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Association of Race With Mortality and Cardiovascular Events in a Large Cohort of US Veterans

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Background—In the general population, blacks experience higher mortality than their white peers, attributed in part to their lower socioeconomic status, reduced access to care, and possibly intrinsic biological factors. Patients with kidney disease are a notable exception, among whom blacks experience lower mortality. It is unclear if similar differences affecting outcomes exist in patients with no kidney disease but with equal or similar access to health care.

Methods and Results—We compared all-cause mortality, incident coronary heart disease, and incident ischemic stroke using multivariable-adjusted Cox models in a nationwide cohort of 547 441 black and 2 525 525 white patients with baseline estimated glomerular filtration rate ≥ 60 mL·min⁻¹·1.73 m⁻² receiving care from the US Veterans Health Administration. In parallel analyses, we compared outcomes in black versus white individuals in the National Health and Nutrition Examination Survey (NHANES) 1999 to 2004. After multivariable adjustments in veterans, black race was associated with 24% lower all-cause mortality (adjusted hazard ratio, 0.76; 95% confidence interval, 0.75–0.77; $P < 0.001$) and 37% lower incidence of coronary heart disease (adjusted hazard ratio, 0.63; 95% confidence interval, 0.62–0.65; $P < 0.001$) but a similar incidence of ischemic stroke (adjusted hazard ratio, 0.99; 95% confidence interval, 0.97–1.01; $P = 0.3$). Black race was associated with a 42% higher adjusted mortality among individuals with estimated glomerular filtration rate ≥ 60 mL·min⁻¹·1.73 m⁻² in NHANES (adjusted hazard ratio, 1.42; 95% confidence interval, 1.09–1.87).

Conclusions—Black veterans with normal estimated glomerular filtration rate and equal access to healthcare have lower all-cause mortality and incidence of coronary heart disease and a similar incidence of ischemic stroke. These associations are in contrast to the higher mortality experienced by black individuals in the general US population. (*Circulation*. 2015;132:1538-1548. DOI: 10.1161/CIRCULATIONAHA.114.015124.)

Key Words: cohort studies ■ continental population groups ■ coronary disease ■ mortality ■ stroke

Blacks represent an estimated 13.2% of the US population, which amounts to >41 million individuals.¹ Poorer health outcomes in blacks have been well documented.^{2–6} These outcome differences have been ascribed largely to the substantial socioeconomic disadvantage of blacks, with resultant lower health literacy, decreased disease awareness, suboptimal access to health care, and overt or latent discrimination in receiving recommended healthcare interventions.⁷

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Notwithstanding the validity and importance of these factors, the underlying causes for differences in the health

outcomes of blacks are likely even more complex and are affected by genetic differences between individuals of African and European ancestry.⁸ A notable example for this is the advanced stages of chronic kidney disease (CKD) and end-stage renal disease (ESRD), the incidence and prevalence of which are disproportionately higher in blacks, in part as a result of recently described common genetic polymorphisms in individuals of African ancestry,^{9–13} but paradoxically, blacks with advanced CKD and ESRD have lower mortality than their white peers.^{14,15} The markedly different pathogenesis of CKD in blacks could affect race-associated clinical outcomes in patients with kidney disease (eg, by affecting differently the age and comorbidity characteristics of affected patients). It is possible that there are also other CKD-independent

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biological mechanisms affecting race-specific cardiovascular and other clinical outcomes. The effects of such mechanisms independently of socioeconomic differences could have different impacts on various clinical outcomes as a result of distinct differences in the pathophysiology of each outcome. Atherosclerosis may have different pathophysiological underpinnings in blacks, who develop significantly less vascular calcification compared with white individuals,^{16–19} which may be the result of (among others) genetic differences in vitamin D and bone metabolism^{8,20} and could result in differences in cardiovascular morbidity and mortality. Blacks also experience a higher incidence of hypertension, more uncontrolled hypertension, and differences in central aortic blood pressure with potential consequences such as higher rates of left ventricular hypertrophy and stroke.²¹ The relative contribution of these various factors to the disparities in outcomes seen in blacks and the extent to which they are affected by socioeconomic factors are not well defined and may vary according to the studied end point and the studied population segment. Furthermore, among the complex socioeconomic factors affecting race-specific outcomes in the United States, the relative contribution of poor access to health care is not well defined.

We hypothesized that blacks without advanced CKD or ESRD will have improved outcomes in a healthcare system that allows enrollment independently of race or socioeconomic status. The US Veterans Health Administration (VHA) is a healthcare system that does not impose the typical access barriers of the US healthcare system that may disproportionately impede enrollment of blacks. We compared all-cause mortality and incident cardiovascular event rates in a large contemporary cohort of black and white individuals with an estimated glomerular filtration rate (eGFR) $\geq 60 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$ followed up in any US VHA facility. We hypothesized that outcome differences between black and white veterans may be attenuated or eliminated by open healthcare access in US VHA facilities.

Methods

Study Design and Participants

We used data from a historic cohort study examining risk factors in patients with incident CKD (Racial and Cardiovascular Risk Anomalies in CKD [RCAV] study).²² The algorithm for cohort definition is shown in Figure 1. US veterans with serum creatinine measurements performed from October 1, 2004, to September 30, 2006, were identified from the national Veterans Affairs (VA) Corporate Data Warehouse LabChem data files.²³ Overall, 4 447 691 veterans had at least 1 available serum creatinine measurement, representing $\approx 94\%$ of all veterans who received VA health care during this time period.²⁴ eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.²⁵ The RCAV cohort included 3 582 478 patients with eGFR $\geq 60 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$, of whom we excluded 509 512 patients with race other than black or white (Hispanic, 73 105 [2.0%]; other races, 68 889 [1.9%]; and missing race, 365 489 [10.2%]). The VA collects information on patients' race primarily from VA Form 10-10EZ (Application for Health Benefits),²⁶ which patients complete at enrollment and is updated as needed. We complemented this self-reported race with race data obtained from Medicare through the VA-Medicare data merge project.²⁶ In case of discrepancies, we used the race determination from Medicare because of its more accurate nature.²⁷ Our final analytic sample consisted of 3 072 966 patients (547 441 black and 2 525 525 white).

Sociodemographic Characteristics, Comorbidities, Medication Use, and Laboratory Variables

Information about sociodemographic characteristics, comorbid conditions, medication use, and laboratory characteristics was obtained as previously described.^{28,29} Briefly, data on patients' age, sex, marital status (married, single, divorced or widowed), mean per capita income, service connectedness (a measure indicating whether 1 or more of a patient's comorbidities were caused by military service, resulting in certain privileges such as preferential access to care and lower copayments), body mass index, systolic and diastolic blood pressures, comorbid conditions, location and frequency of healthcare encounters, and medication use were obtained from various national VA research data files.³⁰ Comorbidities and clinical events were assessed from the VA Inpatient and Outpatient Medical SAS Datasets^{31,32} by use of *International Classification of Diseases, Ninth Revision* diagnostic and procedure codes and *Current Procedural Terminology* codes (online-only Data Supplement). Prevalent comorbidities were defined as the presence of relevant *International Classification of Diseases, Ninth Revision* and *Current Procedural Terminology* codes recorded from October 1, 2004, to September 30, 2006.^{28,29} Prevalent coronary heart disease (CHD) was defined as the presence of diagnostic codes for coronary artery disease, angina, or myocardial infarction or procedure codes for percutaneous coronary interventions or coronary artery bypass grafting. We examined the use of 2 commonly applied medication classes (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and statin-type cholesterol-lowering agents); use of healthcare interventions (influenza vaccinations and blood cholesterol level measurements) from October 1, 2004, to September 30, 2006; and the yearly rate of healthcare encounters over the entire follow-up period to identify discrepancies in basic healthcare delivery. Other baseline characteristics were assessed on the date of cohort entry. In addition to data derived from VA sources, we included select socioeconomic indicators using 2004 county typology codes (housing stress, low education, low employment, and persistent poverty; see the Methods section in the online-only Data Supplement) based on the patients' residential address, obtained from the Area Health Resources Files system issued by the US National Center for Health Workforce Analysis, Bureau of Health Workforce, Health Resources and Services Administration (<http://ahrh.hrsa.gov/>).

Outcomes

Outcomes of interest were all-cause mortality, incident CHD, and incident ischemic strokes. Deaths were ascertained from the VA Vital Status Files, the sensitivity and specificity of which (with the US National Death index used as gold standard) are 98.3% and 99.8%, respectively.³³ Incident CHD was defined as the composite of a first occurrence of an acute myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting; incident ischemic stroke was defined as the first occurrence of an ischemic stroke after October 1, 2006, in patients without such diagnoses before this date.

Statistical Analyses

Data are expressed as means \pm SDs, medians (25th–75th percentiles), and proportions. Because of the large sample size, the significance of differences in the main cohort was established on the basis of what we deemed to be biologically or clinically meaningful differences. Differences between variables in the propensity-matched cohort were examined by calculating standardized differences and were regarded as significant if they were >0.1 . The start of the follow-up period was the date of cohort entry, which was defined as the date of the first eGFR $\geq 60 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$ from October 1, 2004, to September 30, 2006. Patients were followed up until death or were censored at the date of the last healthcare or administrative VA encounter, as documented in the VA Vital Status Files, or on July 26, 2013. Sex-specific crude event rates were calculated from the number of event occurrences and patient-years during the follow-up period, and sex-specific age-adjusted event rates were calculated by the direct standardization method using the US 2000 Census data as the standard population

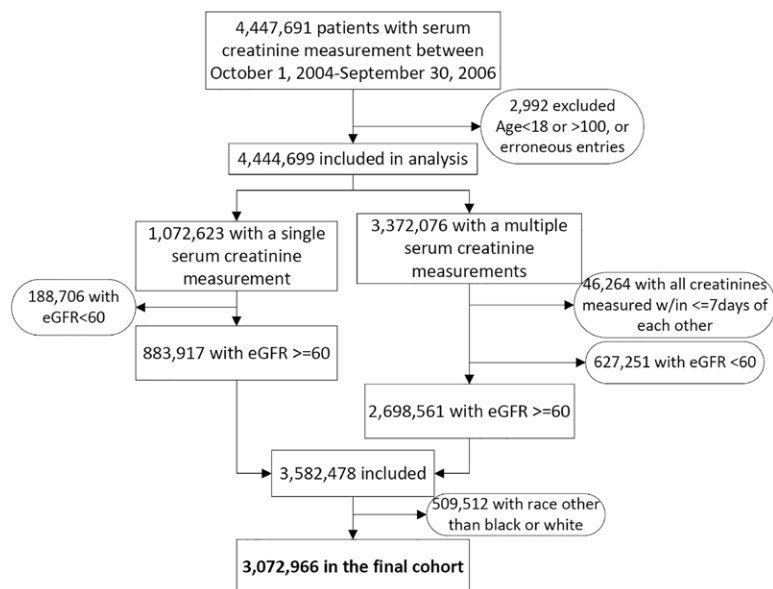


Figure 1. Algorithm used to define the study cohort. eGFR indicates estimated glomerular filtration rate.

(http://www.cdc.gov/nchs/tutorials/NHANES/NHANESAnalyses/agestandardization/age_standardization_intro.htm).

The association of black race with the outcomes of interest was examined in univariable models and after multivariable adjustment. The association of covariates with outcomes was assessed in univariable analyses with the use of Kaplan-Meier curves and log-rank tests or with univariable Cox proportional hazards models and χ^2 tests, as appropriate. We included in multivariable models the covariates showing statistically significant associations with outcomes or those that could be associated with outcomes based on theoretical considerations. Cox models were applied to examine the effect confounders, with adjustments implemented incrementally. Model 1 was unadjusted; model 2, adjusted for age, sex, and baseline eGFR; model 3, model 2 variables plus prevalent comorbidities (diabetes mellitus, hypertension, CHD, congestive heart failure, cerebrovascular disease, peripheral vascular disease, chronic lung disease, peptic ulcer disease, hemiplegia, liver disease, dementia, rheumatic disease, malignancy, HIV/AIDS, and depression); model 4, model 3 variables plus baseline body mass index and systolic and diastolic blood pressures; and model 5, model 4 variables plus mean per capita income, marital status, service connectedness, housing stress, low education, low employment, persistent poverty, frequency of healthcare encounters, use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and statins, receipt of influenza vaccination(s), and each patient's VA healthcare center. Because of previous reports of marked differences in the outcomes of blacks with CKD,^{14,15} we further examined effect modification by decreased kidney function in subgroup analyses of patients who maintained eGFR ≥ 60 mL \cdot min $^{-1}\cdot$ 1.73 m $^{-2}$ throughout follow-up and in those who developed incident stage 3 and above CKD.³⁴ In the latter group, the start of follow-up was the date of eGFR used to define incident CKD. We further assessed whether the occurrence of incident CHD or stroke modifies the association of race with outcomes by including the incident events in the models as time-dependent variables and by including multiplicative interaction terms. Proportionality was tested by the use of Schoenfeld and scaled Schoenfeld residuals. We evaluated the fit of the model by using the Cox-Snell residuals.

Analyses were repeated in a propensity score–matched cohort. Propensity scores quantifying the likelihood of black versus white race were calculated by logistic regression, using all variables included in multivariable models and applying a 1-to-1 nearest neighbor matching without replacement in Stata's `psmatch2` command suite. All outcomes were also examined in subgroups divided by baseline age, sex, prevalent CHD, congestive heart failure, diabetes mellitus, hypertension, eGFR, and income level. Unadjusted analyses for CHD and stroke were repeated in sensitivity analyses using

competing risk regression, with nonevent deaths treated as competing events.³⁵ To compare outcomes associated with black versus white race in the VA system with those in the general population, we also performed an analysis of all-cause, cardiovascular, and stroke-related mortality overall in individuals with eGFR ≥ 60 mL \cdot min $^{-1}\cdot$ 1.73 m $^{-2}$ and in various subgroups using data from the NHANES 1999 to 2004 and adjusting all estimates for the complex NHANES survey design (online-only Data Supplement).

Statistical analyses were performed with STATA MP version 12 (STATA Corp, College Station, TX) and SAS version 9.3 (Research Triangle Park, NC). The study protocol was approved by the Research and Development Committees at the Memphis VA Medical Center and Long Beach VA Medical Center.

Results

The mean \pm SD baseline age of the cohort was 59.9 \pm 14.0 years, and 93.6% were men. Baseline characteristics in the overall cohort are shown in Table 1. Compared with whites, blacks were younger, more likely to be female, service connected, hypertensive, and diabetic and to have HIV/AIDS. They were less likely to be married and to have prevalent CHD and chronic lung disease. Blacks also had more frequent healthcare encounters, higher systolic and diastolic blood pressures, and a lower per capita income and were more likely to live in areas with high housing stress, lower education level, and persistent poverty. The use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and the administration of blood cholesterol measurements were similar in black and white veterans. The use of statins and the administration of influenza vaccinations were slightly less common in blacks. Blacks and whites had characteristics similar to each other in the propensity-matched cohort (Table I in the online-only Data Supplement). Differences in baseline characteristics between black and white individuals (when available) were in general similar in the NHANES cohort and the VA cohort (Table II in the online-only Data Supplement).

Mortality

A total of 638 536 patients died overall (crude rate, 30.16 per 1000 patient-years; 95% confidence interval [CI],

Table 1. Baseline Characteristics

	Unmatched		
	All (n=3 072 966)	Whites (n=2 525 525, 82%)	Blacks (n=547 441, 18%)
Age, y	59.9±13.4	61.0±13.9	54.5±13.2
eGFR, mL·min ⁻¹ ·1.73 m ⁻²	84.0±15.7	82.3±14.4	91.9±18.8
Male sex, n (%)	2 876 626 (94)	2 383 874 (94)	492 752 (90)
Hypertension, n (%)	1 842 120 (60)	1 503 404 (60)	338 716 (62)
DM, n (%)	735 372 (24)	598 022 (24)	137 350 (25)
CHD, n (%)	359 848 (12)	321 545 (13)	38 303 (7)
CHF, n (%)	143 230 (5)	118 970 (5)	24 260 (4)
CVD, n (%)	194 493 (6)	163 514 (6)	30 979 (6)
PAD, n (%)	174 990 (6)	149 833 (6)	25 157 (5)
Chronic lung disease, n (%)	586 672 (19)	504 170 (20)	82 502 (15)
Dementia, n (%)	26 253 (0.9)	21 370 (0.9)	4883 (0.9)
Rheumatologic disease, n (%)	44 044 (1)	37 664 (1)	6380 (1)
Peptic ulcer disease, n (%)	59 130 (2)	47 734 (2)	11 396 (2)
Liver disease, n (%)	38 241 (1)	31 265 (1)	6976 (1)
Hemiplegia, n (%)	15 458 (0.5)	12 187 (0.5)	3271 (0.6)
Malignancies, n (%)	324 508 (11)	271 282 (11)	53 226 (10)
AIDS/HIV, n (%)	20 318 (0.7)	9321 (0.4)	10 997 (2)
Depression, n (%)	301 777 (10)	245 141 (10)	56 636 (10)
Per capita income, \$	22 496 (11 643–35 000)	24 100 (12 284–37 533)	16 732 (10 044–29 416)
Married, n (%)	1 609 343 (54)	1 400 099 (58)	209 244 (40)
Service connected, n (%)	1 273 171 (41)	1 009 039 (40)	264 132 (48)
BMI, kg/m ²	29.2±5.8	29.2±5.7	29.0±6.0
SBP, mm Hg	135.4±19.2	135.2±18.9	136.8±20.5
DBP, mm Hg	77.2±11.9	76.6±11.6	79.9±12.8
ACEI/ARB use, n (%)	1 636 622 (22)	1 342 705 (23)	293 917 (20)
Statin use, n (%)	1 688 623 (15)	1 417 215 (16)	271 408 (9)
Influenza vaccination, n (%)	2 006 550 (30)	1 672 423 (31)	334 127 (26)
Cholesterol measurement, n (%)	2 866 616 (79)	2 355 044 (80)	511 572 (76)
Healthcare encounters >1/mo, n (%)	1 696 067 (56)	1 347 435 (54)	348 632 (64)
Living in area with high housing stress, n (%)	1 014 255 (34)	770 143 (31)	244 112 (47)
Living in area with low education, n (%)	312 812 (11)	238 346 (10)	74 466 (14)
Living in area with low employment, n (%)	275 108 (9)	218 818 (9)	56 290 (11)
Living in area of persistent poverty, n (%)	275 108 (5)	102 782 (4)	37 247 (7)

Data are presented as mean±SD, median (25th–75th percentiles), or number (percent of total). ACEI/ARB indicates angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; BMI, body mass index; CHD, coronary heart disease; CHF, chronic heart failure; CVD, cerebrovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; PAD, peripheral arterial disease; and SBP, systolic blood pressure.

30.09–30.24) during a median follow-up of 7.9 years. There were 551 208 deaths in white patients (crude rate, 31.87 per 1000 patient-years; 95% CI, 31.79–31.96) during a median follow-up of 7.8 years and 87 328 deaths in black patients (crude rate, 22.53 per 1000 patient-years; 95% CI, 22.38–22.68) during a median follow-up of 8.0 years. Table 2 shows sex-specific crude and age-adjusted mortality rates, indicating lower crude mortality rates in blacks for both men and women. This difference disappeared after adjustment for age in men and diminished but remained slightly lower in black women. Compared with whites, blacks had an overall crude mortality hazard ratio (HR) of 0.70 (95% CI, 0.69–0.71; $P<0.001$; model 1, Figure 2).

Adjustment for age, sex, and baseline eGFR resulted in the attenuation of the black mortality advantage (model 2 HR, 0.99; 95% CI, 0.98–0.99; $P<0.001$), but further adjustment for additional covariates resulted in a gradual decrease in the mortality risk associated with black race (HR, 0.76; 95% CI, 0.75–0.77; $P<0.001$; model 5, Figure 2). Incident CHD and stroke modified the association between race and mortality. Compared with white patients who did not experience incident CHD or stroke, blacks without CHD or stroke had significantly lower mortality, whereas mortality rates in white and black patients after an incident CHD or stroke were similar and significantly higher compared with rates in patients without incident events (Figure 2).

Table 2. Crude and Adjusted Event Rates

	White				Black			
	Male		Female		Male		Female	
	Crude Rate (95% CI)	Age-Adjusted Rate (95% CI)	Crude Rate (95% CI)	Age-Adjusted Rate (95% CI)	Crude Rate (95% CI)	Age-Adjusted Rate (95% CI)	Crude Rate (95% CI)	Age-Adjusted Rate (95% CI)
Mortality	33.13 (33.03–33.22)	18.74 (18.67–18.81)	11.06 (10.85–11.27)	13.35 (13.07–13.62)	24.53 (24.36–24.69)	19.31 (19.16–19.46)	5.13 (4.92–5.36)	11.48 (10.66–12.31)
CHD	3.76 (3.73–3.79)	2.38 (2.36–2.41)	1.17 (1.10–1.24)	1.08 (1.01–1.15)	2.97 (2.91–3.03)	2.11 (2.06–2.16)	0.82 (0.74–0.92)	0.94 (0.75–1.13)
Stroke	3.01 (2.98–3.03)	1.83 (1.8–1.85)	1.33 (1.26–1.41)	1.32 (1.24–1.41)	3.75 (3.68–3.82)	2.69 (2.63–2.75)	1.32 (1.21–1.44)	2.03 (1.7–2.36)
AMI	2.52 (2.50–2.55)	1.66 (1.64–1.69)	0.92 (0.86–0.99)	0.87 (0.8–0.93)	2.25 (2.20–2.31)	1.65 (1.6–1.69)	0.67 (0.59–0.76)	0.79 (0.61–0.97)
PCI	1.10 (1.09–1.12)	0.7 (0.68–0.71)	0.28 (0.25–0.31)	0.24 (0.21–0.27)	0.79 (0.76–0.82)	0.53 (0.51–0.56)	0.21 (0.17–0.27)	0.24 (0.15–0.32)
CABG	0.76 (0.75–0.77)	0.43 (0.42–0.44)	0.11 (0.09–0.13)	0.10 (0.08–0.12)	0.41 (0.39–0.43)	0.26 (0.25–0.28)	0.07 (0.05–0.10)	0.05 (0.03–0.07)

Event rates are presented as number per 1000 patient-years and 95% confidence intervals. AMI indicates acute myocardial infarction; CABG, coronary artery bypass grafting; CHD, coronary heart disease; CI, confidence interval; and PCI, percutaneous coronary intervention.

Adjusted all-cause mortality was higher in black versus white individuals both overall (HR, 1.51; 95% CI, 1.19–1.92) and in individuals with eGFR ≥ 60 mL·min⁻¹·1.73 m⁻² in NHANES (HR, 1.42; 95% CI, 1.09–1.87; Figure 3). Mortality in NHANES was also higher in blacks versus whites categorized by age (adjusted HR for age 18–49 versus ≥ 50 years, 1.74 [95% CI, 0.70–4.32] and 1.45 [1.10–1.93], respectively), sex (adjusted HR for men and women, 1.32 [95% CI, 0.91–1.91] and 1.67 [95% CI, 1.19–2.32], respectively), and poverty level (adjusted HR for poverty level $\geq 200\%$ and $<200\%$, 1.30 [95% CI, 0.84–2.00] and 1.45 [95% CI, 1.08–1.94], respectively). Cardiovascular and stroke-related mortality was similar in blacks and whites in NHANES, although the low number of stroke events resulted in imprecise risk estimates (Figure 3).

Incident CHD

A total of 63 808 patients experienced an incident CHD event (crude rate, 3.43 per 1000 patient-years; 95% CI, 3.40–3.46), with 53 988 events in whites (crude rate, 3.60 per 1000 patient-years; 95% CI, 3.57–3.63) and 9820 events in blacks (crude rate, 2.73 per 1000 patient-years; 95% CI, 2.68–2.79). Incident CHD rates in blacks versus whites were lower in both men and women after adjustment for age (Table 2). Both crude (HR, 0.75; 95% CI, 0.74–0.77) and adjusted (HR, 0.63; 95% CI, 0.62–0.65) risks of incident CHD and of the individual components (acute myocardial infarction, coronary artery bypass grafting, and percutaneous coronary intervention) were lower in blacks (Figure 4). The risk of incident CHD was higher in individuals after strokes compared with those who did not have an incident stroke, but incident strokes did

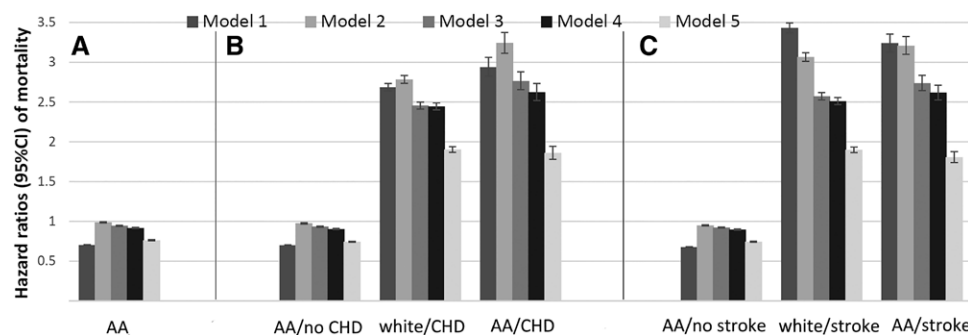


Figure 2. Association of black race with all-cause mortality in the overall cohort of 3 072 966 veterans. **A**, Association of black race with all-cause mortality in the overall cohort with adjustments for baseline characteristics. White patients served as referent. **B**, Associations of race with all-cause mortality in patients with and without an incident coronary heart disease (CHD) event. CHD events were entered into the models as time-dependent covariates, and models were estimated by including multiplicative interaction terms between race and CHD events. White patients without incident CHD served as referent. **C**, Associations of race with all-cause mortality in patients with and without incident strokes. Strokes were entered into the models as time-dependent covariates, and models were estimated by including multiplicative interaction terms between race and strokes. White patients without incident strokes served as referent. Model 1, unadjusted; model 2, adjusted for age, sex, and baseline estimated glomerular filtration rate; model 3, model 2 variables plus comorbidities; model 4, model 3 variables plus baseline body mass index and systolic and diastolic blood pressures; and model 5, model 4 variables plus mean income, marital status, service connectedness, area-level housing stress, low education, low employment, persistent poverty, frequency of Veterans Affairs (VA) healthcare encounters, use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and statins, receipt of influenza vaccination(s), and each patient's VA healthcare center. AA indicates African American; and CI, confidence interval.

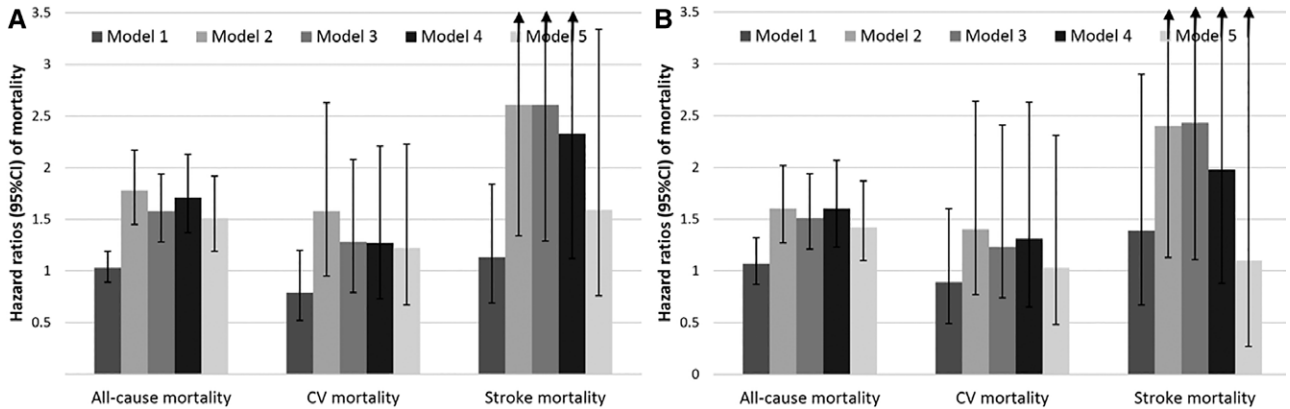


Figure 3. Crude (model 1) and multivariable-adjusted association of black race with all-cause, cardiovascular (CV), and stroke-related mortality in National Health and Nutrition Examination Survey (NHANES) 1999 to 2004 overall (A) and in participants with estimated glomerular filtration (eGFR) $\geq 60 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$ (B). Adjustments were made for age, sex, eGFR (model 2), comorbidities (model 3), body mass index, systolic and diastolic blood pressures (model 4), marital status, and poverty level (model 5). CI indicates confidence interval; and CV, cardiovascular. White patients served as referent.

not modify the association between race and incident CHD, which remained lower in black versus white patients with or without incident strokes (Figure 4).

Incident Stroke

In total, 59734 patients experienced an incident stroke (crude rate, 3.02 per 1000 patient-years; 95% CI, 2.99–3.04), with 46984 events in whites (crude rate, 2.91 per 1000 patient-years; 95% CI, 2.88–2.93) and 12750 events in blacks (crude rate, 3.49 per 1000 patient-years; 95% CI, 3.43–3.55). Incident stroke rates in blacks versus whites remained higher in both men and women after adjustment for age (Table 2). Crude stroke risk was higher in blacks (HR, 1.18; 95% CI, 1.16–1.21), but this was attenuated after multivariable adjustments, especially for socioeconomic characteristics in model 5 (HR, 0.99; 95% CI,

0.97–1.01; Figure 5). Incident CHD did not modify the association between race and incident stroke, which was similar in black and white patients with or without CHD, even though the risk of stroke was higher in patients who experienced an incident CHD event compared with those who did not (Figure 5).

Sensitivity Analyses

The mortality risk associated with black race was also lower in propensity score-matched analyses (HR, 0.86; 95% CI, 0.85–0.87; Table III in the online-only Data Supplement), in patients who maintained eGFR $\geq 60 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$ (n=2732494; HR, 0.83; 95% CI, 0.82–0.84), and in various examined subgroups (Figure 6), but it was similar in those who developed incident eGFR $< 60 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$ (n=328221; HR, 0.99; 95% CI, 0.96–1.01; Figures I and II in the online-only Data Supplement).

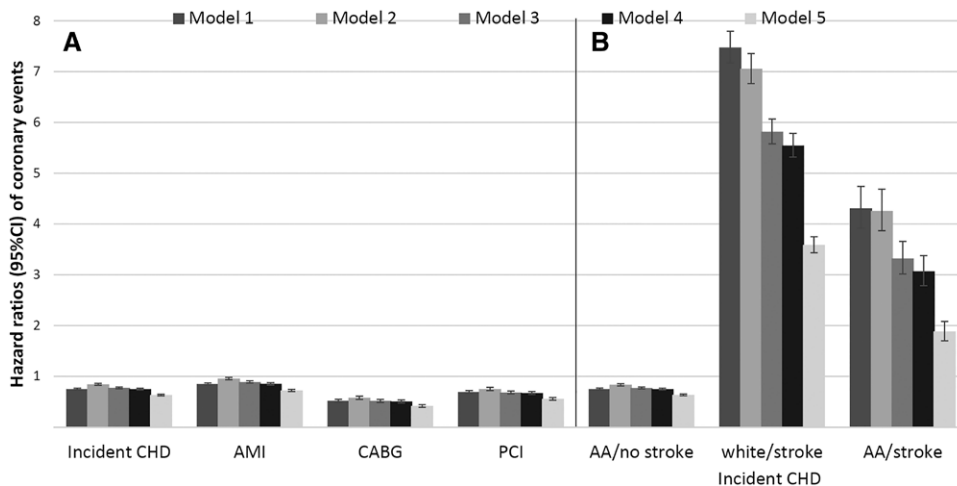


Figure 4. A, Association of black race with incident coronary heart disease (CHD) and with incident acute myocardial infarction (AMI), coronary artery bypass grafting (CABG), and percutaneous coronary intervention (PCI) in the overall cohort of 3072966 veterans. White patients served as referent. **B,** Associations of race with incident CHD in patients with and without an incident stroke. Strokes were entered into the models as time-dependent covariates, and models were estimated by including multiplicative interaction terms between race and stroke. White patients without stroke served as referent. Model 1, unadjusted; model 2, adjusted for age, sex, and baseline estimated glomerular filtration rate; model 3, model 2 variables plus comorbidities; model 4, model 3 variables plus baseline body mass index and systolic and diastolic blood pressures; and model 5, model 4 variables plus mean income, marital status, service connectedness, area-level housing stress, low education, low employment, persistent poverty, frequency of Veterans Affairs (VA) healthcare encounters, use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and statins, receipt of influenza vaccination(s), and each patient’s VA healthcare center. AA indicates African American; and CI, confidence interval.

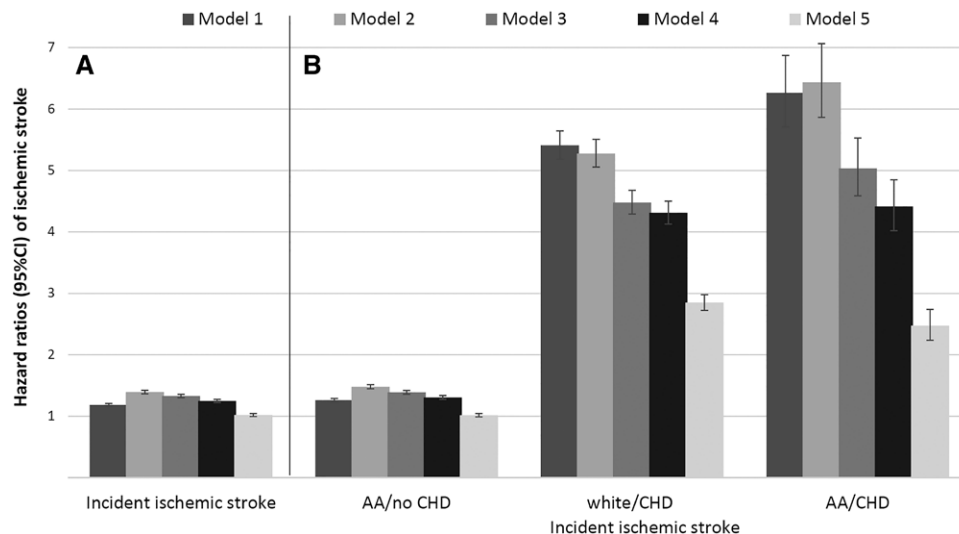


Figure 5. **A**, Association of black race with incident ischemic strokes in the overall cohort of 3 072 966 veterans. White patients served as referent. **B**, Associations of race with incident stroke in patients with and without incident coronary heart disease (CHD). CHD events were entered into the models as time-dependent covariates, and models were estimated by including multiplicative interaction terms between race and CHD. White patients without CHD served as referent. Model 1, unadjusted; model 2, adjusted for age, sex, and baseline estimated glomerular filtration rate; model 3, model 2 variables plus comorbidities; model 4, model 3 variables plus baseline body mass index and systolic and diastolic blood pressures; and model 5, model 4 variables plus mean income, marital status, service connectedness, area-level housing stress, low education, low employment, persistent poverty, frequency of Veterans Affairs (VA) healthcare encounters, use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and statins, receipt of influenza vaccination(s), and each patient's VA healthcare center. AA indicates African American.

The risk of incident CHD was lower in blacks versus whites in the overall propensity-matched cohort (HR, 0.68; 95% CI, 0.66–0.70; Table III in the online-only Data Supplement), in patients who developed incident eGFR <60 mL·min⁻¹·1.73 m⁻² (HR, 0.79; 95% CI, 0.75–0.84), and in those who maintained eGFR ≥ 60 mL·min⁻¹·1.73 m⁻² throughout follow-up (HR, 0.63; 95% CI, 0.61–0.65; Figures III and IV in the online-only Data Supplement), as well as in all examined subgroups except for patients ≥ 80 years old (Figure 6) and in a competing-risk regression model (Table IV in the online-only Data Supplement).

Stroke risk was also higher in blacks in the overall propensity-matched cohort (HR, 1.09; 95% CI, 1.06–1.12; Table III in the online-only Data Supplement), in patients who developed incident CKD (HR, 1.17; 95% CI, 1.10–1.24), and in those who maintained eGFR ≥ 60 mL·min⁻¹·1.73 m⁻² (HR, 1.05; 95% CI, 1.02–1.09; Figures V and VI in the online-only Data Supplement), as well as in competing-risk regression (Table IV in the online-only Data Supplement). Blacks experienced higher stroke risk among older individuals and women and in subgroups with prevalent CHF, lower eGFR, and lower income (Figure 6).

Discussion

In this large cohort of >3 million contemporary US veterans with baseline eGFR ≥ 60 mL·min⁻¹·1.73 m⁻², we found significant differences in major clinical outcomes between blacks and whites not traditionally reported in the general population. We found substantially lower incident CHD rates and, most surprising, lower all-cause mortality in blacks compared with whites. Differences in demographic, comorbidity, and socioeconomic characteristics accounted for some but not all of the difference in mortality and CHD. Contrasting the lower

mortality seen in US veterans, our analyses of NHANES 1999 to 2004 showed higher all-cause mortality in blacks versus whites. Similar to previous reports,³⁶ incident stroke rates were higher in black veterans, but differences were attenuated to nonsignificant after adjustment for socioeconomic characteristics.

Worse health outcomes in blacks have been well described.³⁷ These have included a variety of outcomes transcending age and sex categories.^{2–6} The socioeconomic deprivation of blacks has provided a plausible explanation for these observations⁷ and points to the importance of breaking down the many remaining barriers faced by the black community. In today's typical US healthcare environment, it is difficult to separate the effects on outcomes of poor healthcare access and race-based discrimination in healthcare delivery from the effects of biological mechanisms. This would require not only an egalitarian healthcare system but also a society that does not directly or indirectly discriminate. In a community-based standardized healthcare system, Karter et al³⁸ found similar or even reduced rates of diabetes-related complications in minority compared with white enrollees, with the exception of developing ESRD. The Department of Defense and VHA are open-access healthcare systems in the United States in that they provide comprehensive health care based on a military or veteran status. Thus, it is less likely that institutional barriers or cost would disproportionately prevent black veterans from obtaining health care. In an analysis of Department of Defense enrollees, Gao et al³⁹ found similar rates of quality care indicators for black and white patients with stages 3 and 4 CKD. Previous studies examining all-cause mortality in hospitalized patients⁴⁰ and outcomes associated with various health conditions such as congestive heart failure,⁴¹ *Pneumocystis carinii* pneumonia,⁴² and colorectal and lung cancer^{43,44} have

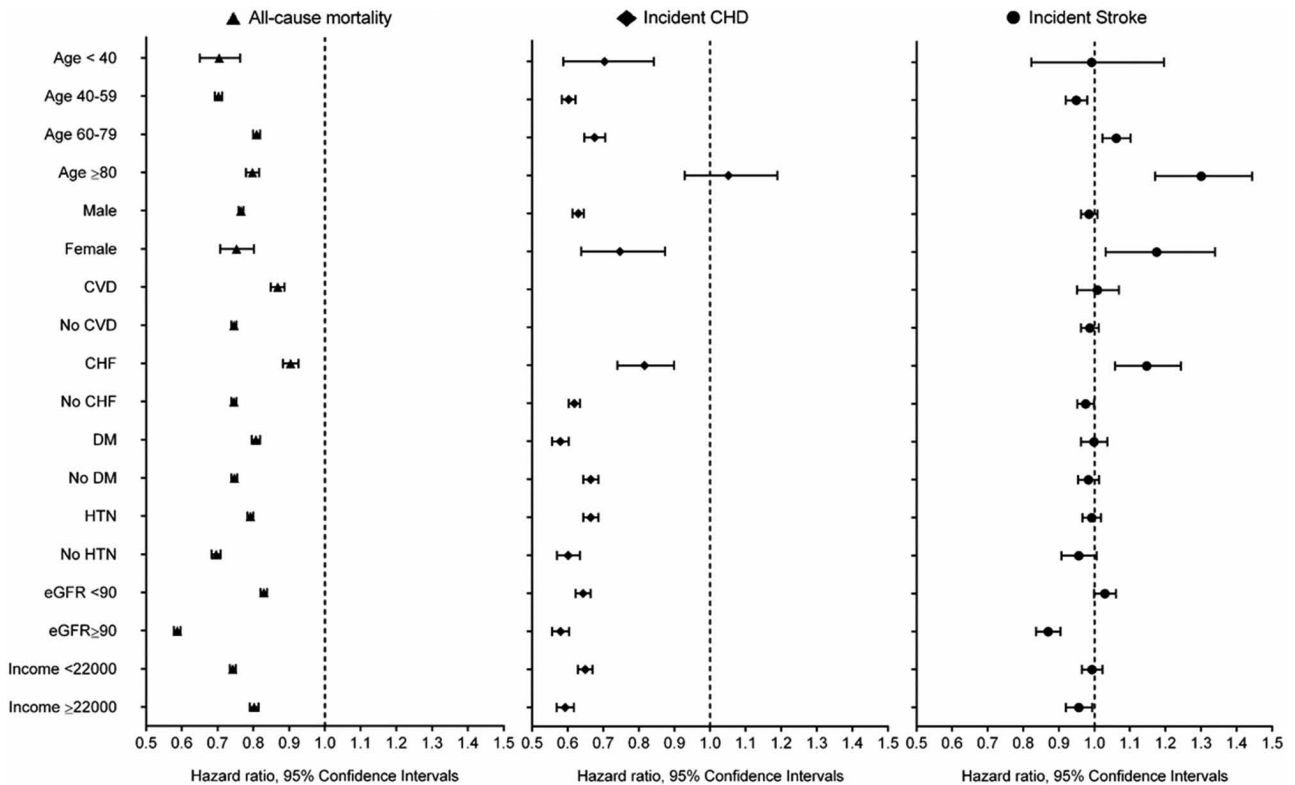


Figure 6. Association of black race with various outcomes in predefined subgroups of the overall cohort of 3 072 966 veterans. White patients served as referent. Models were adjusted for age, sex, baseline estimated glomerular filtration rate (eGFR), comorbidities, baseline body mass index, systolic and diastolic blood pressures, mean income, marital status, service connectedness, area-level housing stress, low education, low employment, persistent poverty, frequency of Veterans Affairs (VA) healthcare encounters, use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and statins, receipt of influenza vaccination(s), and each patient's VA healthcare center. CHD indicates coronary heart disease; CHF, congestive heart failure; CVD, cardiovascular disease; DM, diabetes mellitus; and HTN, hypertension.

also reported better outcomes in black veterans compared with those typically seen in nonveterans. Furthermore, our examination of basic healthcare metrics such as the administration of common health screening procedures and medications suggests that basic health care delivered after enrollment in a contemporary VHA facility is not racially discriminatory. Also supporting this notion, a previous study examining unmet healthcare needs in patients of various races and ethnicities showed that the use of VA ambulatory care eliminated the disparity in the ability to obtain needed healthcare services between black and white veterans.⁴⁵ Finally, among participants in the UK Prospective Diabetes Study (UKPDS), Afro-Caribbean patients experienced substantially reduced risk of all-cause and diabetes-related mortality, myocardial infarctions, but not strokes,^{46,47} suggesting that receiving similar care in a controlled system outside the United States may also result in benefits for minorities that are similar to those reported in our study.

One possible explanation for the observed racial discrepancies in outcomes is the biological differences between blacks and whites that are overwhelmed by the socioeconomic disparities in the general population but uncovered in a system that provides open access to health care. There is now mounting evidence that some blacks have distinctly unique genetic characteristics linked to their African ancestry that have a direct impact on health outcomes.⁸ Aside from the

above-mentioned common genetic polymorphisms responsible for excess CKD and ESRD in blacks,⁹⁻¹³ there may be additional ones affecting cardiovascular pathophysiology and outcomes.⁴⁸⁻⁵⁰ We limited our analysis to patients with eGFR ≥ 60 mL·min⁻¹·1.73 m⁻² to examine patients in whom clinical outcomes would less likely be affected by genetic differences leading to kidney disease or the biological effect of azotemia, which could directly or indirectly affect the lower mortality previously described by us in black veterans with CKD.¹⁵ Our results showing lower mortality and CHD incidence but higher stroke incidence in blacks independently of their level of eGFR suggest that such differences could be a result of genetic or other differences in susceptibility to various cardiovascular processes. Recent findings that blacks experience significantly less vascular calcification compared with white individuals,¹⁶⁻¹⁹ perhaps owing to genetic differences in various physiological processes such as vitamin D and bone metabolism,^{8,20} support such a hypothesis. Other race-specific biological differences that could affect other cardiovascular outcomes such as strokes include a higher incidence of hypertension, more uncontrolled hypertension, and differences in central aortic blood pressure and prevalence of left ventricular hypertrophy in blacks.²¹ The presence of divergent clinical outcomes (lower CHD incidence but higher stroke incidence) could be indicative of distinctly different biological processes underlying these outcomes, with some portending a favorable

but others an unfavorable outcome in blacks. Our finding that mortality after incident cardiovascular events in our cohort was similar in blacks and whites and the lack of difference in cardiovascular and stroke-related mortality between blacks and whites in NHANES suggest that most of the race-based differences could affect the development of cardiovascular lesions, and less so their secondary deleterious consequences.

Our study is notable for the very large number of studied individuals and for its US-wide distribution. Our study also has several limitations. Our cohort consisted predominantly of men; hence, our conclusions may not apply to women. Previous studies have described important sex differences in race-based outcomes.⁵¹ However, our findings were similar in female compared with male veterans, and despite the low percentage of women in our cohort, their absolute number was substantial (>150 000 patients) and eclipsed the number of women examined in most or all previous studies. We used self-identified race as our predictor, which is biologically inferior to gene-based determination of ancestry; however, the former captures social constructs and the latter method is not yet available for large-scale epidemiological studies. Our cohort consisted of US veterans with distinct demographic and clinical characteristics; hence, it is unclear whether our findings can be applied to nonveterans. Enrollment in the US armed services and subsequently into the VHA may include distinct populations of blacks and whites. Although we cannot discount this possibility, the basic characteristics of our cohort suggest that differences between blacks and whites seen in the general population were indeed present in our cohort (eg, differences in income, marital status, and certain comorbidities). Thus, it is less plausible that the observed differences in outcomes were due solely to selection bias. Furthermore, higher stroke rates⁵² and lower incidence of CHD^{47,51} in populations of African ancestry have previously been reported in nonveterans, which also suggests that our findings are not limited to US veterans alone. We examined clinical events recorded during care received in a VA facility and would not have captured similar events recorded at non-VA facilities. We captured clinical events using diagnostic codes, not the more accurate adjudication procedures used in clinical trials, which are not feasible in a study of this size. However, these limitations do not apply to all-cause mortality. We examined all-cause mortality because we had no information about causes of death. We adjusted for a variety of demographic, social, economic, and healthcare-quality indexes that could affect race-based differences in care, but we cannot exclude the possibility that unmeasured confounders may also play a role in the observed differences. We defined our cohort on the basis of an eGFR ≥ 60 mL \cdot min $^{-1}$ \cdot 1.73 m $^{-2}$, but we did not have markers of earlier stages of CKD (eg, proteinuria). We imply that the described associations are present in the overall VA population regardless of level of kidney function using separate analyses in patients with eGFR ≥ 60 and < 60 mL \cdot min $^{-1}$ \cdot 1.73 m $^{-2}$ but without analyzing all VA-enrolled patients as a single cohort.

Conclusions

There are significant differences in major clinical outcomes experienced by black patients enrolled in an open-access health-care system (US VHA) compared with their white counterparts.

Black veterans experienced a lower incidence of CHD, higher incidence of stroke, and lower all-cause mortality compared with white veterans. Differences in mortality and in incident CHD could not be explained by differences in demographic, comorbidity, and socioeconomic characteristics, suggesting that there may be important sociocultural or evolutionary transmitted biological differences (eg, neurohormonal, epigenetic, gene variants) explaining the development of cardiovascular or other diseases in individuals of different races. Future studies will need to elucidate the nature of such putative differences to determine whether race-specific measures are needed for the prevention and treatment of cardiovascular disease.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Blacks experience significantly worse mortality and clinical outcomes than white individuals in the general population. These differences are the result of a complex interplay between socioeconomic deprivation, lack of access to health care, overt or latent racial discrimination, and ancestry-related biological differences. The relative contribution of each of these factors is not well defined and may vary according to the studied end point. It is unclear what the clinical outcomes experienced by blacks would be in a system that does not pose the typical barriers to healthcare access seen in the United States. We examined all-cause mortality, incident coronary heart disease, and incident strokes in a cohort of black versus white US veterans with normal estimated glomerular filtration rate. Among US veterans, blacks experienced significantly lower all-cause mortality and incident coronary heart disease but higher incident strokes. These results contrasted the results of a parallel analysis in the National Health and Nutrition Examination Survey (NHANES) 1999 to 2004, which showed higher multivariable-adjusted all-cause mortality in blacks and trends toward higher coronary heart disease and stroke mortality. Our results could be explained by a beneficial effect of free healthcare access on some clinical outcomes in blacks, by selection bias in that black veterans may not be representative of the black community at large, or by a combination of these. Further studies are needed to corroborate the benefits of unhindered access to health care in disadvantaged populations and to uncover potential biological mechanisms that may differentiate individuals who are more resilient within the black community and the unique differential outcomes for coronary heart disease and stroke mortality across races.

Association of Race With Mortality and Cardiovascular Events in a Large Cohort of US Veterans

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SUPPLEMENTAL MATERIAL

SUPPLEMENTAL METHODS

ICD9 codes used to define prevalent comorbid conditions

<u>Comorbid condition</u>	<u>ICD9 code</u>
Hypertension	401-405
Diabetes mellitus	250.x
Myocardial infarction	410-410.9, 412
Angina	411, 413
CAD	414.0, 414.8, 414.9
PCI	36.03, 36.04, 36.06, 36.07, 36.09
CABG	36.10-36.17, 36.19
CHF	428-428.9

Peripheral arterial disease	440.0-440.9, 443, 443.x, 38.0, 38.1, 39.50, 39.22, 39.24, 39.25, 39.26, 39.28
Cerebrovascular disease	430-438
Chronic lung disease	490-496, 500-505, 506.4
Dementia	290-290.9
Rheumatologic disease	710.0, 710.1, 710.4, 714.0-714.2, 714.81, 725
Peptic ulcer disease	531-534.9, 531.4-531.7, 532.4-532.7, 533.4-533.7, 534.4-534.7
Liver disease	571.x, 572.x, 456.0-456.21
Hemiplegia or paraplegia	344.1, 342-342.9
Malignancy	140-172.9, 174-195.8, 200-208.9, 196-199.1
HIV/AIDS	042, V08, 795.71

Depression

296.x

CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CHF, congestive heart failure

ICD9 codes used to define incident clinical events

<u>Incident event</u>	<u>ICD9 code</u>
Acute myocardial infarction	410.x
PCI	36.03, 36.04, 36.06, 36.07, 36.09
CABG	36.10-36.17, 36.19
Ischemic stroke	433.x, 434.x, 436.x

PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting

Procedure (CPT) codes used to define coronary interventions

<u>Coronary intervention</u>	<u>CPT code</u>
PCI	92980 92981 92982 92984 92985 92986 92987 92988 92989 92990 92991 92992 92993 92994 92995 92996
CABG	33510 33511 33512 33513 33514 33515 33516 33517 33518 33519 33521 33522 33523 33533 33534 33535 33536

PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting

Area-based socio-economic indicators

The Area Health Resources Files (AHRF, <http://ahrf.hrsa.gov/>) system is issued by the National Center for Health Workforce Analysis, Bureau of Health Workforce, Health Resources and Services Administration.

Within the AHRF, we used select **2004 County Typology Codes** from the Economic Research Service (ERS), U.S. Department of Agriculture, www.ers.usda.gov. The 2004 County Typology Codes were developed for all 3,141 counties, county equivalents, and independent cities in the United States.

-Housing stress: 30 percent or more of households had one or more of these housing conditions in 2000: lacked complete plumbing, lacked complete kitchen, paid 30 percent or more of income for owner costs or rent, or had more than 1 person per room.

-Low-education: 25 percent or more of residents 25 through 64 years old had neither a high school diploma nor GED in 2000.

-Low-employment: Less than 65 percent of residents 21 through 64 years old were employed in 2000.

-Persistent poverty: 20 percent or more of residents were poor as measured by each of the last 4 censuses: 1970, 1980, 1990 and 2000.

Methods used in analyses of NHANES data

Survey design and data collection

The NHANES is conducted by the National Center for Health Statistics and implements a stratified multistage probability design to obtain a representative sample of the civilian, non-institutionalized U.S. population. Details on the sampling strategy and weighting methods are available in electronic form (2). Baseline data were linked to the National Center for Health Statistics mortality follow-up file. Mortality status was ascertained by matching National Death Index screen from the time of survey until 31 December 2006. Cause of death was coded using ICD-10 codes. (3). Using special mobile examination centers, the NHANES conducts household interviews and collects sociodemographic and clinical information, standardized physical examinations including height, weight and blood pressure, and a collection of blood samples. Because NHANES data are publicly available and subjects are de-identified the project was exempt from IRB review.

Data for our study were drawn from NHANES 1999-2004, which included a sample of approximately 31,126 persons from randomly selected U.S. locations. The study population was restricted to adult participants, self-reported as non-Hispanic white or African American, age \geq 18 years at the time of interview (n=11,634). Participants with non-positive sample weights were excluded (n=863). The final study cohort was comprised of 10,771 participants.

Study Variables

Variables included: age (years), estimated GFR (ml/min/1.73m²), gender, BMI (kg/m²), SBP (mmHg), DBP (mmHg), income (above/below 200% federal poverty level), marital status

(married, widowed, divorced, single) and prevalence rates of hypertension, diabetes, hypercholesterolemia, and history of CHD, CHF, stroke, heart attack, and liver disease.

Statistical analyses

Study population characteristics were described overall by race/ethnicity, respectively, using mean and standard deviation for continuous variables and proportions for categorical variables. All estimates were weighted to adjust for the differential probabilities of sampling and non-response, to represent the total civilian, non-institutionalized US population. Estimates derived from a sample size smaller than the recommended lower limit in the NHANES analytic guidelines were considered unreliable¹. Regression analyses based on the Cox proportional hazards model were used to obtain hazard rates comparing race/ethnicity for all-cause mortality, CV and cerebrovascular mortality (derived from ICD 10 codes). Model 1: unadjusted; model 2: adjusted for age, gender, baseline estimated glomerular filtration rate; model 3: adjusted for model 2 variables plus comorbidities; model 4: adjusted for model 3 variables plus baseline body mass index; and model 5: adjusted for model 4 variables plus mean income and marital status. Analyses for mortality were repeated in participants with eGFR ≥ 60 ml/min/1.73m², in in participants categorized by baseline age (18-49 vs. ≥ 50 years old), gender (male vs. female) and poverty level (above/below 200% federal poverty level). All analyses were performed with SAS v 9.3 (Research Triangle Park, NC), a statistical package that adjusts all estimates for the complex NHANES survey design. Because the observations contributed by each participant in the sample were weighted for the differential probabilities of selection and non-response, actual sample sizes are not reported along with percentages.

References

1. Duru OK, Harawa NT, Kermah D, Norris KC. Allostatic load burden and racial disparities in mortality. *Journal of the National Medical Association*. Jan-Feb 2012;104(1-2):89-95.
2. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Analytic Guidelines. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, [1999-2010][http://www.cdc.gov/nchs/data/series/sr_02/sr02_161.pdf]
3. NHANES (1999–2004) Linked Mortality Files. Available: http://www.cdc.gov/nchs/data_access/data_linkage/mortality/nhanes_99_04_linkage.htm. Accessed April 10th, 2015.

Supplemental Table 1. Baseline characteristics of a propensity matched cohort of 937,560 US veterans.

	Whites	African-Americans	Standardized difference
	N=468,780	N=468,780	
Age (years)	54.5 ± 13.1	54.2 ± 14.3	0.02
Estimated GFR (ml/min/1.73m ²)	91.7 ± 18.7	90.8 ± 15.5	0.05
Gender (males)	424,545(91)	426,761 (91)	0.02
Hypertension	294,985 (63)	291,979 (62)	0.01
DM	119,599 (26)	119,617 (26)	-0.0
CHD	33,646 (7)	33,069 (7)	0.004
CHF	20,860 (4)	20,470 (4)	0.004
Cerebrovascular disease	26,520 (6)	26,087 (6)	0.004
PAD	21,872 (5)	22,036 (5)	-0.002
Chronic Lung disease	71,903 (15)	71,450(15)	0.003
Dementia	3,975 (0.9)	4,005 (0.9)	-0.001
Rheumatologic disease	5,564 (1)	5,307 (1)	0.005
Peptic ulcer disease	9,957 (2)	9,931 (2)	0.0
Liver disease	5,885 (1)	6,000 (1)	-0.002
Hemiplegia	2,777 (0.6)	2,733 (0.6)	0.001
Malignancies	45,996 (10)	46,374 (10)	-0.003
AIDS/HIV	9,239 (2)	6,413 (1)	0.05
Depression	49,844 (11)	50,643 (11)	-0.006
Per capita income	16,713 (10,084-29,348)	16,744 (9,736-29,732)	0.02
Married	281,292 (60)	281,349 (60)	-0.0
Service-connected	232,190 (50)	235,786 (50)	-0.02
BMI (kg/m ²)	29.0 ± 6.0	29.1 ± 5.9	-0.01
SBP (mmHg)	136.8 ± 20.4	136.7 ± 19.7	0.004
DBP (mmHg)	80.0 ± 12.7	79.9 ± 12.1	0.007
ACEI/ARB use	95,412 (20)	95,046 (20)	0.002
Statin use	44,033 (9)	43,054 (9)	0.007
Influenza vaccination	120,887 (26)	120,215 (26)	0.003
Healthcare encounters >1/month	304,946 (65)	305,419 (65)	-0.002
Living in area with high housing stress	219,950(47)	218,963 (47)	0.004
Living in area with low education	67,642 (14)	66,167 (14)	0.009
Living in area with low employment	50,827 (11)	49,478 (11)	0.009
Living in area of persistent poverty	34,008 (7)	32,682 (7)	0.01

Data is presented as means \pm SD, medians (25-75 percentile) or number (% of total).

ACEI/ARB, angiotensin converting enzyme inhibitors/angiotensin receptor blockers; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; CHD, coronary heart disease; CHF, chronic heart failure; PAD, peripheral arterial disease.

Supplemental Table 2a. Baseline characteristics in the overall NHANES 1999-2004 sample

	All N=10771	Whites N=7545 (87)	African- Americans N=3226 (13)	p-value
Age (years)	46 ± 0.3	47 ± 0.3	42 ± 0.3	<0.0001
Estimated GFR(ml/min/1.73m ²)	99 ± 0.7	97 ± 0.7	115 ± 1.4	<0.0001
Gender (males)	5167(48)	3630(48)	1537(44)	0.0004
Hypertension	4375(36)	3002(35)	1373(41)	0.0002
Diabetes	1181(9)	747(8)	434(12)	<0.0001
High Cholesterol	4816(49)	3639(50)	1177(42)	<0.0001
CHD	508(4)	431(4)	77(2)	<0.0001
CHF	358(3)	275(2)	83(2)	0.8
Stroke	393(3)	278(3)	115(3)	0.07
Heart attack	531(4)	428(4)	103(3)	0.01
Liver disease	297(3)	240(3)	57(2)	0.0003
Below 200% poverty level	3940(31)	2360(28)	1580(53)	<0.0001
Marital Status				
Married	6034(65)	4682(67)	1352(47)	
Widowed	1097(7)	815(7)	282(7)	
Divorced	937(9)	615(9)	322(12)	
Single	2385(19)	1214(17)	1171(34)	<0.0001
BMI (kg/m ²)	28 ± 0.1	28 ± 0.1	30 ± 0.2	<0.0001
SBP (mmHg)	123 ± 0.4	123 ± 0.4	126 ± 0.5	<0.0001
DBP(mmHg)	72 ± 0.2	71 ± 0.3	73 ± 0.4	0.001

Data is presented as means ± SE, or number (weighted %)

Supplemental Table 2b. Baseline characteristics in NHANES 1999-2004 participants with estimated glomerular filtration rate ≥ 60 ml/min/1.73m²

	All N=9257	Whites N=6481 (87)	African- Americans N=2776 (13)	p-value
Age (years)	45 \pm 0.3	45 \pm 0.3	41 \pm 0.3	<0.0001
Estimated GFR(ml/min/1.73m ²)	102 \pm 0.7	100 \pm 0.6	117 \pm 1.4	<0.0001
Gender (males)	4498(49)	3167(49)	1331(44)	0.0004
Hypertension	3432(33)	2338(33)	1094(38)	0.0004
Diabetes	884(8)	549(7)	335(11)	<0.0001
High Cholesterol	4412(49)	3305(50)	1107(41)	<0.0001
CHD	344(3)	291(3)	53(2)	<0.0001
CHF	193(2)	149(2)	44(2)	0.7
Stroke	237(2)	174(2)	63(2)	0.7
Heart attack	356(3)	288(3)	68(2)	0.01
Liver disease	244(3)	203(3)	41(2)	0.0005
Below 200% poverty level	3316(30)	1973(27)	1343(52)	<0.0001
Marital Status				
Married	5297(66)	4124(68)	1173(48)	
Widowed	710(5)	509(5)	201(6)	
Divorced	803(10)	541(9)	262(11)	
Single	2164(19)	1113(17)	1051(35)	<0.0001
BMI (kg/m ²)	28 \pm 0.1	28 \pm 0.1	30 \pm 0.2	<0.0001
SBP (mmHg)	122 \pm 0.4	122 \pm 0.4	125 \pm 0.5	<0.0001
DBP(mmHg)	72 \pm 0.2	72 \pm 0.3	73 \pm 0.4	0.02

Data is presented as means \pm SE, or number (weighted %)

Supplemental Table 3a: Hazard ratios and 95% confidence intervals of various outcomes associated with African American vs. white race in a propensity matched cohort of 937,560 patients.

	Overall	eGFR≥60 throughout follow-up	Incident eGFR<60 during follow-up	
	Hazard Ratio (95% CI)			
Mortality	0.86 (0.85 - 0.87)	0.83 (0.82 - 0.84)	0.99 (0.96 - 1.01)	
Stroke	1.09 (1.06 - 1.12)	1.05 (1.02 - 1.09)	1.17 (1.1 - 1.24)	
CHD Composite	0.68 (0.66 - 0.7)	0.63 (0.61 - 0.65)	0.79 (0.75 - 0.84)	
AMI	0.75 (0.72 - 0.77)	0.69 (0.67 - 0.72)	0.87 (0.81 - 0.93)	
CABG	0.47 (0.44 - 0.5)	0.44 (0.41 - 0.48)	0.55 (0.47 - 0.63)	
PCI	0.63 (0.6 - 0.67)	0.6 (0.57 - 0.64)	0.67 (0.6 - 0.76)	

Overall				
	White/no CHD	AA/ no CHD	white/CHD	AA/CHD
Mortality	1.00 (referent)	0.84 (0.83 - 0.85)	3.16 (3.04 - 3.28)	3.69 (3.53 - 3.86)
Stroke	1.00 (referent)	1.09 (1.06 - 1.13)	4.7 (4.32 - 5.12)	5.15 (4.64 - 5.7)

eGFR≥60 throughout follow-up				
	White/no CHD	AA/ no CHD	white/CHD	AA/CHD
Mortality	1.00 (referent)	0.81 (0.8 - 0.82)	3.09 (2.95 - 3.24)	3.53 (3.33 - 3.74)
Stroke	1.00 (referent)	1.06 (1.02 - 1.1)	4.42 (3.97 - 4.92)	4.93 (4.32 - 5.63)

Incident eGFR<60 during follow-up				
	White/no CHD	AA/ no CHD	white/CHD	AA/CHD
Mortality	1.00 (referent)	0.98 (0.95 - 1)	2.27 (2.11 - 2.44)	2.55 (2.37 - 2.76)
Stroke	1.00 (referent)	1.16 (1.08 - 1.24)	3.06 (2.56 - 3.65)	3.22 (2.66 - 3.89)

Overall				
	White/no stroke	AA/ no stroke	white/ stroke	AA/ stroke
Mortality	1.00 (referent)	0.83 (0.82 - 0.84)	3.95 (3.8 - 4.11)	4.23 (4.07 - 4.39)
CHD	1.00 (referent)	0.65 (0.63 - 0.67)	6.33 (5.82 - 6.88)	3.69 (3.33 - 4.09)

eGFR≥60 throughout follow-up				
	White/no CHD	AA/ no CHD	white/CHD	AA/CHD
Mortality	1.00 (referent)	0.80 (0.79 - 0.81)	4.18 (3.98 - 4.39)	4.37 (4.17 - 4.59)
CHD	1.00 (referent)	0.61 (0.59 - 0.63)	4.42 (3.97 - 4.92)	4.93 (4.32 - 5.63)

Incident eGFR<60 during follow-up				
	White/no CHD	AA/ no CHD	white/CHD	AA/CHD
Mortality	1.00 (referent)	0.97 (0.94 - 0.99)	2.32 (2.15 - 2.51)	2.48 (2.32 - 2.66)

CHD	1.00 (referent)	0.76 (0.71 - 0.82)	4.04 (3.41 - 4.79)	2.26 (1.85 - 2.75)
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CHD, coronary heart disease; AMI; acute myocardial infarction; CABG, coronary artery nypass grafting; PCI, percutaneous coronary intervention

Supplemental Table 3b: Hazard ratios and 95% confidence intervals of various outcomes associated with African American vs. white race in select subgroups of a propensity matched cohort of 937,560 patients

	All-cause Mortality	Incident ischemic strokes	Incident CHD Composite
	Hazard Ratio (95% CI)		
Age < 40	0.72 (0.67 - 0.78)	1.18 (0.98 - 1.43)	0.98 (0.82 - 1.18)
Age 40-59	0.71 (0.7 - 0.73)	0.96 (0.93 - 0.99)	0.58 (0.56 - 0.6)
Age 60-79	0.98 (0.97 - 1)	1.21 (1.15 - 1.26)	0.76 (0.72 - 0.8)
Age ≥ 80	1.06 (1.04 - 1.09)	1.61 (1.41 - 1.83)	1.18 (1.02 - 1.37)
Male	0.87 (0.86 - 0.88)	1.1 (1.07 - 1.13)	0.68 (0.66 - 0.7)
Female	0.55 (0.52 - 0.59)	1.04 (0.91 - 1.19)	0.68 (0.58 - 0.8)
CHD	1.02 (0.99 - 1.04)	1.15 (1.07 - 1.23)	-
No CHD	0.84 (0.83 - 0.85)	1.08 (1.05 - 1.12)	-
CHF	0.94 (0.92 - 0.97)	1.32 (1.2 - 1.45)	0.89 (0.8 - 0.99)
No CHF	0.84 (0.83 - 0.85)	1.07 (1.04 - 1.1)	0.66 (0.65 - 0.68)
DM	0.91 (0.89 - 0.92)	1.12 (1.08 - 1.17)	0.63 (0.6 - 0.65)
No DM	0.83 (0.82 - 0.84)	1.07 (1.04 - 1.11)	0.72 (0.69 - 0.74)
HTN	0.88 (0.87 - 0.89)	1.1 (1.07 - 1.13)	0.68 (0.66 - 0.7)
No HTN	0.78 (0.76 - 0.8)	1.06 (1 - 1.13)	0.67 (0.63 - 0.72)
eGFR <90	0.84 (0.83 - 0.85)	1.14 (1.09 - 1.18)	0.71 (0.68 - 0.74)
eGFR ≥ 90	0.85 (0.84 - 0.87)	1.02 (0.98 - 1.06)	0.63 (0.61 - 0.66)
Income < \$22000	0.9 (0.89 - 0.92)	1.15 (1.11 - 1.19)	0.72 (0.69 - 0.74)
Income ≥ \$22000	0.77 (0.75 - 0.78)	0.99 (0.95 - 1.04)	0.62 (0.59 - 0.64)

eGFR, estimated glomerular filtration rate; DM, diabetes mellitus; CHD, coronary heart disease;

CHF, chronic heart failure; HTN, hypertension.

Supplemental Table 4. Incident coronary heart disease and incident stroke outcomes associated with African American race in Cox models censored for mortality and in competing risk regression models.

	Primary events (N, %)	Competing events (deaths; N, %)	HR (95%CI) – censored for all-cause deaths	SHR (95%CI) – competing risk all-cause deaths
Unmatched				
Incident CHD events	63,808 (2.3)	507,795 (18.7)	0.70 (0.69-0.71)	0.78 (0.76-0.80)
Incident stroke	59,734 (2.1)	545,562 (19.0)	1.18 (1.16-1.21)	1.23 (1.21-1.26)
Matched				
Incident CHD events	19,115 (2.3)	130,918 (15.0)	0.63 (0.55-0.72)	0.69 (0.67-0.71)
Incident stroke	21,304 (2.4)	131,373 (15.0)	1.09 (1.06-1.12)	1.12 (1.09-1.15)

Primary events represent incident CHD events or incident stroke events, respectively. Competing events are all-cause deaths for both primary events. HR, hazard ratio; SHR, sub-hazard ratio

Supplemental Figure legends

Supplemental Figure 1. Association of African-American race with all-cause mortality in patients with eGFR ≥ 60 ml/min/1.73m² throughout follow-up (N=2,732,494).

Panel A shows association of African-American race with all-cause mortality, with various adjustments for baseline characteristics. Patients with white race served as referent. Panel B shows associations of race with all-cause mortality in patients with and without an incident coronary heart disease event. Coronary heart disease events were entered in the models as time dependent covariates, and models were estimated by including multiplicative interaction terms between race and incident coronary heart disease events. Patients with white race and no incident coronary heart disease events served as referent. Panel C shows associations of race with all-cause mortality in patients with and without an incident stroke event. Stroke events were entered in the models as time dependent covariates, and models were estimated by including multiplicative interaction terms between race and incident stroke events. Patients with white race and no incident stroke events served as referent.

Model 1: unadjusted, Model 2: adjusted for age, gender, baseline estimated glomerular filtration rate; Model 3: adjusted for Model 2 variables plus comorbidities; Model 4: adjusted for Model 3 variables plus baseline body mass index, systolic and diastolic blood pressure; Model 5: adjusted for Model 4 variables plus mean income, marital status, service connectedness, area-level housing stress, low education, low employment and persistent poverty, frequency of VA healthcare encounters, use of angiotensin converting enzyme inhibitors/angiotensin receptor blockers and statins, and receipt of influenza vaccination(s), and an indicator of each patient's VA healthcare center.

AA: African-American; CHD: coronary heart disease

Supplemental Figure 2. Association of African-American race with all-cause mortality in patients with incident eGFR <60 ml/min/1.73m² (N=328,221).

Panel A shows association of African-American race with all-cause mortality, with various adjustments for baseline characteristics. Patients with white race served as referent. Panel B shows associations of race with all-cause mortality in patients with and without an incident coronary heart disease event. Coronary heart disease events were entered in the models as time dependent covariates, and models were estimated by including multiplicative interaction terms between race and incident coronary heart disease events. Patients with white race and no incident coronary heart disease events served as referent. Panel C shows associations of race with all-cause mortality in patients with and without an incident stroke event. Stroke events were entered in the models as time dependent covariates, and models were estimated by including multiplicative interaction terms between race and incident stroke events. Patients with white race and no incident stroke events served as referent.

Model 1: unadjusted, Model 2: adjusted for age, gender, baseline estimated glomerular filtration rate; Model 3: adjusted for Model 2 variables plus comorbidities; Model 4: adjusted for Model 3 variables plus baseline body mass index, systolic and diastolic blood pressure; Model 5: adjusted for Model 4 variables plus mean income, marital status, service connectedness, area-level housing stress, low education, low employment and persistent poverty, frequency of VA healthcare encounters, use of angiotensin converting enzyme inhibitors/angiotensin receptor blockers and statins, and receipt of influenza vaccination(s), and an indicator of each patient's VA healthcare center.

AA: African-American; CHD: coronary heart disease

Supplemental Figure 3. Panel A: Association of African-American race with incident coronary heart disease and with incident acute myocardial infarctions, coronary artery bypass grafting and percutaneous coronary interventions in patients with $eGFR \geq 60$ ml/min/1.73m² throughout follow-up. Patients with white race served as referent. Panel B: Associations of race with incident coronary heart disease in patients with and without an incident stroke event, and with $eGFR \geq 60$ ml/min/1.73m² throughout follow-up. Stroke events were entered in the models as time dependent covariates, and models were estimated by including multiplicative interaction terms between race and incident stroke events. Patients with white race and no incident stroke events served as referent.

Model 1: unadjusted, Model 2: adjusted for age, gender, baseline estimated glomerular filtration rate; Model 3: adjusted for Model 2 variables plus comorbidities; Model 4: adjusted for Model 3 variables plus baseline body mass index, systolic and diastolic blood pressure; Model 5: adjusted for Model 4 variables plus mean income, marital status, service connectedness, area-level housing stress, low education, low employment and persistent poverty, frequency of VA healthcare encounters, use of angiotensin converting enzyme inhibitors/angiotensin receptor blockers and statins, and receipt of influenza vaccination(s), and an indicator of each patient's VA healthcare center.

AA: African-American

Supplemental Figure 4. Panel A: Association of African-American race with incident coronary heart disease and with incident acute myocardial infarctions, coronary artery bypass grafting and percutaneous coronary interventions in patients with incident $eGFR < 60$ ml/min/1.73m². Patients with white race served as referent. Panel B: Associations of race with incident coronary heart

disease in patients with and without an incident stroke event, and with incident eGFR <60 ml/min/1.73m². Stroke events were entered in the models as time dependent covariates, and models were estimated by including multiplicative interaction terms between race and incident stroke events. Patients with white race and no incident stroke events served as referent.

Model 1: unadjusted, Model 2: adjusted for age, gender, baseline estimated glomerular filtration rate; Model 3: adjusted for Model 2 variables plus comorbidities; Model 4: adjusted for Model 3 variables plus baseline body mass index, systolic and diastolic blood pressure; Model 5: adjusted for Model 4 variables plus mean income, marital status, service connectedness, area-level housing stress, low education, low employment and persistent poverty, frequency of VA healthcare encounters, use of angiotensin converting enzyme inhibitors/angiotensin receptor blockers and statins, and receipt of influenza vaccination(s), and an indicator of each patient's VA healthcare center.

AA: African-American

Supplemental Figure 5. Panel A: Association of African-American race with incident ischemic strokes in patients with eGFR ≥ 60 ml/min/1.73m² throughout follow-up. Patients with white race served as referent. **Panel B:** Associations of race with incident stroke in patients with and without an incident coronary heart disease event, and with eGFR ≥ 60 ml/min/1.73m² throughout follow-up. Coronary heart disease events were entered in the models as time dependent covariates, and models were estimated by including multiplicative interaction terms between race and incident coronary heart disease events. Patients with white race and no incident coronary heart disease events served as referent.

Model 1: unadjusted, Model 2: adjusted for age, gender, baseline estimated glomerular filtration rate; Model 3: adjusted for Model 2 variables plus comorbidities; Model 4: adjusted for Model 3 variables plus baseline body mass index, systolic and diastolic blood pressure; Model 5: adjusted for Model 4 variables plus mean income, marital status, service connectedness, area-level housing stress, low education, low employment and persistent poverty, frequency of VA healthcare encounters, use of angiotensin converting enzyme inhibitors/angiotensin receptor blockers and statins, and receipt of influenza vaccination(s), and an indicator of each patient's VA healthcare center.

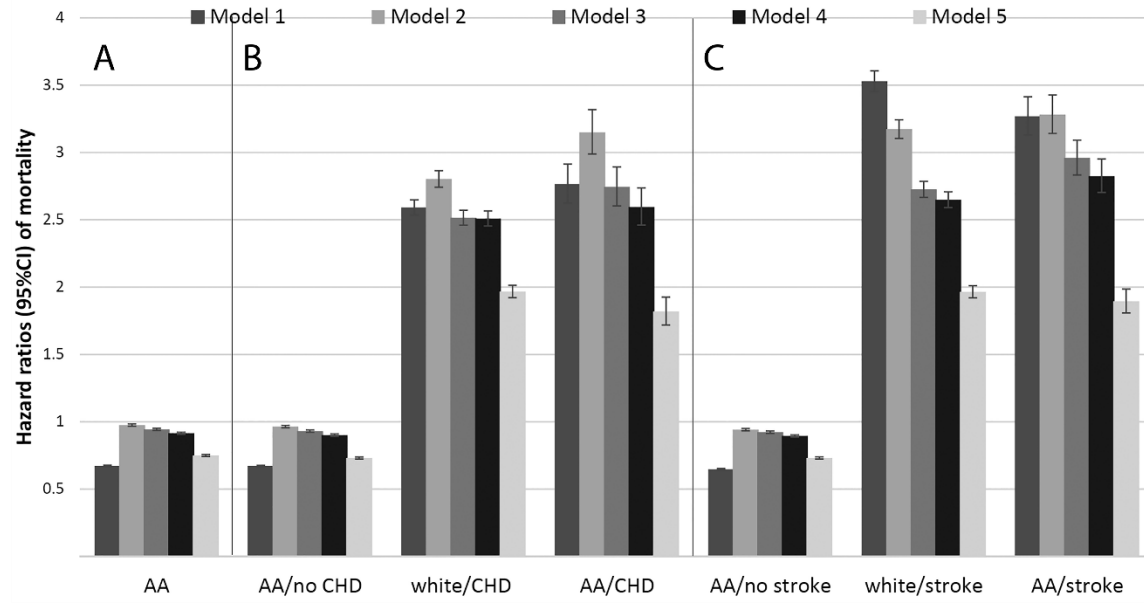
AA: African-American

Supplemental Figure 6. Panel A: Association of African-American race with incident ischemic strokes in patients with incident eGFR <60 ml/min/1.73m². Patients with white race served as referent. Panel B: Associations of race with incident stroke in patients with and without an incident coronary heart disease event, and with incident eGFR <60 ml/min/1.73m². Coronary heart disease events were entered in the models as time dependent covariates, and models were estimated by including multiplicative interaction terms between race and incident coronary heart disease events. Patients with white race and no incident coronary heart disease events served as referent.

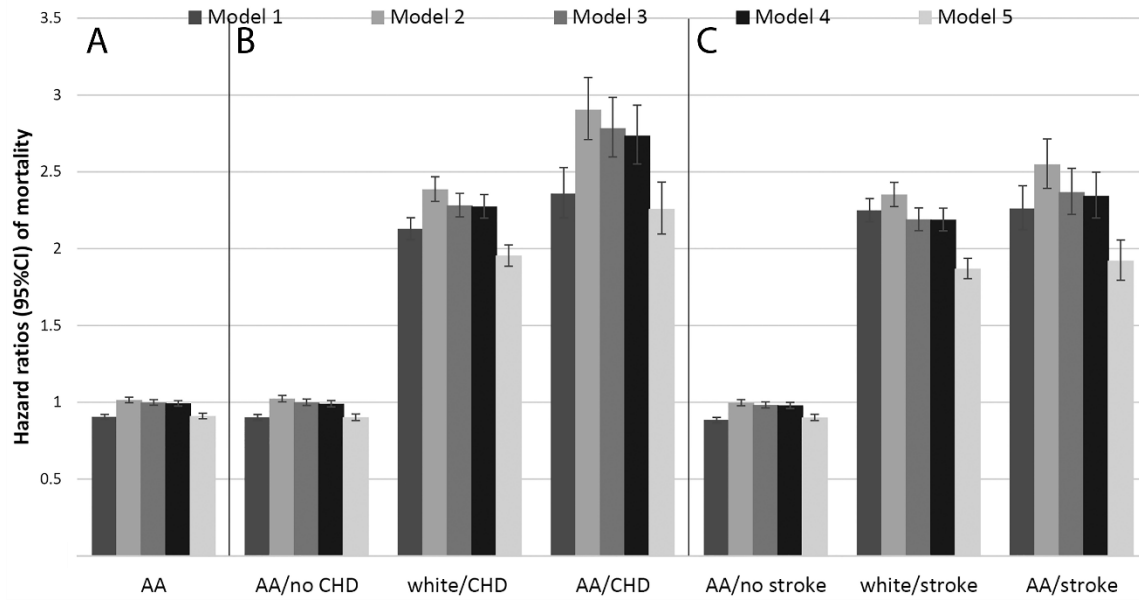
Model 1: unadjusted, Model 2: adjusted for age, gender, baseline estimated glomerular filtration rate; Model 3: adjusted for Model 2 variables plus comorbidities; Model 4: adjusted for Model 3 variables plus baseline body mass index, systolic and diastolic blood pressure; Model 5: adjusted for Model 4 variables plus mean income, marital status, service connectedness, area-level housing stress, low education, low employment and persistent poverty, frequency of VA

healthcare encounters, use of angiotensin converting enzyme inhibitors/angiotensin receptor blockers and statins, and receipt of influenza vaccination(s), and an indicator of each patient's VA healthcare center.

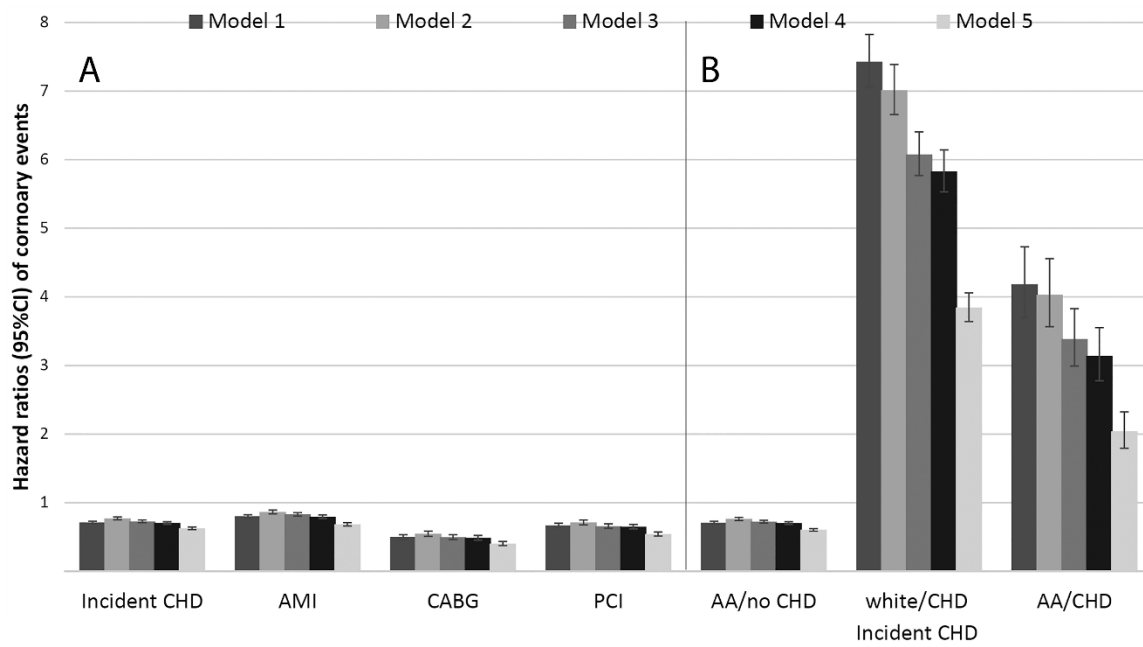
AA: African-American



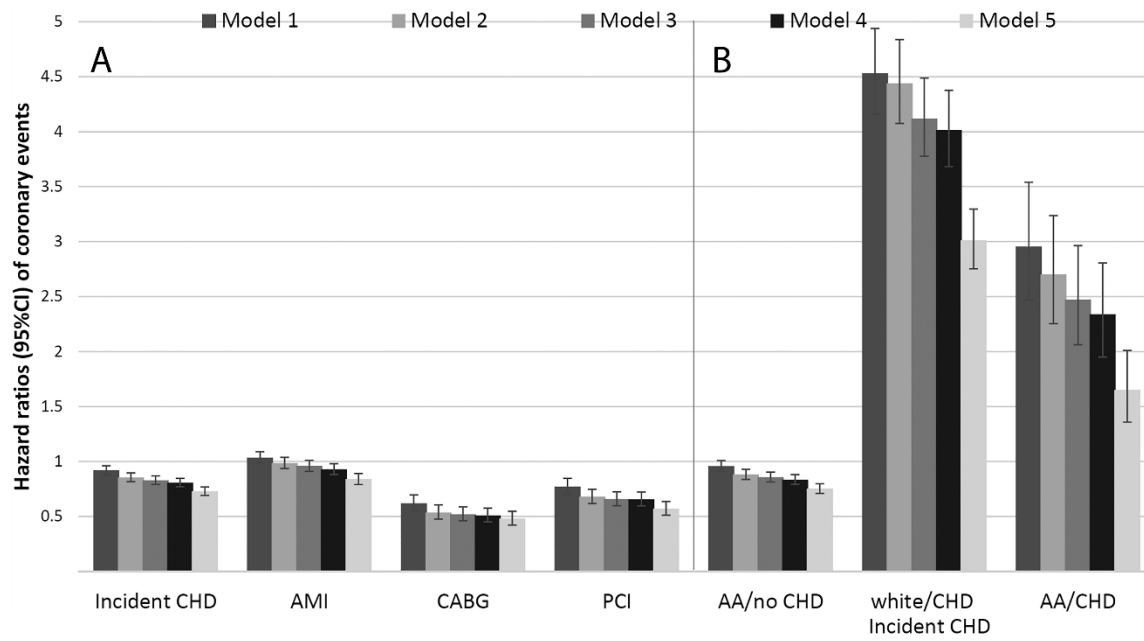
Supplemental Figure 1



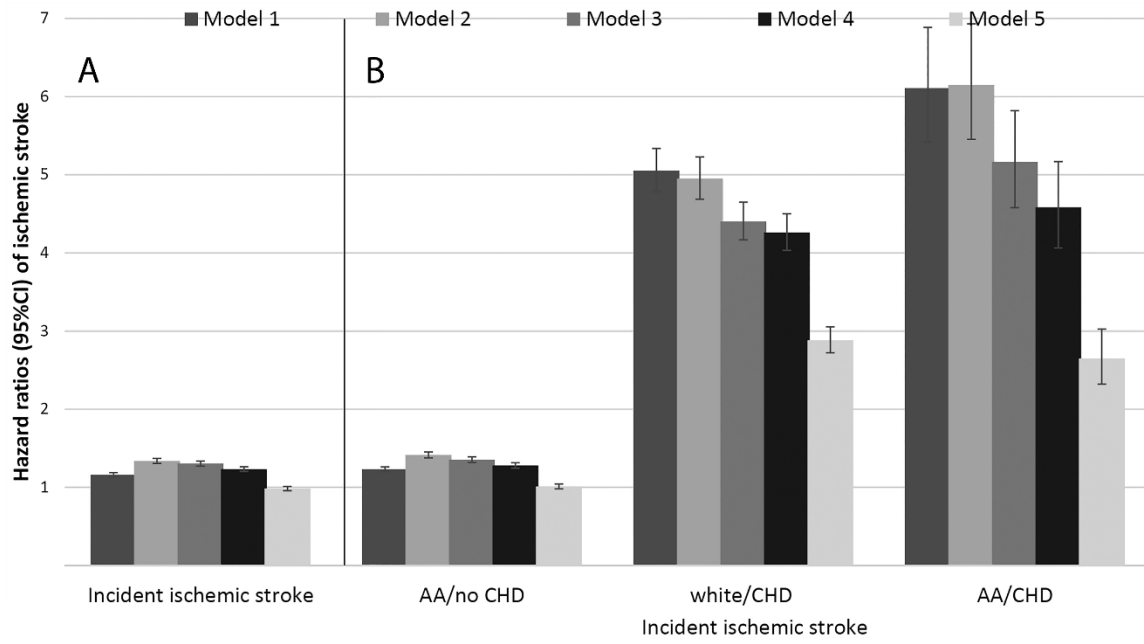
Supplemental Figure 2



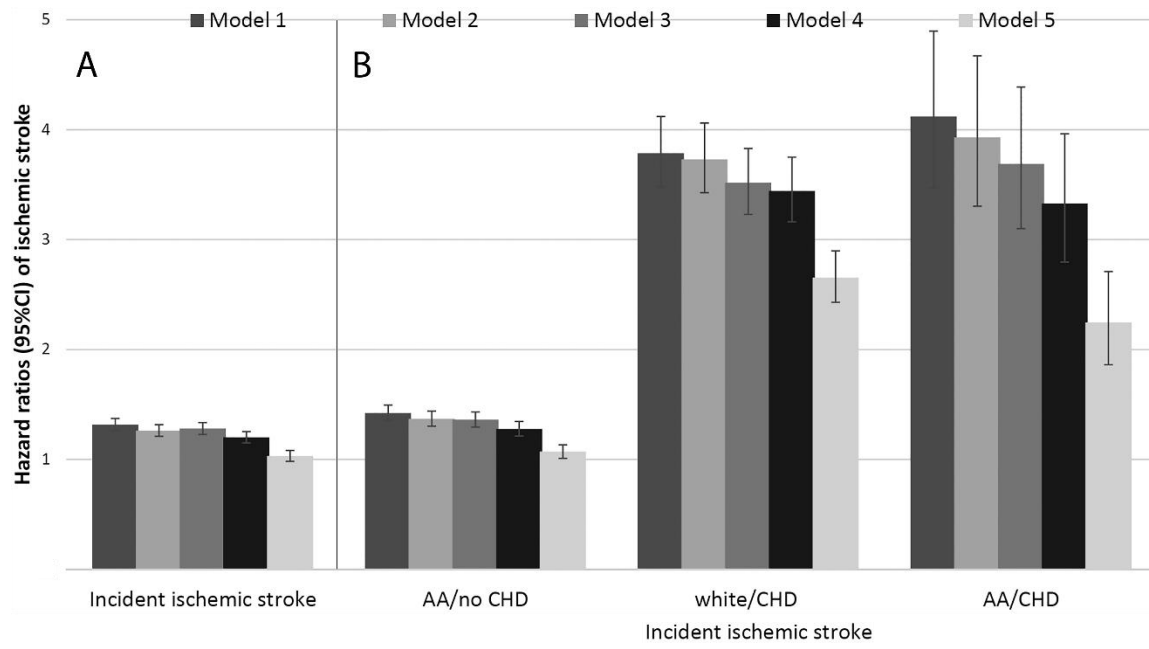
Supplemental Figure 3



Supplemental Figure 4



Supplemental Figure 5



Supplemental Figure 6