Racial and Ethnic Differences in Mortality among Individuals with Chronic Kidney Disease: Results from the Kidney Early Evaluation Program (KEEP)

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Summary
Background and objectives Chronic kidney disease (CKD) is prevalent in minority populations and racial/ethnic differences in survival are incompletely understood.

Design, setting, participants, & measurements Secondary analysis of Kidney Early Evaluation Program participants from 2000 through 2008 with CKD, not on dialysis, and without previous kidney transplant was performed. Self-reported race/ethnicity was categorized into five groups: non-Hispanic white, African American, Asian, American Indian/Alaska Native, and Hispanic. CKD was defined as a urinary albumin to creatinine ratio of ≥30 mg/g among participants with an estimated GFR (eGFR) ≥60 ml/min per 1.73 m² or an eGFR of <60 ml/min per 1.73 m². The outcome was all-cause mortality. Covariates used were age, sex, obesity, diabetes, hypertension, albuminuria, baseline eGFR, heart attack, stroke, smoking, family history, education, health insurance, geographic region, and year screened.

Results 19,205 participants had prevalent CKD; 55% (n = 10,560) were White, 27% (n = 5237) were African American, 9% (n = 1638) were Hispanic, 5% (n = 951) were Asian, and 4% (n = 813) were American Indian/Alaska Native. There were 1043 deaths (5.4%). African Americans had a similar risk of death compared with Whites (adjusted Hazard Ratio (AHR) 1.07, 95% CI 0.90 to 1.27). Hispanics (AHR 0.66, 95% CI 0.50 to 0.94) and Asians (AHR 0.63, 95% CI 0.41 to 0.97) had a lower mortality risk compared with Whites. In contrast, American Indians/Alaska Natives had a higher risk of death compared with Whites (AHR 1.41, 95% CI 1.08 to 1.84).

Conclusions Significant differences in mortality among some minority groups were found among persons with CKD detected by community-based screening.


Introduction
Chronic kidney disease (CKD) affects over 10% of the U.S. population and is a burgeoning public health problem (1–3). Considerable racial and ethnic disparities exist in the prevalence of CKD and end-stage renal disease (ESRD) (4–6). Additionally, CKD has been consistently shown to be an independent risk factor for mortality (7,8).

Few studies have evaluated the association of race/ethnicity with mortality among those with CKD not on dialysis (9). Some studies show a survival advantage among blacks compared with whites with very late stage CKD (10) or among those insured (11). Others have found a similar adjusted mortality for blacks, whites, and Hispanics with CKD, although subgroup analyses revealed a higher mortality for younger blacks in comparison with whites (12). Overall mortality for blacks is higher than that for whites in the general population (13–15). In contrast, among the Hispanic population, there is the finding of lower mortality despite a greater number of risk factors in what has been termed the “Hispanic Paradox” (16). This has been shown among Hispanic patients with CKD as well (17). Few studies have looked at the American Indian/Alaska Native or Asian populations (18–20).

Using a large racially/ethnically diverse screened study population from the Kidney Early Evaluation Program (KEEP), we investigated the associations between race/ethnicity and risk for all-cause mortality among those with prevalent CKD. We then adjusted for important factors that might confound any differences observed. We further categorized participants as having early (stages 1 to 2) or later (stages 3 to 5) CKD, according to the current recommended staging system, and repeated analyses within each stratum (21). Understanding racial/ethnic differences in mortality among those with CKD can help focus future research and may lead to the targeted development of novel prevention and management strategies to improve outcomes.

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Materials and Methods

KEEP Study Population

KEEP is a free, community-based, voluntary screening program designed to detect CKD, to identify individuals at increased risk for kidney disease, and to encourage follow-up care (22). The KEEP definition for increased risk for kidney disease is persons with either a personal diagnosis of diabetes or hypertension, or with a family history of diabetes, hypertension, or kidney disease. KEEP screenings are conducted in urban and rural locations throughout the United States through each state’s local National Kidney Foundation affiliate (22). Officially launched nationwide in August 2000, KEEP has screened more than 128,000 participants.

Screening Protocol

Screening data were collected on participant demographic characteristics, personal and family medical history, and health behaviors (22). One-time systolic and diastolic BP measurements and height and weight measurements were obtained (22). Blood and urine specimens were collected and processed to determine serum creatinine, fasting blood glucose, and urine albumin levels (22). Serum creatinine values for KEEP participants were calibrated against values measured at the Cleveland Clinic Research Laboratory using the Roche enzymatic assay. Subsequently, eGFR using the original (raw) serum creatinine value was recalculated using the four-variable Modification of Diet in Renal Disease (MDRD) Study equation with the newly calibrated serum creatinine values (23,24). Spot urine specimens were collected and tested semiquantitatively for urine albumin levels, using Micral assay (Roche Pharmaceuticals, Indianapolis) until September 2001. Since then, they have been analyzed with the Clinitek assay (Bayer Diagnostics, Tarrytown, PA) (22).

CKD-Albuminuria and Reduced eGFR

Albuminuria, or early stage CKD, is defined as a urinary albumin to creatinine ratio (ACR) of ≥30 mg/g among participants with eGFR ≥60 ml/min per 1.73 m², corresponding to CKD stages 1 to 2 according to current Kidney Disease Outcomes Quality Initiative guidelines (21). Reduced eGFR, or later stage CKD, is defined as an eGFR of <60 ml/min per 1.73 m², equivalent to CKD stages 3 to 5 (21).

CKD Study Population

In this study, we evaluated only those participants screened from August 2000 to December 2008 (total \( n = 122,716 \)). Of these, we included those who were aged at least 18 years, with a self-reported diagnosis of diabetes or hypertension, or with a family history of diabetes, hypertension, or kidney disease (\( n = 107,309 \)). Participants who had undergone kidney transplant or were on regular dialysis treatment were excluded from this analysis (\( n = 85 \)), leaving an eligible KEEP study population of 107,224 participants. Subsequently, we excluded 13,405 participants with missing serum creatinine and 1763 participants with missing race/ethnicity data or who self-identified as non-Hispanic/other race. Of the 92,056 participants remaining, a total of 77,298 participants (84%) had data for all variables of interest. Next from that group, 25% (\( n = 19,205 \)) had CKD as defined above, thus constituting our study population (Figure 1).

Predictor Variables and Covariates

Race and ethnicity information was obtained by self-report at the time of KEEP screening and was categorized into five racial/ethnic groups: non-Hispanic white, African American, Asian, American Indian/Alaska Native, and Hispanic. Persons of Hispanic origin may be of any race. The other four racial categories, white, African American, Asian, American Indian/Alaska Native, did not include persons who reported Hispanic origin. In the paper we use the terms whites and non-Hispanic whites, and blacks and African Americans, interchangeably.

Potential covariates were determined a priori as characteristics well described to influence CKD and mortality risk: age, sex, obesity, diabetes, hypertension, and smoking; family history of diabetes, hypertension, or kidney disease; educational level and presence of health insurance; and geographic region. Age was determined by self-reported date of birth at the time of screening. Obesity was defined as body mass index ≥30 kg/m². Diabetes was defined as a history of diabetes (self-report or retinopathy), use of medications to treat diabetes, or fasting blood glucose level ≥126 mg/dl or nonfasting blood glucose level ≥200 mg/dl in the absence of self-report or medication use (25). Hypertension was defined by participant self-report or by systolic BP ≥130 mmHg or diastolic BP ≥80 mmHg since all participants in this analysis had CKD (21).

Smoking status was self-reported and categorized as current/former versus never. Family history of diabetes, hypertension, and kidney disease were determined by participant self-report of having a first-degree relative with the condition. Educational level was self-reported and dichotomized as less than high school or high school equivalent and higher. Health insurance status was determined by the participant’s report at the time of screening. To account for potential regional differences in CKD by race/ethnicity, we categorized the United States into the four defined census geographic regions: Northeast, Midwest, South, and West (26).

Additional covariates included were albuminuria, cardiovascular comorbidity, and baseline eGFR as they are important and could influence CKD and mortality risk. Albuminuria status was categorized as microalbuminuria (30 to 299 mg/g) and macroalbuminuria (≥300 mg/g). Cardiovascular comorbidities were defined as self-report of a history of heart attack or stroke. Our results did not change and so we present the fully adjusted models.

Mortality

Our outcome variable was all-cause mortality, determined using a previously validated multilevel tracking system by the Chronic Disease Research Group at Minneapolis Medical Research Foundation, Hennepin County Medical Center. This system is capable of using name and social security number data and incident ESRD patient records with cross-checks against the U.S. Medicare database and the Social Security Administration Death Files.
To calculate death rates, we defined follow-up time from the KEEP screening date until censoring at May 31, 2009, or the date of death.

Statistical Analyses

We used a complete-case analysis approach in which we analyzed participants with available data for all covariates of interest. Of the 92,056 participants available, a total of 77,298 participants (84%) had data for all variables of interest. Demographics were similar for included and excluded participants, except that participants excluded because of missing values (n = 14,758) had slightly higher prevalence of diabetes (31% versus 28%) and hypertension (60% versus 54%). Of the 14,758 excluded, 44% self-reported their race/ethnicity as white, 34% as African American, 14% as Hispanic, 5% as Asian, and 3% as American Indian/Alaska Native; relative to the overall KEEP registry, African Americans and Hispanics were disproportionately excluded.

We compared demographics and clinical characteristics by race/ethnicity using ANOVA or chi-squared analyses as appropriate. We calculated mortality rates (per 1000 person-years) by race/ethnicity for all participants with CKD, and then separately for early and later stage CKD. Additionally, to explore the effect of age, we dichotomized age <65 versus ≥65 years and calculated the death rates by race/ethnicity for all participants with CKD for these subgroups.

We conducted multivariate Cox proportional hazards regression analyses to determine the association of race/ethnicity with all-cause mortality among all participants with CKD, and then separately among those with early and later stage CKD. All covariates were included in the multivariate analyses.

Statistical analyses were performed with the SAS statistical package (release 9.1; SAS Institute Inc., Cary, NC). Cleveland Clinic Institutional Review Board (IRB) approved this study. The Hennepin County Medical Center

Figure 1. Flow diagram illustrating how the cohort was built for analyses for this study.
IRB approved the KEEP program, including research protocol, process of obtaining informed consent, and data management procedures related to KEEP.

**Results**

Of the 19,205 KEEP participants from 2000 through 2008 with prevalent CKD, 55% ($n = 10,560$) self-reported their race/ethnicity as white, 27% ($n = 5237$) as African American, 9% ($n = 1638$) as Hispanic, 5% ($n = 951$) as Asian, and 4% ($n = 813$) as American Indian/Alaska Native. The overall mean age was 60 years, most participants were women, the vast majority had hypertension, and nearly half had diabetes (Table 1). Whites were the oldest group on average, American Indian/Alaska Natives had highest prevalence of obesity and diabetes, and African Americans had the highest hypertension prevalence. Whites were more likely to be included because of low eGFR and the other groups more likely to be included because of albuminuria.

Among our study population with CKD, 1043 deaths (23 per 1000 person-years) occurred, of which 214 deaths were among those with albuminuria (16 per 1000 person-years) and 829 deaths (28 per 1000 person-years) were among those with a reduced eGFR <60 ml/min per 1.73 m². American Indians/Alaska Natives had the highest unadjusted death rates compared with all other race/ethnic groups in each category of CKD (Figure 2). Conversely, Hispanics had the lowest death rates in each CKD category (Figure 2). In subgroup analyses, results were similar. For the <65 years subgroup, deaths per 1000-person years was 7 for whites, 7 for African Americans, 4 for Hispanics, 6 for Asians, and 14 for American Indian/Alaska Natives. For the ≥65 years subgroup, deaths per 1000-person years was 26 for whites, 26 for African Americans, 18 for Hispanics, 17 for Asians, and 40 for American Indian/Alaska Natives.

African Americans had a similar risk of death compared with whites in each CKD category after adjustment for age, sex, clinical and socioeconomic factors, geographic region, and year screened (Table 2). However, American Indian/Alaska Natives had a 43% increased hazard ratio risk of death compared with whites after adjustment (Table 2). Results were similar for any CKD and early versus later

**Table 1. Baseline demographic characteristics of participants with chronic kidney disease, by race/ethnicity, Kidney Early Evaluation Program, 2000 through 2008**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>White (n = 10,560)</th>
<th>African American (n = 5237)</th>
<th>Hispanic (n = 1638)</th>
<th>Asian (n = 957)</th>
<th>American Indian/Alaska Native (n = 813)</th>
<th>p^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years], mean^b</td>
<td>65 (14)</td>
<td>59 (14)</td>
<td>56 (15)</td>
<td>61 (13)</td>
<td>58 (16)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Female, %</td>
<td>69</td>
<td>73</td>
<td>68</td>
<td>57</td>
<td>74</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Obesity, %</td>
<td>43</td>
<td>57</td>
<td>48</td>
<td>24</td>
<td>59</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>40</td>
<td>42</td>
<td>44</td>
<td>45</td>
<td>51</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>89</td>
<td>92</td>
<td>84</td>
<td>86</td>
<td>83</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Microalbuminuria, % c</td>
<td>33</td>
<td>55</td>
<td>54</td>
<td>51</td>
<td>53</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Macroalbuminuria, % c</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>6</td>
<td>11</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>eGFR &lt;60%, %</td>
<td>78</td>
<td>56</td>
<td>55</td>
<td>60</td>
<td>58</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Baseline eGFR, mean^b</td>
<td>56 (18)</td>
<td>68 (28)</td>
<td>69 (28)</td>
<td>64 (24)</td>
<td>67 (29)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Heart attack, %</td>
<td>12</td>
<td>9</td>
<td>8</td>
<td>8</td>
<td>11</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Stroke, %</td>
<td>8</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>8</td>
<td>0.33</td>
</tr>
<tr>
<td>Current or former smoker, %</td>
<td>44</td>
<td>43</td>
<td>36</td>
<td>31</td>
<td>56</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Family history of, % diabetes</td>
<td>52</td>
<td>62</td>
<td>65</td>
<td>51</td>
<td>74</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>74</td>
<td>82</td>
<td>72</td>
<td>71</td>
<td>71</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>18</td>
<td>22</td>
<td>21</td>
<td>15</td>
<td>25</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>High school education or higher, %</td>
<td>88</td>
<td>81</td>
<td>63</td>
<td>80</td>
<td>73</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Health insurance, yes, %</td>
<td>92</td>
<td>83</td>
<td>63</td>
<td>80</td>
<td>72</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Region, %</td>
<td>92</td>
<td>92</td>
<td>92</td>
<td>92</td>
<td>92</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Note: total, n = 19,205. The racial categories did not include persons who reported Hispanic origin, and persons of Hispanic origin may be of any race. eGFR, estimated glomerular filtration rate (ml/min per 1.73 m²).

^bMean ± SD.

^cExcluding missing values for percentage.


References:

CKD in each group except among Asians where there was a significantly lower risk of death among those with albuminuria (Table 2). In a final sensitivity analysis limiting the analyses to those with eGFR $\geq 45$ ($n = 3063$), our results were essentially unchanged for African Americans (hazard ratio [HR] 1.00, 95% confidence interval [CI] 0.73 to 1.37), Asians (HR 0.43, 95% CI 0.18 to 1.01), and American Indian/Alaska Natives (HR 1.37, 95% CI 0.87 to 2.16). For Hispanics the association was weakened (HR 0.87, 95% CI 0.50 to 1.54).

Discussion

We examined differences in mortality by race/ethnicity among those with prevalent CKD detected at a community-based voluntary screening. We found that risk of death was similar among African Americans, lower for Hispanics and Asians, and considerably higher for American Indians/Alaska Natives compared with that of whites. This pattern persisted in the subgroup analyses among those <65 and $\geq 65$ years of age. A similar pattern of racial/ethnic differences in mortality risk existed among those with albuminuria and eGFR $\geq 60$ ml/min per 1.73 m$^2$, or early stage CKD, and for those with eGFR <60 ml/min per 1.73 m$^2$, or later stage CKD. These differences persisted, even after adjustment for possible confounders such as age, sex, obesity, diabetes, hypertension, education, insurance status, as well as region and year screened. Our age-stratified death rates were consistent with our adjusted results. Given that the racial/ethnic minority and the CKD populations in the United States are growing, our study underscores the importance of having a national CKD surveillance system to track and elucidate patterns of disease, understand mechanisms of disease progression, and help create programs to improve outcomes for all (28).

Table 2. Adjusted hazards ratios of risk of death for participants with chronic kidney disease, by race/ethnicity, Kidney Early Evaluation Program, 2000 through 2009

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>CKD ($n = 19,205$)</th>
<th>Albuminuria and eGFR $\geq 60$ ($n = 6068$)</th>
<th>eGFR &lt;60 ($n = 13,137$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>African American</td>
<td>1.07 (0.90 to 1.27)</td>
<td>1.08 (0.78 to 1.49)</td>
<td>1.03 (0.84 to 1.27)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.66 (0.50 to 0.94)</td>
<td>0.52 (0.27 to 1.01)</td>
<td>0.70 (0.45 to 1.07)</td>
</tr>
<tr>
<td>Asian</td>
<td>0.63 (0.41 to 0.97)</td>
<td>0.44 (0.20 to 0.99)$^b$</td>
<td>0.71 (0.41 to 1.20)</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>1.41 (1.08 to 1.84)$^b$</td>
<td>1.22 (0.73 to 2.03)</td>
<td>1.37 (0.99 to 1.89)</td>
</tr>
</tbody>
</table>

Note: KEEP censored on May 31, 2009. CKD, chronic kidney disease; CI, confidence interval; eGFR, estimated glomerular filtration rate (ml/min per 1.73 m$^2$); KEEP, Kidney Early Evaluation Program.

$^a$Adjusted for age, sex, obesity, diabetes mellitus, hypertension, albuminuria (macroalbuminuria only for albuminuria and eGFR $\geq 60$ group), baseline eGFR, heart attack, stroke, smoking status, family history of diabetes mellitus, family history of hypertension, family history of CKD, education level, presence of health insurance, region where screened, and year screened.

$^bP < 0.05$. 

Figure 2. | Racial/ethnic differences in death rates among participants with chronic kidney disease, Kidney Early Evaluation Program, 2000 through 2009.
Mortality was highest among the American Indian/Alaska Native population with CKD, even after adjustment for their greater risk factor burden. Exact reasons for this higher mortality risk are unclear. One possibility is an increased burden of a multitude of chronic diseases, such as obesity, diabetes, cardiovascular disease, and liver disease (29,30). Importantly, the American Indian/Alaska Native population is made up of over 500 federally recognized tribes, and there are substantial regional differences in the prevalence of diseases (19, 31–34). We attempted to account for obesity, diabetes, and hypertension in our adjustments; however, we cannot account for severity of disease, all comorbidities, or all regional differences. Thus, it may be that certain subgroups of this broad population are driving the higher mortality that we cannot capture in our analyses.

We found a lower mortality among Hispanics with CKD. This is consistent with the literature on the existence of a “Hispanic paradox,” describing their high chronic disease risk factor profile yet lower mortality compared with whites (16,35–36). Recently, a first-ever life expectancy report for the U.S. Hispanic population was released, showing higher life expectancy compared with whites and blacks (37). Additionally, among an insured Hispanic population with CKD, Peralta et al. found a higher risk of development of ESRD and a lower mortality compared with whites (17). Hispanics with ESRD on dialysis have generally had better prognosis than their white counterparts (38–40). We were unable to look at subgroups within the Hispanic population, and there may be heterogeneity in findings based upon country of origin (41).

We did not find mortality differences among African Americans and whites in this screened cohort, similar to a population level study which also found no difference in the overall cohort, although black individuals who were younger than 65 years were distinct and found to be 78% more likely to die than white individuals (12). Our study was consistent with findings from an insured population (11). Although there are similarities between the NHANES and KEEP populations, KEEP is an enriched sample by nature of the target population for screening (27). Observed socioeconomic differences, such as education level and health insurance status, between African Americans and whites are narrower in KEEP than in society at large. Over 80% of African Americans in KEEP reported having health insurance; our findings thus may indicate that racial differences in CKD outcomes could narrow or disappear with equalization of socioeconomic status and access to care. Nonetheless, African Americans with CKD do have an elevated ESRD risk that is incompletely understood (4).

We found a significantly lower risk of death among Asians compared with whites, especially among those with early CKD. Prior studies found that overall Asians have a similar or better life expectancy than whites (9). Additionally, there is heterogeneity in the Asian population by country of origin that is not accounted for in our analyses (20). It is unclear if our findings are unique to CKD or due to the Asian population’s lower risk overall.

There are clear strengths to this study, such as its inclusion of Asian and American Indian/Alaska Native populations, its national scope and perspective, its contemporary status, extending 2000 through 2008, and the participants being almost universally insured. However, there are also several limitations. We cannot determine causality or account for changes in CKD status or risk factors over time. In KEEP, as with other epidemiologic studies, CKD diagnosis is made on a single sample, rather than the repeated measures as currently recommended in clinical practice. Our cohort is derived from a group of voluntary, screened participants, of which more than 68% were women. We categorized participants according to their self-identified race/ethnicity status into one of five major racial/ethnic categories; however, the groups themselves are heterogeneous and we cannot account for differences in subgroups among them. We did not have complete data on all KEEP participants from which the study population was derived. There could also be an effect of misclassification of early CKD as determination was made by a single urine sample. Our outcome is all-cause mortality, and we do not have access to cause-specific mortality or other relevant outcomes. At this time, we have inadequate data to evaluate the incidence and survival of ESRD among KEEP participants; however, in prior studies racial/ethnic minorities with ESRD have had better survival than whites with ESRD (42–44).

Using a large, diverse screened population, we found racial/ethnic differences in the risk of death among those with CKD. Future studies are needed to explore these differences among racial/ethnic subgroups in more depth, such as influences of neighborhood or census tract, racial/ethnic heterogeneity, disease progression, and disease-specific mortality.

Acknowledgments

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Disclosures

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