having CRI in 1991, but the progression rate from CRI to ESRD in blacks remained substantially elevated compared with whites (RR, 2.6; 95% CI, 1.6 to 4.1).

Comparing characteristics of blacks and whites with CRI in NHANES III, we found that blacks had substantially higher systolic (147 *versus* 136 mmHg; *P* = 0.001) and diastolic (82 *versus* 77 mmHg; *P* = 0.02) BP compared with whites. Blacks also had greater levels of albuminuria (422 *versus* 158  $\mu\text{g}$  urine albumin/mg urine creatinine; *P* = 0.01). There were no statis-

Table 1. Estimated prevalence of CRI in 1991 (from NHANES III) and number of new ESRD cases in 1996 (from USRDS) in birth cohort<sup>a</sup>

	Total population 1991 (aged 20–74)	CRI cases 1991 (aged 20–74)	CRI prevalence 1991 (per 100,000 population) (aged 20–74)	Incident ESRD 1996 (aged 25–79)	New ESRD cases (1996) per CRI prevalence (1991)
Overall					
blacks	19,140,000 ( <i>n</i> = 4112)	394,000 ( <i>n</i> = 110)	2060	21,307	0.054
whites	138,900,000 ( <i>n</i> = 9238)	3,500,000 ( <i>n</i> = 287)	2520	39,016	0.011
Age 20–60					
blacks	16,860,000 ( <i>n</i> = 3439)	150,000 ( <i>n</i> = 37)	880	14,593	0.099
whites	115,500,000 ( <i>n</i> = 6954)	1,200,000 ( <i>n</i> = 60)	1000	20,323	0.017
Age 61–74					
blacks	2,290,000 ( <i>n</i> = 673)	250,000 ( <i>n</i> = 73)	11,000	6714	0.027
whites	23,370,000 ( <i>n</i> = 2284)	2,330,000 ( <i>n</i> = 227)	9990	18,693	0.008
Men (aged 20–74)					
blacks	8,505,000 ( <i>n</i> = 1834)	150,000 ( <i>n</i> = 49)	1800	10,555	0.069
whites	67,720,000 ( <i>n</i> = 4411)	1,500,000 ( <i>n</i> = 135)	2210	22,001	0.015
Women (aged 20–74)					
blacks	10,640,000 ( <i>n</i> = 2278)	240,000 ( <i>n</i> = 61)	2300	10,752	0.044
whites	71,200,000 ( <i>n</i> = 4827)	2,000,000 ( <i>n</i> = 152)	2810	17,015	0.008
Diabetic (aged 20–74)					
blacks	1,220,000 ( <i>n</i> = 301)	110,000 ( <i>n</i> = 33)	9400	10,727	0.093
whites	5,870,000 ( <i>n</i> = 639)	610,000 ( <i>n</i> = 79)	10,000	20,349	0.034
Nondiabetic (aged 20–74)					
blacks	17,920,000 ( <i>n</i> = 3811)	280,000 ( <i>n</i> = 77)	1600	10,580	0.038
whites	133,000,000 ( <i>n</i> = 8599)	2,890,000 ( <i>n</i> = 208)	2170	18,668	0.006

<sup>a</sup> CRI, chronic renal insufficiency; NHANES III, Third National Health and Nutrition Examination Survey; USRDS, United States Renal Data System. CRI defined as Modification of Diet in Renal Disease formula estimated GFR 15–59 ml/min per 1.73 m<sup>2</sup>. *n* = number of NHANES III examinees sampled.

tically significant racial differences in the use of angiotensin-converting enzyme inhibitors (24% versus 18%; *P* = 0.19) or the level of glycemic control among the black and white CRI subjects who also had diabetes (glycated hemoglobin, 8.5% versus 8.2%; *P* = 0.46).

## Discussion

Black Americans experience a disproportionate burden of ESRD in the United States compared with whites. A better understanding of the origins of this epidemic would have important implications regarding screening and preventive

strategies. Previous studies have concluded that higher prevalence of diabetes and hypertension among blacks in the general community is not sufficient to explain this increased risk (4–7). Previous ecological studies (6,7) or nonconcurrent cohort studies (8,9) did not address potential differences in the prevalence of CRI among blacks and whites before development of ESRD.

We found no support for the hypothesis that the population prevalence of CRI was greater among blacks compared with whites. Rather, our analysis led us to conclude that blacks with CRI presumably progressed to ESRD at five times the rate of

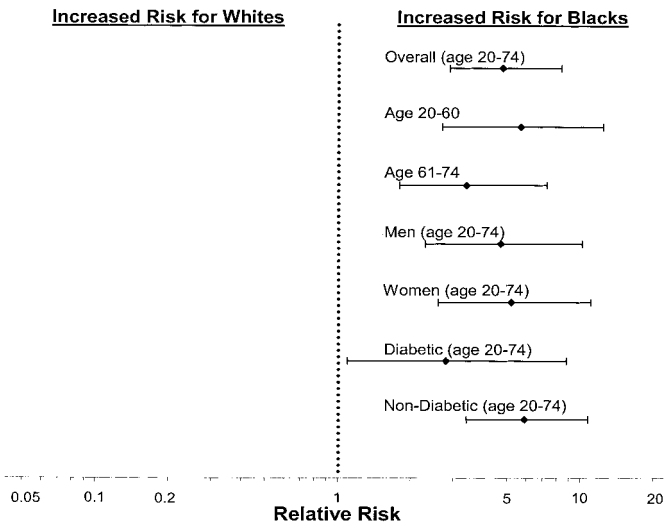


Figure 1. Black versus white relative risks for progression from chronic renal insufficiency (CRI) to ESRD cases, overall and by subgroup.

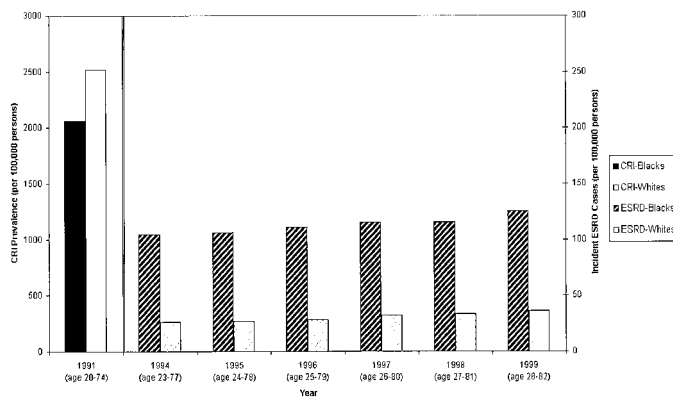


Figure 2. U.S. prevalence of CRI in 1991 and subsequent incident cases of ESRD. \*CRI prevalence defined as proportion of people with CRI in 1991 from Third National Health and Nutrition Examination Surveys projected to overall population in 1991. Incident cases of ESRD defined as new cases from United States Renal Data System in a particular year for birth cohort divided by overall population in 1991.

whites with CRI. The increased progression of blacks relative to whites seemed not to have changed over the past 25 yr since NHANES II was conducted, although ESRD incidence has risen steadily in both groups.

Previous studies, using serum creatinine alone to categorize renal function, found that more blacks than whites had elevated serum creatinine levels in the United States (25,28,29). However, blacks on average have higher creatinine production than whites, perhaps reflecting physiologic differences in muscle mass and metabolism (19,21,30); there may also be racial differences in tubular handling of creatinine (21). Therefore, at any given serum creatinine level, blacks on average have higher GFR levels than whites. This differential association of creatinine with GFR in blacks and whites is reflected in the

multiplicative 1.212 term in the MDRD equation. Older estimating equations such as the Cockcroft-Gault systematically underestimate renal function among blacks (19). Our results were confirmed using the AASK equation, which was explicitly derived from a large cohort of blacks who underwent gold-standard iothalamate clearance-measured GFR (19).

We believe that the adverse risk factor profile of blacks contributes to their increased risk of progression compared with whites. Two key determinants of renal disease progression—BP and proteinuria control—were substantially worse in blacks. However, it seems unlikely that the magnitude of these differences could explain the almost fivefold increased risk that we observed. It is moreover debatable whether proteinuria is truly causal or merely an adverse prognostic sign. Other researchers have also concluded that differences in conventional clinical, sociodemographic, or lifestyle factors, although important, are insufficient to account satisfactorily for the excess risk of ESRD among blacks (4–9).

This article indicates that the key to understanding black-white differences in ESRD incidence lies in understanding their differences in progression from CRI to ESRD, rather than differences in CRI prevalence. Studies that will compare renal disease progression in a multiethnic cohort of subjects with established CRI, such as the Chronic Renal Insufficiency Cohort sponsored by the National Institutes of Health, should improve our understanding of this subject. Our findings suggest that any genetic difference between blacks and whites would relate more to differential susceptibility to “promoters” rather than “initiators” of renal disease (31). To date, polymorphisms in two genes—the plasma kallikrein gene and the human homologue of the rodent renal failure 1 gene—have demonstrated linkage or association with ESRD in the American black population (32).

Another implication of this study pertains to the recently proposed National Kidney Foundation Chronic Kidney Disease classification—in which subjects with GFR 30 to 59 ml/min per 1.73 m<sup>2</sup> are categorized as stage 3 and those with GFR 15 to 29 ml/min per 1.73m<sup>2</sup> are categorized as stage 4 chronic kidney disease (17). The National Kidney Foundation classification does not account for the fact that subjects within a given stage of chronic kidney disease may be at different risk for adverse events and progression to ESRD. Our study clearly demonstrates that the implications of experiencing stages 3 to 4 chronic kidney disease are very different for blacks and whites. Perhaps a refinement of the classification system would be warranted to integrate the likelihood of progression, based on characteristics such as age, race, and the extent of proteinuria. Risk stratification within chronic kidney disease stages is important to obtain a realistic picture of the public health burden of CRI and to prioritize interventions for patients with CRI.

Among the limitations of this study, renal function among NHANES enrollees was estimated, not directly measured; however, measurement of GFR remains impractical in large-scale epidemiologic studies. The MDRD and AASK equations were derived and validated in trial participants, and their generalizability to the general population has not been completely

validated. It is possible that some people progressed very rapidly and developed ESRD without being observed in the “at risk” 15 to 59 ml/min per 1.73 m<sup>2</sup> GFR range, but their number was likely to be small. Diabetes was ascertained among NHANES participants only by self-report. Our Poisson models were able to adjust only for individual patient-level characteristics that were defined in both NHANES and USRDS. Further stratified analyses were limited by sample size. For the same reason, analysis by geographic region was not undertaken. Although NHANES is a nationally representative survey and survey weights were designed to adjust for noncoverage and nonresponse, residual selection bias is still possible. This is a birth cohort/ecological study, and individuals identified in NHANES III were not actually observed to enter the USRDS registry. Finally, because longitudinal individual-level data on renal function were not available, our conclusions regarding racial differences in progression rates from CRI to ESRD are deduced, not directly observed. They are, however, consistent with previous clinical trial data showing that blacks with CRI have a steeper decline in measured GFR than whites (33). Our results cannot be accounted for by racial differences in mean GFR at initiation of dialysis (on the order of 0.2 ml/min per 1.73 m<sup>2</sup>) (34). Biases from misclassification of race between the data sources or from missing creatinine data (overall only 7% in NHANES III) or errors in estimation of GFR are also unlikely to have produced the large robust relative risk that we observed (4.8; 95% CI, 2.9 to 8.4).

In summary, the severalfold higher rate of new ESRD cases among blacks compared with whites in the United States is not due to greater prevalence of CRI among blacks in the general population. A better understanding of the excess incidence of ESRD in blacks will require additional investigation into their rapid progression from CRI to ESRD.

## Acknowledgments

This study was supported by the National Institutes of Health DK61520 (to C.-y.H.) and HL68099 (to M.G.S.). M.G.S. is also funded by a Research Career Development Award from the Health Services Research and Development Service of the Veterans Affairs Administration.

We thank Dr. Warren Browner, Dr. Glenn Chertow, Dr. Steve Cummings, Dr. Charles McCulloch, Love Julian and Michelle Odden for assistance.

Some of the data reported here were supplied by the United States Renal Data System. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the United States government.

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