Racial/Ethnic Differences in the Prevalence of Proteinuric and Nonproteinuric Diabetic Kidney Disease

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OBJECTIVE—To examine racial/ethnic differences in the prevalence of diabetic kidney disease (DKD), with and without proteinuria, in an outpatient health care organization.

RESEARCH DESIGN AND METHODS—We examined electronic health records for 15,683 persons of non-Hispanic white (NHW), Asian (Asian Indian, Chinese, and Filipino), Hispanic, and non-Hispanic black (NHB) race/ethnicity with type 2 diabetes and no prior history of kidney disease from 2008 to 2010. We directly standardized age- and sex-adjusted prevalence rates of proteinuric DKD (proteinuria with or without low estimated glomerular filtration rate [eGFR]) or nonproteinuric DKD (low eGFR alone). We calculated sex-specific odds ratios of DKD in racial/ethnic minorities (relative to NHWs) after adjustment for traditional DKD risk factors.

RESULTS—Racial/ethnic minorities had higher rates of proteinuric DKD than NHWs (24.8–37.9 vs. 24.8%) and lower rates of nonproteinuric DKD (6.3–9.8 vs. 11.7%). On adjusted analyses, Chinese (odds ratio 1.39 for women and 1.56 for men), Filipinos (1.57 for women and 1.34 for men), and NHBs (1.50 for women and 1.55 for men) exhibited significantly (P<0.05) higher odds of proteinuric DKD than NHWs. Conversely, Chinese, Hispanic, and NHB women and Hispanic men had significantly lower odds of nonproteinuric DKD than NHWs.

CONCLUSIONS—We found novel racial/ethnic differences in DKD among patients with type 2 diabetes. Racial/ethnic minorities were more likely to have proteinuric DKD and less likely to have nonproteinuric DKD. Future research should examine diverse DKD-related outcomes by race/ethnicity to inform targeted prevention and treatment efforts and to explore the etiology of these differences.

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Diabetic kidney disease (DKD), defined broadly as persistent proteinuria and/or low estimated glomerular filtration rate (eGFR) (<60 mL/min/1.73 m²) in patients with diabetes (1), is the single leading cause of end-stage renal disease (ESRD) in the U.S. (2). Although only a small fraction of patients with type 2 diabetes progress to ESRD (3), type 2 diabetes is widely prevalent in adults (4), and thus, a majority of patients starting on dialysis have type 2 diabetes.

Conventional wisdom has suggested that the natural history of DKD begins with the onset of proteinuria (microalbuminuria followed by macroalbuminuria) followed by a decrease in eGFR and eventually ESRD. However, over the last decade several observational studies have demonstrated that between one-third and one-half of patients with type 2 diabetes and low eGFR do not have proteinuria (5–7). The pathogenesis for these patients is still controversial, but possibilities for this clinical picture include the following: classic diabetic nephropathy treated effectively with renin-angiotensin system inhibition, hypertensive nephrosclerosis, cholesterol microemboli, renovascular disease, or tubulo-interstitial fibrosis. Patients with type 2 diabetes and low eGFR without proteinuria progress at a slower rate to ESRD than patients with proteinuria, but the risks of cardiovascular disease (CVD) and other sequelae of chronic kidney disease (CKD) are still high in this population (8,9). Moreover, while risk factors for proteinuric or classic DKD are well-known, nonproteinuric DKD is less well described (9). Therefore, examining rates of clinically important DKD requires analysis of both proteinuria and low eGFR.

Racial/ethnic differences have been reported in the prevalence of DKD and in associated cases of ESRD. Compared with the prevalence in Caucasians, the prevalence of DKD is approximately two- to threefold higher in African Americans, Hispanics (10–13), and Asians (2,14) and up to 18-fold higher in Native Americans (15). Racial/ethnic differences in prevalence rates also vary depending on the definition of DKD (e.g., proteinuria versus low eGFR) (16) and whether races are subdivided or considered in aggregate (2,14,17–19).

Asian Americans are the fastest growing racial/ethnic groups in the U.S. (20) and have a higher prevalence of diabetes than Caucasians and most other racial/ethnic minority groups in the U.S. (21). The largest Asian subgroups in the U.S. are Asian Indian, Chinese, and Filipino (22). There are differences in prevalence of risk factors for DKD among these Asian American subgroups, with higher rates of obesity in Asian Indians and Filipinos, higher rates of hypertension in Filipinos, and higher rates of smoking in Filipinos relative to other Asian subgroups (23). Despite population growth and greater...
intraracial diversity than any other racial/ethnic groups, we are aware of no comparative data on the prevalence of different manifestations of DKD (proteinuria or low eGFR) among Asian American racial subgroups. Moreover, few epidemiologic studies have carefully examined prevalence and correlates of DKD in Asians (14,19). Using a large, diverse sample of primary care patients with type 2 diabetes in a managed-care setting, we investigated racial/ethnic differences in the prevalence and correlates of DKD among Asian Indians, Chinese, and Filipinos compared with other racial/ethnic groups. We hypothesized that there would be wide variation in the prevalence of manifestations of DKD among Asian subgroups, with higher rates of proteinuric DKD in Filipinos, given associated risk factors.

**RESEARCH DESIGN AND METHODS**

**Study setting**
We conducted this study in a mixed-payer, outpatient health care organization serving ~800,000 active patients in the San Francisco Bay area of northern California. The demographic characteristics of the clinical population are similar to those of residents in the underlying service area in northern California (Alameda, San Mateo, and Santa Clara counties) for race/ethnicity and age distribution, but the clinical population has a slightly higher proportion of women, non-Hispanic whites (NHWs), and Asians and a lower proportion of blacks/African Americans and Hispanic/Latinos. The patient population is insured (58% PPO, 23% HMO, 16% Medicare, 2% self-payer, and 1% Medicaid) and thus under-represents the medically underserved.

**Study design**
We studied a 3-year, cross-sectional sample of patients in the EpicCare electronic health record (EHR) system (24) and identified 15,683 persons with type 2 diabetes, 35 years of age or older, who had primary care activity between 1 January 2008 and 31 December 2010. The overall prevalence of diabetes in our clinical population was 7.9% (21). We excluded patients with type 1 diabetes or patients with evidence of kidney disease (proteinuria, low eGFR, or other kidney conditions such as kidney failure) prior to a diagnosis of type 2 diabetes. We extracted data on demographics, anthropometric measures, physician diagnoses, laboratory results, and medication orders from the EHR. We included persons identified as NHW, Asian Indian, Chinese, Filipino, Hispanic, or Non-Hispanic black (NHB) through self-report (25) (72.7%) or by name analysis (27.3%) (26). Japanese, Korean, and Vietnamese and other racial/ethnic groups were excluded owing to small sample sizes. We deidentified all datasets analyzed by the research team according to Health Insurance Portability and Accountability Act standards and did not contact any patients for the study. This study was approved by the Palo Alto Medical Foundation Institutional Review Board.

**Measures: type 2 diabetes**
We identified persons with type 2 diabetes using physician-recorded diagnosis (ICD-9 codes 250.X0, 250.X2, 91.4%), abnormal laboratory values according to American Diabetes Association guidelines (any two of the following: hemoglobin A1c $\geq$ 6.5%, fasting blood glucose $\geq$ 126 mg/dL, random blood glucose $\geq$ 200 mg/dL, or oral glucose tolerance test $\geq$ 200 mg/dL, additional 5.0%) (27) or prescription of any antidiabetes medications (additional 3.6%).

**Measures: patient characteristics**
Patient factors included race/ethnicity; age; hemoglobin A1c; fasting blood glucose; Quetelet BMI (measured as kilograms divided by the square of height in meters); weight classification by BMI (underweight, $<18.5$ kg/m$^2$; normal weight, $\geq 18.5$ and $<25$ kg/m$^2$; overweight, $\geq 25$ and $<30$ kg/m$^2$; and obese, $\geq 30$ kg/m$^2$); hypertension (ICD-9 codes 401.X, blood pressure $>140/90$ mmHg twice, or use of antihypertensive medications); dyslipidemia (ICD-9 codes 272–272.9, use of lipid-modifying agents, or one of the following: 1) fasting LDL $\geq 160$ mg/dL, 2) fasting HDL $<40$ mg/dL for men and HDL $<50$ mg/dL for women, 3) fasting total cholesterol $\geq 240$ mg/dL, and 4) fasting triglycerides $\geq 150$ mg/dL); CVD, defined as physician-recorded diagnosis (ICD-9 codes for stroke, 430–436; coronary heart disease, 410–414; or peripheral vascular disease, 415, 451, and 453); smoking status (ever, never, or missing); primary insurance (PPO, HMO, and other); and frequency of office visits. Use of renin-angiotensin system inhibitors was defined as a medication order for renin inhibitors, ACE inhibitors, or angiotensin II receptor blockers during the study period.

**Outcome measures: manifestations of DKD**
Over 81% of our study population had at least one urine measure available for classification of proteinuria, and 93% of our population had at least one serum creatinine available for calculation of eGFR during the study period. Patients without measured urine protein or serum creatinine were more likely to be older, female, and NHW (Supplementary Table 1). Very few patients (N = 154, 1.0%) had an ICD-9 code for diabetic nephropathy (250.4X) without associated abnormal laboratory values (proteinuria or low eGFR), and these patients were excluded from our analyses. We classified manifestations of DKD as proteinuria with or without low eGFR (proteinuric DKD) or low eGFR alone (nonproteinuric DKD):

1. Proteinuric DKD (74.2% of patients with DKD), defined as having one abnormal result for microalbuminuria (urine albumin-to-creatinine ratio 30–299 mg/g creatinine, urine albumin 30–299 mg/24 h, or timed urine albumin 20–199 $\mu$g/min, 87.9%), macroalbuminuria (urine albumin-to-creatinine ratio $\geq 300$ mg/g creatinine, urine albumin $\geq 300$ mg/24 h, or timed urine albumin $\geq 200$ $\mu$g/min, additional 6.8%), elevated urine protein test (urine protein-to-creatinine ratio $\geq 0.3$ or 24-h total urine protein $\geq 300$ mg, additional 3.7%), or physician-recorded diagnosis (ICD-9 code 791.0, additional 1.6%)

2. Low eGFR alone (nonproteinuric DKD, 25.8% of patients with DKD), defined as either having at least two abnormal estimated GFR results (eGFR $\leq 60$ ml/min/1.73m$^2$, 92.3%) more than 3 months apart, using the four-variable Modification of Diet in Renal Disease (MDRD) equation for standardized creatinine measurements (28), or physician-recorded diagnosis (ICD-9 codes 585, 585.3–585.5, or 585.9, additional 7.7%) without any manifestations of proteinuria as defined above.

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines (1) define proteinuria by the use of two of three measurements within a 6-month window, i.e., persistent proteinuria. In our clinical cohort, patients may have outside laboratory data not listed in the EHR but available to the physician for diagnosis...
and coding. To assess whether use of a single voided specimen for classification of proteinuria was sufficiently representative, we estimated the rate of persistent proteinuria in patients with micro- or macroalbuminuria and at least one additional albumin excretion measurement during the time window of this cohort. Sixty-seven percent of these patients with microalbuminuria had persistent proteinuria. Among patients with macroalbuminuria and an additional measurement, 92% of these patients had persistent proteinuria. These rates of persistent proteinuria are comparable with other epidemiologic studies of manifestations of DKD (5,29). Serum and urine creatinine measurements were obtained by the kinetic Jaffe method using a uniform instrument (Siemens Dimension) across all laboratories in the EHR catchment area.

Statistical analyses

We compared patient baseline demographics using Wilcoxon tests or Wilson CIs as appropriate and calculated age- and sex-standardized prevalence rates for proteinuric and nonproteinuric DKD using direct standardization to the NHW.

Table 1—Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>NHWs</th>
<th>Asian Indians</th>
<th>Chinese</th>
<th>Filipinos</th>
<th>Hispanics</th>
<th>NHBs</th>
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<td>N</td>
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<td>1,862</td>
<td>1,650</td>
<td>1,070</td>
<td>1,916</td>
<td>457</td>
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<td>Age (years)</td>
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<td>50.6 (12.3)***</td>
<td>61.3 (14.0)***</td>
<td>57.4 (12.2)***</td>
<td>57.8 (13.7)***</td>
<td>58.3 (12.2)***</td>
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<td>47.2</td>
<td>53.7***</td>
<td>49.8*</td>
<td>56.7**</td>
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<td>10.4</td>
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<td>6.8**</td>
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<td>6.5***</td>
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<td>5.8–6.4</td>
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<td>26.4**</td>
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<td>≥7.1</td>
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<td>27.1**</td>
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<td>27.9 (4.9)***</td>
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<td>11.0***</td>
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<td>76.7***</td>
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<td>84.8</td>
<td>90.6</td>
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<td>74.3 (9.8)***</td>
<td>71.8 (10.8)***</td>
<td>74.4 (10.7)*</td>
<td>74.1 (10.5)</td>
<td>76.5 (10.5)***</td>
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<tr>
<td>Last systolic BP</td>
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<td>122.9 (15.8)***</td>
<td>123.5 (16.5)***</td>
<td>127.9 (16.5)</td>
<td>127.1 (16.1)**</td>
<td>131.1 (16.7)**</td>
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<td>79.7***</td>
<td>84.9</td>
<td>88.6*</td>
<td>86.1</td>
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<td>71.3**</td>
<td>63.8</td>
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<td>42.1 (10.9)***</td>
<td>50.7 (13.1)***</td>
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<td>46.0 (11.9)***</td>
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<td>Last LDL value</td>
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<td>98.3 (31.1)***</td>
<td>95.4 (32.4)</td>
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<td>102.8 (36.0)**</td>
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<td>175.0 (41.3)</td>
<td>171.9 (37.3)</td>
<td>172.8 (37.8)</td>
<td>179.2 (41.2)**</td>
<td>178.9 (45.3)***</td>
<td>176.5 (43.1)</td>
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<td>151.1 (113.2)</td>
<td>136.8 (91.4)***</td>
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<td>71.2***</td>
<td>82.4*</td>
<td>74.9**</td>
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<td>CVDs</td>
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<td>13.5***</td>
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<td>14.7***</td>
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<td>Smoking</td>
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<td>15.8***</td>
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<td>75.0***</td>
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<td>2.6**</td>
<td>0.9</td>
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<td>2.0</td>
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<td>8.6 (5.9)**</td>
<td>9.1 (7.2)***</td>
<td>9.6 (6.7)***</td>
</tr>
</tbody>
</table>

Data are means (SD) or percent. BP, blood pressure. Statistically significant compared with NHWs at ***P < 0.0001, **P < 0.01, and *P < 0.05 by pairwise Wilcoxon tests or nonoverlapping Wilson CI.
distribution. We used multivariable logistic regression to determine the adjusted odds of DKD. We considered two-tailed P values <0.05 as statistically significant and also reported that P values <0.01 and <0.001 due to multiple comparisons; odds ratios and 99% CIs are reported when appropriate. We conducted statistical analyses using SAS 9.3 (Cary, NC).

**RESULTS**—We identified a total of 15,683 eligible records (8,728 NHWs, 1,862 Asian Indians, 1,650 Chinese, 1,070 Filipinos, 1,916 Hispanics, and 457 NHBs) (Supplementary Fig. 1) and describe the patient characteristics in Table 1. Reviewing traditional risk factors for DKD (1,30), we note several similarities and differences among racial/ethnic minorities and NHWs. Overall, each racial/ethnic subgroup was significantly younger than NHWs. All racial/ethnic minorities had higher mean hemoglobin A1c, with the exception of Chinese, Asian Indians, Chinese, and Filipinos had significantly lower BMI than NHWs. Asian Indians and Chinese had lower systolic blood pressure and lower rates of hypertension. All Asian subgroups had lower rates of having ever smoked compared with NHWs. All racial/ethnic minority patients except NHBs with type 2 diabetes had statistically significant lower rates of CVD history than NHWs. Filipinos and NHBs had significantly higher rates of renin-angiotensin system inhibitor use than NHWs in our cohort.

Within this cohort of patients with type 2 diabetes, we classified patients with proteinuria or low eGFR. Twenty-six percent of patients had proteinuria. Overall, 9% of patients had low eGFR alone. Age- and sex-adjusted prevalence rates for DKD across different racial/ethnic groups are shown in Table 2. Prevalence of individual manifestations of DKD differed markedly across racial/ethnic minorities. Asian Indians and Chinese had similar prevalence rates of proteinuric DKD than NHWs, but Filipinos, Hispanics, and NHBs had significantly higher rates of proteinuria. These latter subgroups also had higher rates of renin-angiotensin system inhibitor use. On the other hand, compared with NHWs, Chinese, Hispanics, and NHBs had significantly lower prevalence rates of nonproteinuric DKD. Next, we calculated odds ratios after adjustment for multiple additional confounders related to the pathogenesis of DKD (i.e., hyperglycemia, obesity, high blood pressure, dyslipidemia, smoking history, or CVD) (1) or access to health care (e.g., insurance status, number of office visits); these measures are graphically shown in Fig. 1. After multivariable analysis, racial/ethnic minorities had higher odds of proteinuric DKD but not nonproteinuric DKD. Similar to the age- and sex-adjusted prevalence rates, the odds of proteinuric DKD among Chinese, Filipino, Hispanic, and NH women were higher. We observed a similar pattern for men compared with NHWs, although the odds ratio for nonproteinuric CKD in NH men was not significantly lower.

**CONCLUSIONS**—Several investigators have demonstrated associations between race/ethnicity and the development of DKD. However, many consider the Asian population in aggregate or only consider a single subgroup (31,32). Other studies that estimate racial/ethnic differences in DKD consider single outcomes such as proteinuria, low eGFR (with or without significant proteinuria), or ESRD. In a prospective cohort study, Kanaya et al. (14) queried a diabetes registry with a large Asian population (7,494 patients) to demonstrate significantly higher rates of ESRD in all non-Caucasian populations including several Asian subgroups (Chinese, Japanese, and Filipinos). However, only a minority of persons (2–18%) with existing DKD progress to ESRD (33,34).

A substantially larger cohort of persons with type 2 diabetes has albuminuria and/or low eGFR (~40% of the 25–30 million persons with type 2 diabetes in the U.S.) (29,35). Furthermore, albuminuria and low eGFR are independent risk factors for cardiovascular or renal events in patients with type 2 diabetes (8,36,37).

This study suggests that differences inherent in, or associated with, race/ethnicity may help to explain differential clinical manifestations of DKD. Filipinos are known to have a high incidence of CKD, but a prior study suggested that a higher incidence of diabetes accounted for much of this association (38). After adjustment for multiple confounders, we found a higher prevalence of kidney disease in Filipinos with diabetes relative to other Asian groups, suggesting that other factors, such as socioeconomic or cultural issues, dietary factors, or genetics, may play a unique role in this group. Asian Indians have shown variable rates of proteinuria and low eGFR in different studies (19,39), but we found no significant differences between this subgroup and NHWs. Among Hispanics and NHBs, we also observed higher odds of proteinuric DKD. Nonproteinuric DKD was less prevalent among minorities than NHWs.

We suggest three factors that could account for the discrepancy between odds of proteinuric versus nonproteinuric DKD in racial/ethnic minorities. First, we classified patients with proteinuria based on a single voided urine specimen. If false positive rates for proteinuria were lower in racial/ethnic minorities compared with NHWs, we would then estimate comparatively lower rates of nonproteinuric kidney disease in racial/ethnic minorities. Second, the method for estimating eGFR may underestimate the number of patients with low eGFR in racial/ethnic minorities other than blacks. Several other studies have suggested modifications of the eGFR formula to reflect racial/ethnic differences in

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**Table 2—Age- and sex-adjusted prevalence rates of proteinuric and nonproteinuric DKD**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>NHWs</th>
<th>Asian Indians</th>
<th>Chinese</th>
<th>Filipinos</th>
<th>Hispanics</th>
<th>NHBs</th>
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<tr>
<td>Proteinuric DKD</td>
<td>24.8 (23.9–25.7)</td>
<td>24.8 (21.7–27.9)</td>
<td>27.6 (25.5–29.8)</td>
<td>37.9 (34.6–41.2)***</td>
<td>32.5 (30.3–34.8)***</td>
<td>35.3 (30.6–40.0)**</td>
</tr>
<tr>
<td>Nonproteinuric DKD</td>
<td>11.7 (11.0–12.3)</td>
<td>9.7 (7.2–12.1)</td>
<td>6.3 (5.2–7.5)***</td>
<td>9.8 (7.6–12.0)</td>
<td>7.6 (6.2–8.9)***</td>
<td>6.9 (4.0–9.8)***</td>
</tr>
<tr>
<td>Treatment with RAS</td>
<td>64.7 (63.7–65.7)</td>
<td>61.9 (51.9–64.9)</td>
<td>57.4 (55.1–59.8)***</td>
<td>74.5 (71.8–77.3)***</td>
<td>67.8 (65.6–69.9)</td>
<td>73.2 (68.6–77.8)**</td>
</tr>
</tbody>
</table>

Data are percent (95% CI). RAS, renin-angiotensin system. Statistically significant compared with NHWs at ***P < 0.0001 and **P < 0.01 by pairwise Wilcoxon tests or nonoverlapping Wilson CI.
relative muscle and fat mass (40). There are already modifications in the Modification of Diet in Renal Disease formula (28) to reflect differences in serum creatinine for women (lower) and blacks (higher), but future studies should strive to tailor eGFR-estimating equations for specific Asian subgroups and Hispanics to improve precision and avoid potential misclassification (41). Lastly, our results may suggest that the pathophysiologic mechanisms that determine these disparate forms of DKD are truly influenced by racial/ethnic differences. Different pathophysiologic mechanisms that manifest as nonproteinuric DKD have been proposed (9), and our data suggest that among patients with type 2 diabetes and CKD, NHWs are predisposed to these less progressive phenotypes.

Our study was strengthened by the relatively large sample size, the diverse cohort, and the comparison of several renal manifestations in a single cohort with similar insurance status and access to care. We used a comprehensive EHR, but in addition to administrative (coding) data, we had access to specific laboratory data to enhance case ascertainment. We also used stringent definitions of DKD as supported by the K/DOQI guidelines (1). With exclusion of patients with kidney disease prior to the first diagnosis of diabetes, our prevalence rates might be underestimated, but we opted for increased specificity over sensitivity to compare racial/ethnic disparities.

Our study was also limited in several respects. Our observations are from a cross-sectional study, and thus, we cannot draw causal inference. We included in our multivariable analysis all available factors known to be associated with DKD but could not capture all potential relevant covariates or severity, so there may be residual confounding for which we did not adjust. Increased use of renin-angiotensin system inhibitors was higher among racial/ethnic groups with higher prevalence rates of proteinuric DKD (Table 2), which likely represents confounding by indication (1). Including renin-angiotensin system inhibitor treatment status in the multivariable logistic models did not significantly alter racial/ethnic differences in the odds ratios of proteinuric or nonproteinuric DKD (Supplementary Table 2). Our findings may have limited generalizability to the prevalence of DKD in certain racial/ethnic groups because we used a cohort of patients with health insurance, but conversely, we have reduced confounding.

![Figure 1](https://example.com/image1.png)

**Figure 1**—Multivariable-adjusted odds ratios of proteinuric DKD (proteinuria with or without low eGFR) (top panel) and nonproteinuric DKD (low eGFR alone) (bottom panel) by sex and racial/ethnic subgroup relative to NHWs. □, point estimate; bar, 99% CI; ■, statistical significance compared with NHWs at \( P < 0.01 \). Though included in the model, odds ratios for other covariates (age in 2008, hemoglobin A1c levels, BMI, prehypertension or hypertension, dyslipidemia, CVD, smoking status, primary insurance, and number of office visits) are not presented. NH, non-Hispanic.
Racial/ethnic differences in diabetic kidney disease

by poverty and lack of access to care that track with race/ethnicity. The significant differences in clinical characteristics between different racial/ethnic groups may not be fully accounted for by adjustment (e.g., age). We were also unable to adjust further for income, education, or other socioeconomic factors. Lastly, without individual chart review or biopsy data, we are unable to formally exclude other causes of kidney disease in these patients (e.g., hypertensive nephrosclerosis or renovascular disease), but regardless of the etiology, diabetes is an independent risk factor for progressive kidney disease (42), and thus understanding racial/ethnic differences in prevalence rates in this cohort is important.

In summary, rates of proteinuric and nonproteinuric DKD vary significantly across racial/ethnic groups. Additional prospective studies are needed to confirm these associations, as such studies could lead to improved public health surveillance of diabetes complications within diverse communities.

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V.B. contributed to study design and wrote the manuscript. B.Z. assembled data and performed statistical analysis. K.M.J.A. contributed to study design and reviewed and edited the manuscript. E.J.W. reviewed and edited the manuscript. S.C. provided background research and wrote the manuscript. E.C.W. reviewed the statistical analysis. S.P.F. reviewed and edited the manuscript. L.P.P. contributed to study design and reviewed and edited the manuscript. L.P.P. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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