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White/Black Racial Differences in Risk of End-Stage Renal Disease and Death

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Abstract

Background—End-stage renal disease disproportionately affects black persons, but it is unknown when in the course of chronic kidney disease racial differences arise. Understanding the natural history of racial differences in kidney disease may help guide efforts to reduce disparities.

Methods—We compared white/black differences in the risk of end-stage renal disease and death by level of estimated glomerular filtration rate (eGFR) at baseline in a national sample of 2,015,891 veterans between 2001 to 2005.

Results—Rates of end-stage renal disease among black patients exceeded those among white patients at all levels of baseline eGFR. The adjusted hazard ratios (HR) for end-stage renal disease associated with black versus white race for patients with an eGFR ≥90, 60-89, 45-59, 30-44, 15-29, and <15 mL/min/1.73m^2, respectively were 2.14 (95% confidence interval [CI], 1.72-2.65), 2.30 (95% CI, 2.02-2.61), 3.08 (95% CI, 2.74-3.46), 2.47 (95% CI, 2.26-2.70), 1.86 (95% CI, 1.75-1.98), and 1.23 (95% CI, 1.12- 1.34). We observed a similar pattern for mortality, with equal or higher rates of death among black persons at all levels of eGFR. The highest risk of mortality associated with black race was also observed among those with an eGFR 45-59 mL/min/1.73m^2 (HR 1.32, 95% CI, 1.27-1.36).

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Conclusion—Racial differences in the risk of end-stage renal disease appear early in the course of kidney disease and are not explained by a survival advantage among blacks. Efforts to identify and slow progression of chronic kidney disease at earlier stages may be needed to reduce racial disparities.

Keywords

kidney disease; racial disparities; mortality

Introduction

Chronic kidney disease is now recognized as a major public health concern.[1, 2] It is estimated that approximately 26.3 million adults in the US have non-dialysis dependent kidney disease and over 470,000 have end-stage renal disease, collectively representing over 13% of the US population.[3-5] In the next 20 years, the burden of chronic kidney disease is expected to increase, with over 2 million individuals projected to be receiving renal replacement therapy (dialysis or kidney transplant) by 2030.[2] In the US, black individuals shoulder a disproportionate burden of end-stage renal disease, comprising 32% of the end-stage renal disease population, but only 13% of the general population.[5, 6] The increased risk for end-stage renal disease among blacks has been established by a large number of studies, [7-9] and the goal to eliminate this racial disparity has now found a place in the national health care agenda.[10, 11]

To date, research in this area has focused on the optimal delivery of care and treatment of complications associated with later stages of chronic kidney disease, such as dialysis and kidney transplantation, where race disparities have been well-documented.[12-14] However, there is limited information on the presence and extent of racial differences in risk of adverse events at earlier stages of chronic kidney disease, where there may be the greatest potential to prevent or slow progression. The primary objective of this study was to compare white/black differences in end-stage renal disease and death through the course of kidney disease and to identify at what level of kidney function that racial disparities are greatest.

Method

Study Sample

The Department of Veterans Affairs (VA) health care system is the largest integrated health maintenance organization in the US.[15] Geographically, the VA health care system is national in scope and offers comprehensive clinical services to US veterans. To be eligible for the study, we included all veterans of white or black race with one or more outpatient serum creatinine level recorded at a VA facility between October 2000 and September 2001. Patients entered the study at the time of their first creatinine measurement during this enrollment period. We excluded subjects who had already reached end-stage renal disease at the time of study entry, defined as receipt of chronic dialysis or kidney transplant.

Data Sources

We assembled the study cohort with multiple VA and non-VA data sources using previously described methods.[16, 17] Briefly, creatinine measurements associated with outpatient visits were obtained from the VA Decision Support System Laboratory Results file.[18] We used the VA National Patient Care Database, VA Fee Basis files, Medicare Denominator File, Immunology Case Registry, and inpatient and outpatient Medicare claims to ascertain demographic and comorbidity information.[18, 19] We determined the date of death for cohort members using a validated VA death registry, the Beneficiary Identification and Records Locator Subsystem.[20-22] Area-level socioeconomic data were obtained by matching an individual's residential zip code at the time of cohort entry to year 2000 United States Census

zip code tabulation areas.[6] Patients treated with chronic dialysis or kidney transplant during follow-up were identified by linking our cohort to the United States Renal Data System (USRDS), a comprehensive national end-stage renal disease registry.[23]

Patient Characteristics

The primary predictor variable for all analyses was white/black race. We preferentially designated race using the Medicare Denominator File based on its superior reliability to VA sources.[24, 25] When Medicare race data were not available, we used race reported in VA data sources. Since the establishment of federal race reporting guidelines on October 1, 2002, the VA has achieved 95% agreement between observer reported data and self-reported race.[24]

We estimated glomerular filtration rate (eGFR) using the abbreviated Modification of Diet in Renal Disease (MDRD) formula based on age, sex, race, and serum creatinine level at the time of cohort entry.[3] Patients were classified according to National Kidney Foundation guidelines by baseline eGFR level as follows: normal or increased (eGFR $\geq$90 ml/min/1.73m^2), mildly decreased (eGFR 60-89 ml/min/1.73m^2), moderately decreased (eGFR 45-59 and 30-44 ml/min/1.73m^2), severely decreased (eGFR 15-29 ml/min/1.73m^2) and kidney failure (eGFR <15 ml/min/1.73m^2, not on dialysis). We identified co-existing illnesses using previously described methods, based on hospitalization discharge diagnoses, outpatient encounters, and procedure codes in VA and Medicare data sources between January 1999 and the time of cohort entry.[16, 17, 26] We identified the following diagnosed conditions: coronary heart disease, heart failure, peripheral arterial disease, chronic obstructive lung disease, cerebrovascular disease, hypertension, diabetes mellitus, dementia, atrial fibrillation, hepatitis C virus (HCV) infection and human immunodeficiency virus (HIV) infection. Reliable information on individual-level socioeconomic status was not available in our data sources; we therefore assigned patients to categories of low, middle, or high socioeconomic status based on multiple residential zip code-level socioeconomic characteristics derived from the US Census using previously described techniques.[6, 17, 27]

Outcomes

The primary outcomes were time from cohort entry to onset of end-stage renal disease (defined as initiation of chronic dialysis or kidney transplantation) and time from cohort entry to death, respectively. The observation period for end-stage renal disease extended through 2004, based on the availability of USRDS data, and through 2005 for death. Patients were censored at the time of death for the outcome of time to end-stage renal disease.

The decision to initiate renal replacement therapy may not be dictated by uniform clinical criteria in practice. In order to support our assumption that rates of end-stage renal disease represent progression of disease, as a secondary outcome, we also calculated mean annual rates of change in eGFR based on serial creatinine measurements available during follow-up among those with moderate to severe kidney disease at baseline (eGFR 15-60 ml/min/1.73m^2).

Statistical Analyses

We compared baseline characteristics between patients of white and black race using the t-test for continuous variables and the chi square test for categorical variables. Incidence rates for death and end-stage renal disease were obtained using a parametric survival-time model fitted to the exponential distribution and standardized to the median age of the overall cohort. We used Cox proportional hazard analysis to examine the association of white/black race with time to death and end-stage renal disease, respectively. Estimates were adjusted for age, sex, baseline comorbidities, and socioeconomic status. All analyses were stratified by level of eGFR at baseline. In order to account for potential differences in the delivery of health care and population served by each facility, estimates were adjusted for a fixed effect for VA center.

We estimated the rate of change in eGFR (ml/min/1.73m^2 per year) using a mixed effects linear regression model which accounted for variations in the number and spacing of creatinine measurements and length of follow-up for each subject. For this analysis, we excluded patients who had already reached renal failure at the time of cohort entry (eGFR <15 mL/min/1.73m^2) and individuals with an eGFR ≥60 mL/min/1.73m^2, in whom estimates may be less precise. To avoid analyzing creatinine measurements which may not reflect chronic rates of progression, we excluded creatinine measurements that occurred 90 days before onset of end-stage renal disease or death.

All regression models were validated when checked by bootstrap methods or by comparing robust standard errors. For Cox models, the proportional hazards assumption was checked using the Schoenfeld test and by graphically comparing stratified log minus log(survivor function) versus time curves. Assumptions of the mixed effects model were tested and satisfied.

As a supplemental analysis, we analyzed end-stage renal disease and mortality among the subgroup of 86,649 women in the cohort. Analyses were conducted using Stata version 9.2 (Stata Corp, College Station, Tx). This study was approved by the Committee on Human Research at the San Francisco VA Medical Center.

Results

We identified 2,352,584 veterans aged 18-100 years with at least one outpatient serum creatinine measurement. There were 11,125 (0.5%) end-stage renal disease patients and 325,568 (13.9%) patients with non-white/black or unknown race who were excluded, leaving 2,015,891 patients for analysis. This group consisted of 1,704,101 (84.5%) white and 311,790 (15.5%) black patients (Table 1). Black individuals in our cohort were younger and included a greater proportion of women. White individuals had a higher prevalence of cardiovascular and lung disease, but a lower prevalence of diabetes, hypertension, HCV and HIV. A higher percentage of black (55.6%) compared with white (29.9%) patients were in the lowest tertile of socioeconomic status.

The distribution of eGFR at baseline differed substantially between black and white individuals. The prevalence of an eGFR <60 mL/min/1.73m^2 was much higher among white (22.2%) than black patients (13.3%). However, this primarily reflected a difference in the prevalence of moderate kidney disease (eGFR 30-59 mL/min/1.73m^2), which was present in 20.7% of white but in only 11.5% of black persons. In contrast, the prevalence of severe kidney disease (eGFR 15-29 mL/min/1.73m^2) was equal among white and black individuals (1.4%), while renal failure (eGFR <15 mL/min/1.73m^2) was slightly more common in black (0.4%) compared with white patients (0.2%).

The median observation time was 3.7 (inter-quartile range [IQR] 3.4-4.0) years for end-stage renal disease and 4.8 (IQR 4.5-5.0) years for mortality. Death was far more common than incident end-stage renal disease: 14.3% (n=287,827) of patients died during 8,986,646 total person-years of observation, while only 0.8% (n=15,148) reached end-stage renal disease over 7,072,237 person-years. There were 4,379 cases of end-stage renal disease and 41,715 deaths among black members of the cohort and 10,769 cases of end-stage renal disease and 246,112 deaths among white individuals.

End-stage renal disease

The age-standardized incidence of end-stage renal disease per 1,000 person-years was consistently higher among black compared to white individuals at all levels of baseline eGFR (Table 2). In multivariate Cox proportional hazard analysis (Figure 1), the risk of end-stage renal disease was higher for black compared with white patients in all eGFR categories.

However, the strength of this association varied by level of baseline eGFR and was of greatest magnitude for those with an eGFR 45-59 mL/min/1.73m^2 and attenuated at eGFR levels above and below. While black patients with an eGFR 45-59 mL/min/1.73m^2 had a greater than 3-fold increased risk of end-stage renal disease compared to their white counterparts, the excess risk was only 23% (95% CI, 12-34%) in the eGFR <15 mL/min/1.73m^2 category.

Death

Death rates were higher among black compared with white cohort members at all eGFR levels between 15 and 90 mL/min/1.73m^2 (Figure 2). In adjusted analyses, the association of black race with mortality was strongest among patients with an eGFR 45-59 mL/min/1.73m^2 (HR 1.32, 95% CI, 1.27-1.36) and was progressively attenuated at lower levels of eGFR (Figure 3). The adjusted risk of mortality associated with black race was two-fold greater among those with an eGFR 45-59 mL/min/1.73m^2 (HR 1.32, 95% CI, 1.27-1.36) compared to those with an eGFR ≥60 mL/min/1.73m^2 (HR 1.15, 95% CI, 1.11-1.18).

Mean annual change in eGFR

For the outcome of mean annual change in eGFR, we included 420,334 patients with a baseline eGFR 15-60 mL/min/1.73m^2 and analyzed 2,866,397 and 376,066 creatinine measurements among white and black individuals, respectively. Rates of estimated GFR decline were greater among black versus white patients for all eGFR categories studied. The mean annual change in eGFR (mL/min/1.73m^2 per year) was -0.4 (95% CI, -0.4, -0.4), -0.4 (95% CI, -0.4, -0.3), and -0.5 (95% CI, -0.6, -0.4) for white patients and -0.5 (95% CI, -0.5, -0.4), -0.9 (95% CI, -1.0, -0.8), and -1.6 (95% CI, -1.9, -1.4) for black patients with a baseline eGFR 45-59, 30-44, and 15-29 mL/min/1.73m^2.

Among the 86,649 women in this cohort, there were 4,485 deaths in 405,852 person-years, and 247 end-stage renal disease events in 316,358 person-years of observation. Rates of end-stage renal disease were greater among black versus white women for all categories of eGFR, but absolute rates were lower than among men. There was also a similar relationship between race, mortality and eGFR with comparable rates of death among black and white women in the eGFR >90 mL/min/1.73m^2 category, but higher rates of death below this range. Fully adjusted models were consistent with these results and revealed that the association of race with time to end-stage renal disease and death reported for the primary analysis did not differ materially among women compared to men.

Discussion

In this large national cohort of patients receiving care in the Veterans Health Administration, black individuals were at higher risk for end-stage renal disease at all levels of kidney function when compared to whites, with the most pronounced differences observed in those with normal to moderately decreased eGFR. Differences in the risk of end-stage renal disease between blacks and whites were not explained by a lower competing risk of mortality. Instead, the risk of mortality associated with black race was increased in the setting of renal dysfunction, with the greatest relative increase in risk found among those with mild to moderate reductions of eGFR (30-89 mL/min/1.73m^2). These findings demonstrate the presence of marked racial differences in end-stage renal disease and death early in the course of kidney disease and provide support for disparities research focused on prevention, targeted screening, and timely provision of therapies for chronic kidney disease among blacks.

Our findings highlight the importance of ongoing efforts in the renal community to improve awareness and recognition of chronic kidney disease.[1, 3, 28] Current guidelines classify kidney disease primarily based on level of kidney function, to identify earlier stages of kidney disease

and its antecedent risk factors, with the hope that adverse events can be prevented or delayed through targeted screening and early detection.[1, 3] The classification of kidney disease by level of eGFR may also provide a platform for identifying groups vulnerable to poor renal outcomes. Our results demonstrate pronounced white/black differences in the risk of end-stage renal disease and death with mild reductions of eGFR, suggesting that these disparities will persist without interventions aimed at earlier stages of kidney disease.

It is noteworthy that the higher incidence of end-stage renal disease among members of this cohort did not reflect a survival advantage among blacks with chronic kidney disease, as some have postulated.[29-31] Consistent with a prior pooled analysis of four different cohorts and a recent analysis of data from the third National Health And Nutrition Examination Survey, we found that mortality rates were higher, not lower, in blacks with kidney disease.[32, 33] Thus, it is likely that observed racial differences in the risk of end-stage renal disease underestimate true differences in rates of progression. Furthermore, the finding that the relative hazard of death and end-stage renal disease for blacks were both highest in patients with moderate reductions in eGFR (30-59 mL/min/1.73m^2) suggests that the paradoxically lower prevalence of moderate kidney disease may be attributed to a relatively rapid exodus (due to death or progression) from this stage among blacks.[31, 32, 34]

While racial differences in risk of end-stage renal disease are widely recognized, explanatory mechanisms are poorly understood.[7, 35, 36] Prior studies have found that black patients are more likely to have inadequately controlled diabetes, hypertension, and proteinuria than their white counterparts, despite a similar intensity of treatment, and are less likely to achieve quality of care goals.[37-39] We observed significant differeces in the risk of end-stage renal disease despite uniform access to health care and extensive adjustment for sociodemographic variables and comorbid conditions. However, we did not adjust for blood pressure and proteinuria because these measures were not available for most patients. Thus, it is possible that the association of black race with end-stage renal disease and death observed here may be partly explained by racial differences in these characteristics which are known targets for intervention.

There are several other limitations to our study. Data were obtained during the course of regular outpatient clinical care; therefore, estimates of kidney function were not available for the entire source population. Although our results are consistent with other population based estimates of kidney disease, differences may exist in populations which include healthier patients who are not in clinical care.[4, 34, 40] Findings may also not be generalizable to non-veterans, uninsured patients, women, or patients of other race/ethnicity groups. Finally, as mentioned above, we were unable to measure the contribution of several key predictors of progression including signs of kidney damage (such as proteinuria or hematuria), and blood pressure measurements, or individual-level socioeconomic factors because these were not available in our data sources.

Conclusions

Black patients have a higher risk of end-stage renal disease regardless of their baseline level of kidney function, that is most pronounced among those with moderate kidney disease. Similarly, racial differences in mortality arise and peak in the setting of mild to moderate reductions in eGFR. These findings support the substantial public health importance of efforts to prevent and slow progression of early kidney disease in blacks.

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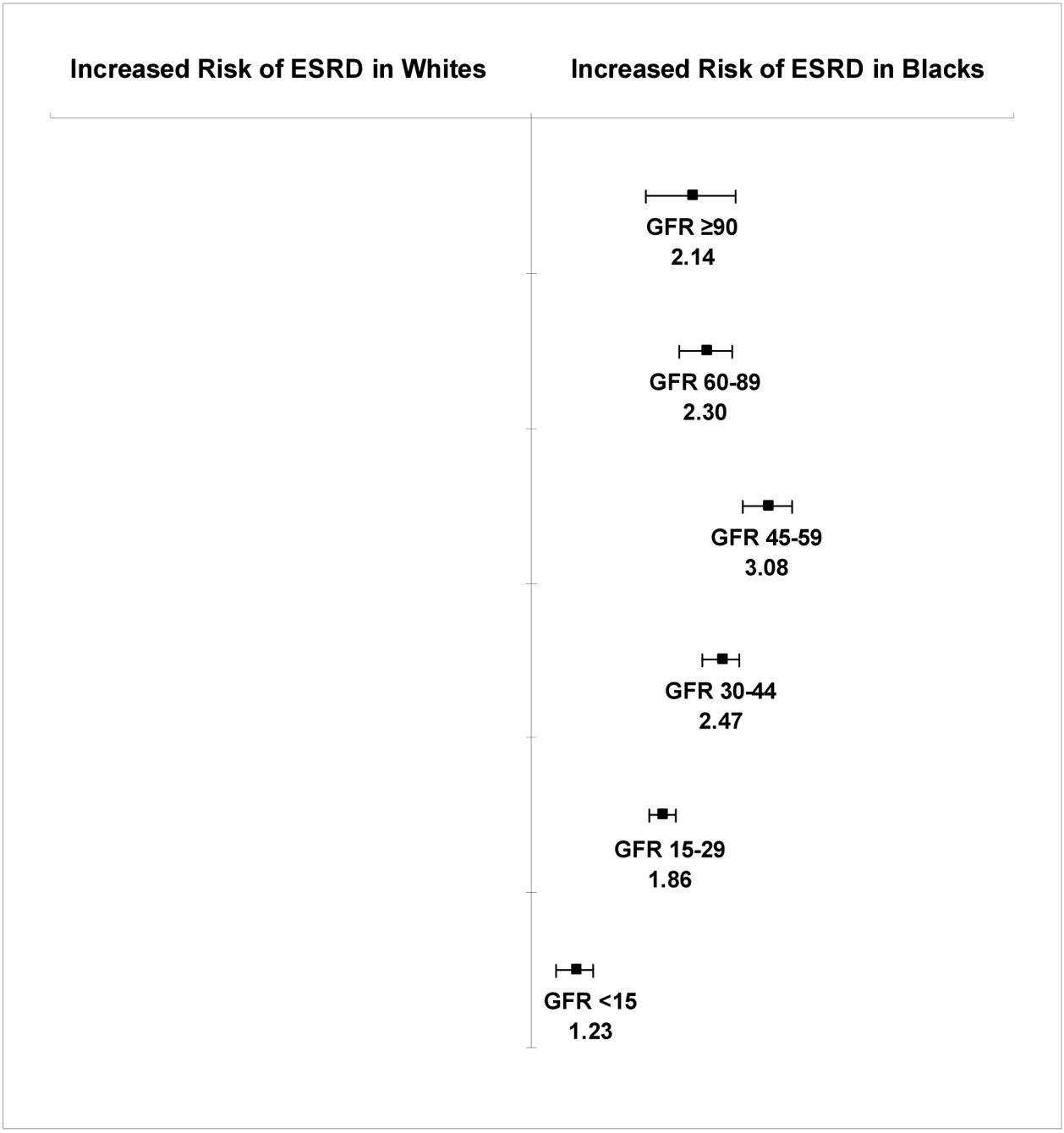

Figure 1. Adjusted hazard ratios (HR) for end-stage renal disease (ESRD) in black versus white patients stratified by level of estimated glomerular filtration rate (GFR) at baseline

Models adjusted for all variables listed in Table 1. Estimated GFR reported in mL/min/ $1.73m^2$. Error bars indicate 95% confidence intervals.

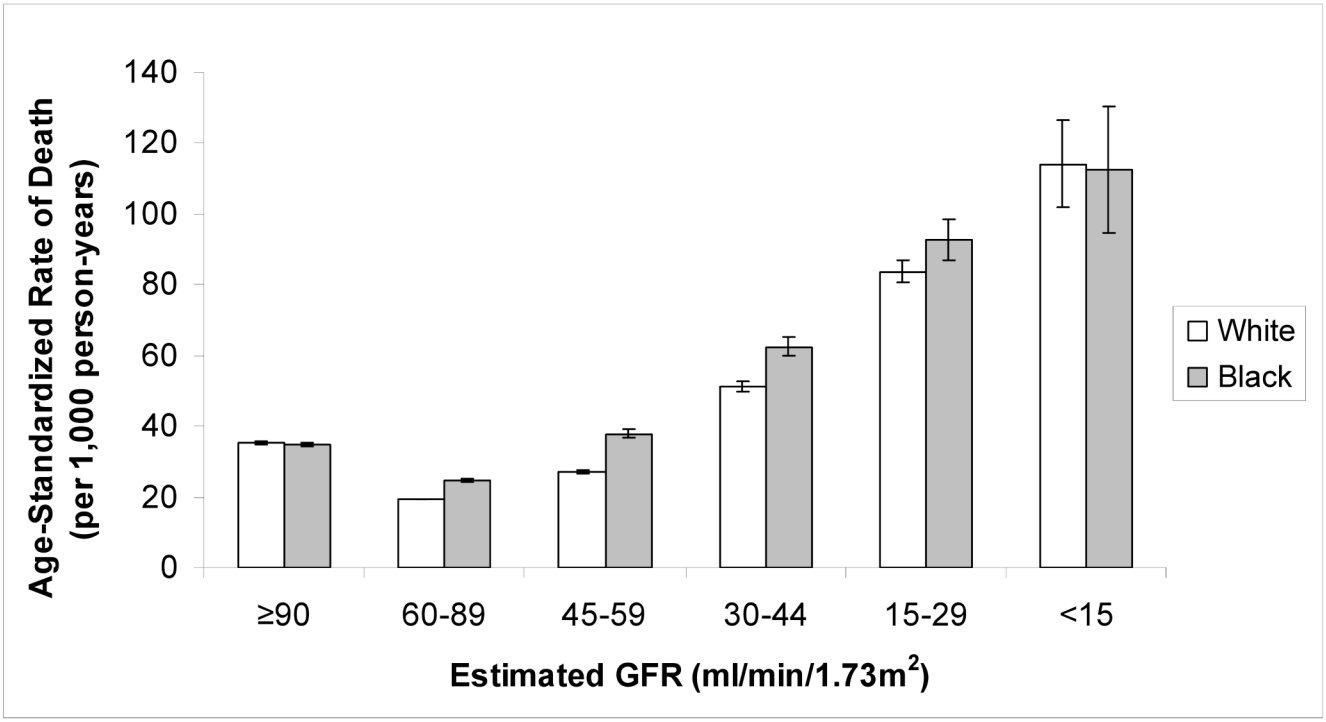

Figure 2. Age-standardized incidence of death by estimated glomerular filtration rate (GFR) at baseline

Error bars indicate 95% confidence intervals.

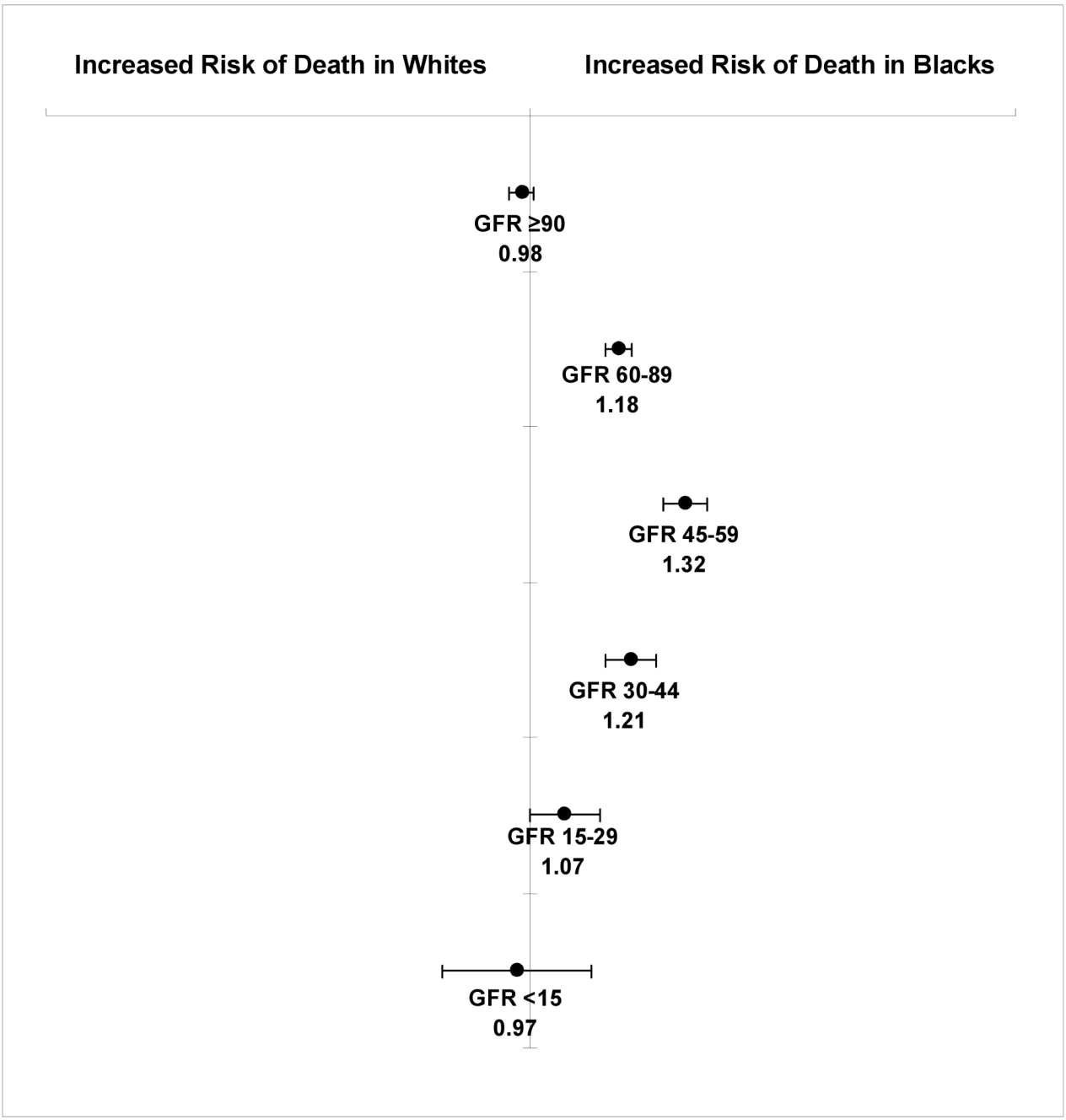

Figure 3. Adjusted hazard ratios for death in black versus white patients stratified by level of estimated glomerular filtration rate (GFR) at baseline

Models adjusted for all variables listed in Table 1. Estimated GFR reported in mL/min/ $1.73m^2$. Error bars indicate 95% confidence intervals.

Table 1

Baseline Characteristics of 2,015,891 Outpatient Veterans, According to White/Black Race*

Characteristic	White Race	Black Race
Total (%)	1,704,101 (84.5)	311,790 (15.5)
Age (years)	66.0 ± 12.4	59.1 ± 13.8
Female Sex (%)	4.0	6.1
Estimated glomerular filtration rate, mL/min/1.73m^2 (%)		
≥90	21.5	44.2
60-89	56.3	42.5
45-59	15.2	8.2
30-44	5.5	3.3
15-29	1.4	1.4
<15	0.2	0.4
Comorbidities (%)		
Diabetes mellitus	29.1	31.5
Coronary heart disease	39.4	25.7
Stroke or transient ischemic attack	15.6	12.3
Heart failure	15.8	12.0
Peripheral arterial disease	15.4	10.7
Atrial fibrillation	10.6	4.8
Hypertension	67.7	70.5
Chronic obstructive lung disease	30.0	23.3
Dementia	5.5	5.6
Hepatitis C virus infection	2.1	5.3
Human immunodeficiency virus infection	0.4	2.6
Socioeconomic status, tertile (%)		
Low	29.9	55.6
Middle	35.0	24.6
High	35.2	19.8

* $p<0.001$ for all characteristics; age reported as mean ± standard deviation.

Table 2

Age-Standardized Rates of End-Stage Renal Disease

Rates are reported as end-stage renal disease events per 1,000 person-years with 95% confidence intervals in parentheses. Estimated glomerular filtration rate (GFR) reported in mL/min/1.73m^2.

Baseline Estimated GFR	*Persons at Risk*	*Number of Events*	*Observation Time (person-years)*	Age-Standardized Rate of End-Stage Renal Disease (per 1000 person-years)
White Race				
≥90	365,484	182	1,296,354	0.2 (0.1, 0.3)
60-89	959,619	929	3,419,386	0.1 (0.1, 0.2)
45-59	258,144	1,116	892,314	1.7 (1.5, 1.8)
30-44	93,850	2,288	300,680	12.5 (11.8, 13.1)
15-29	23,674	4,318	62,649	94.3 (90.7, 97.9)
<15	3,330	1,936	4,540	472.3 (448.3, 496.4)
Black Race				
≥90	137,806	164	493,031	0.4 (0.2, 0.6)
60-89	132,648	367	474,320	0.4 (0.3, 0.4)
45-59	25,520	495	86,128	6.3 (5.7, 7.0)
30-44	10,242	871	31,497	32.8 (30.4, 35.2)
15-29	4,305	1,596	9,907	179.5 (169.8, 189.3)
<15	1,269	886	1,432	615.6 (571.0, 660.3)