Diabetes and CKD in the United States Population, 2009–2014

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Abstract

Background and objectives Diabetes is an important cause of CKD. However, among people with diabetes, it is unclear to what extent CKD is attributable to diabetes itself versus comorbid conditions, such as advanced age and hypertension. We examined associations of diabetes with clinical manifestations of CKD independent of age and BP and the extent to which diabetes contributes to the overall prevalence of CKD in the United States.

Design, setting, participants, & measurements We performed a cross-sectional study of 15,675 participants in the National Health and Nutrition Examination Surveys from 2009 to 2014. Diabetes was defined by use of glucose-lowering medications or hemoglobin A_{1c} ≥6.5%. eGFR was calculated using the CKD Epidemiology Collaboration formula, and albumin-to-creatinine ratio was measured in single-void urine samples. We calculated the prevalence of CKD manifestations by diabetes status as well as prevalence ratios, differences in prevalence, and prevalence attributable to diabetes using binomial and linear regression, incorporating data from repeat eGFR and urine albumin-to-creatinine ratio measurements to estimate persistent disease.

Results For participants with diabetes (n=2279) versus those without diabetes (n=13,396), the estimated prevalence of any CKD (eGFR<60 ml/min per 1.73 m^2; albumin-to-creatinine ratio ≥30 mg/g, or both) was 25% versus 5.3%, respectively; albumin-to-creatinine ratio ≥30 mg/g was 16% versus 3.0%, respectively; albumin-to-creatinine ratio ≥300 mg/g was 4.6% versus 0.3%, respectively; eGFR<60 ml/min per 1.73 m^2 was 12% versus 2.5%, respectively; and eGFR<30 ml/min per 1.73 m^2 was 2.4% versus 0.4%, respectively (each P<0.001). Adjusting for demographics and several aspects of BP, prevalence differences were 14.6% (P<0.001), 10.8% (P<0.001), 4.5% (P<0.001), 6.5% (P<0.001), and 1.8% (P=0.004), respectively. Approximately 24% (95% confidence interval, 19% to 29%) of CKD among all United States adults was attributable to diabetes after adjusting for demographics.

Conclusions Diabetes is strongly associated with both albuminuria and reduced GFR independent of demographics and hypertension, contributing substantially to the burden of CKD in the United States.

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Introduction

Diabetes mellitus has long been known to be an important cause of CKD (1). Over the last 30 years, the number of people with diabetes and CKD has grown in step with the rising prevalence of diabetes itself (2,3). Approximately 8.4 million adults in the United States now have diabetes and CKD, and diabetes is now the presumed cause of ESRD for approximately one half of patients with incident cases (3,4). Among people with diabetes, CKD markedly increases risks of cardiovascular events and premature mortality (5,6). Therefore, in diabetes care, effective diagnosis and treatment of CKD are important to improve patient outcomes and public health.

However, for patients with diabetes and CKD, the underlying cause of kidney damage is rarely known with confidence. Aging and comorbidities (particularly hypertension) also contribute to risk of CKD, and CKD prevalence varies by sex and race/ethnicity (7,8). In addition, among adults with diabetes and CKD, the clinical manifestations of kidney disease have changed over time, with a decreasing prevalence of albuminuria and an increasing prevalence of low eGFR (3). As a result, it is not clear to what extent diabetes *per se* contributes to CKD in contemporary clinical care. This uncertainty complicates both clinical evaluation and the development of new strategies for CKD prevention and treatment.

In this study, we aimed to determine the extent to which clinical manifestations of CKD can be attributed to diabetes (as opposed to demographics and BP) among adults with diabetes. We further aimed to determine the extent to which diabetes contributes to the overall prevalence of CKD in the general United States population.

Materials and Methods

Study Population

The National Health and Nutrition Examination Survey (NHANES) is a series of cross-sectional studies designed to assess the health and nutritional status of adults and children in the United States, and it combines both physical examinations and interviews consisting of demographic, socioeconomic, dietary, and health-related questions (9). It uses a probability sampling design, intentionally oversampling participants of black race, Hispanic ethnicity, or both.

For this study, we used data from three NHANES cycles: 2009–2010, 2011–2012, and 2013–2014; data collection details have been published elsewhere (9). We included all participants ages 20 years old or older who underwent a health examination in the NHANES mobile examination center and had available data for medication use, hemoglobin A_{1c}, serum creatinine concentration, and urine albumin and creatinine concentrations. Of 17,547 participants in the NHANES 2009–2014 ages 20 years old or older, we excluded 581 participants who did not attend a mobile examination center visit and 1291 participants with missing data (hemoglobin A_{1c}, n=802; serum creatinine, n=1066; urine albumin and creatinine, n=370; prescription medication, n=1; some participants were missing multiple measurements), resulting in a final analytic sample of 15,675 (Supplemental Figure 1). Participants who were included (versus excluded) were more likely to be men and white, tended to use antihypertensive medications and angiotensin receptor blockers less often, and had slightly lower systolic BP (Supplemental Table 1). Because this study is not considered human subjects research by the University of Washington Institutional Review Board, no human subjects approval was obtained.

Diabetes Definition

For the purposes of this study, diabetes mellitus was defined as the use of glucose-lowering medications (insulin or other hypoglycemic medications), a hemoglobin A_{1c} ≥6.5%, or both (2,3). Hemoglobin A_{1c} was measured using HPLC (coefficients of variation <2.0%) (9), and it was calibrated using a previously developed equation (10).

Measurement of CKD

We examined several clinical manifestations of kidney disease. Microalbuminuria was defined as a urine albumin-to-creatinine ratio (ACR) of ≥30 mg/g, and macroalbuminuria was defined as a urine ACR of ≥300 mg/g. Urine albumin concentration was ascertained from a singly voided urine sample *via* a solid-phase fluorescent immunoassay, whereas creatinine concentration was measured with a Jaffe rate reaction. Serum creatinine concentrations were measured using the kinetic Jaffe rate reaction method. eGFR was then derived using the creatinine-based Chronic Kidney Disease Epidemiology Collaboration equation (11). Reduced eGFR was defined as eGFR<60 ml/min per 1.73 m^2, and severely reduced eGFR was defined as eGFR<30 ml/min per 1.73 m^2. CKD was defined as ACR≥30 mg/g, eGFR<60 ml/min per 1.73 m^2, or both.

To account for the biologic variability inherent in urine ACR and eGFR, we estimated the persistence of albuminuria and reduced eGFR among participants with repeated urine or serum measurements. During the NHANES 2009–2010, participants who provided a urine sample at the time of their Mobile Examination Center visit were asked to collect a second urine sample from a first morning void at home; repeat urine samples were collected by 4268 participants without diabetes and 727 participants with diabetes within 10 days of their Mobile Examination Center visit. During the NHANES III, a subset of 2483 participants without diabetes and 304 participants with diabetes returned for a second blood draw approximately 2 weeks after their Mobile Examination Center visit. We estimated persistence separately in those with and without diabetes, because we anticipated that persistence may differ according to the range of observed urine ACR and eGFR values for each subpopulation. In all cases, persistence was defined as the proportion of participants with abnormal values (albuminuria or reduced eGFR) in the initial collection whose values were also abnormal on repeat testing. Estimates of persistence were incorporated into prevalence estimates as described in the section on the statistical methods.

Other Clinical Characteristics

Age, sex, race/ethnicity, and duration of diabetes were assessed by a questionnaire administered by trained interviewers. Participants of all race/ethnicities were included in analysis, but estimates are presented only for those of non-Hispanic white, non-Hispanic black, and Mexican-American race/ethnicities. Type 1 diabetes was defined (for descriptive purposes) as a diagnosis before 30 years of age with use of insulin within 2 years of diabetes diagnosis and current insulin use. For each participant, systolic and diastolic BPs were reported as the mean of three consecutive seated BP readings. Prescription drug use information was determined by personal interview and reflects usage during a 1-month period before the survey date. The duration of hypertension was defined to be the difference between the participant's age at examination and age at which the participant reported being told of hypertension, whereas a history of hypertension was defined as having ever been told that the participant had high BP. The duration of diabetes was defined to be the difference between a participant's age at examination and age when the participant reported being diagnosed with diabetes. Participants with undiagnosed diabetes at the time of examination were assigned a diabetes duration of 0 years.

Statistical Analyses

All analyses were performed using Stata, version 11.0 (StataCorp) and R, version 3.3.0 (R Foundation for Statistical Computing) (12) and incorporated recommended NHANES weights to account for nonresponse bias and the sampling design (9). Stata svy commands were used to estimate the prevalence of CKD and other clinical characteristics by diabetes strata.

Complete information on age, sex, race/ethnicity, prescription medication usage, self-identified hypertension ascertained by questionnaire, diabetes status, and all CKD outcomes was available for the final analytic sample. Small numbers of participants were missing data of systolic and diastolic BPs (n=569). In models involving these covariates, use of the recommended NHANES sampling weights ensured that estimates still reflected the broader intended population.

We used a bootstrap approach with 500 replicates to account for the variability in the estimate of the probability of persistence. In each bootstrap sample, the prevalence of persistent albuminuria among those with or without diabetes was estimated by multiplying the prevalence of elevated urine ACR by the bootstrap probability of persistence in that group. A final estimate of persistent albuminuria prevalence and 95% confidence intervals (95% CIs) were obtained by calculating the mean and 2.5th/97.5th percentiles across bootstrap samples. A similar process was followed to estimate the prevalence of persistently reduced GFR.

To estimate the prevalence of persistent CKD, the prevalence of persistence in each subtype was calculated (albuminuria only, low eGFR only, or both albuminuria and low eGFR), and a weighted average across these clinical phenotypes was calculated. For participants with albuminuria only or impaired eGFR only, the respective estimates of persistence were calculated in each bootstrap sample as described above. For participants with both albuminuria and low eGFR, the probability of persistence was calculated as one minus the probability of having neither persistent albuminuria nor persistently low GFR. For each outcome, the probability of persistence was calculated separately for those with and without diabetes (Supplemental Table 2).

We used binomial and linear regression to estimate adjusted prevalence ratios and adjusted differences, respectively, between those with and without diabetes. A first adjusted model was adjusted for age (including both linear and quadratic terms), sex, and race/ethnicity; a subsequent model additionally adjusted for measures of BP control: systolic BP (continuous variable), current use of antihypertensive medications, current use of renin-angiotensin system (RAS) inhibitors (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers), a history of hypertension (yes/no), and years since diagnosis of hypertension. For each outcome, we incorporated a bootstrap estimate of persistence, which accounted for the uncertainty in the estimate of the probability of persistence. The attributable risk percentage associated with the presence of diabetes for each outcome was calculated as $100\times(PR-1)/PR$, where PR was the prevalence ratio observed for that outcome (13). Five hundred bootstrap samples were used to obtain 95% CIs for each measure.

The population attributable risk percentage was calculated as 100 times the prevalence of the outcome attributable to diabetes divided by the prevalence of the outcome among all United States adults. The prevalence of the outcome attributable to diabetes was defined as the difference between the prevalence among all United States adults and the prevalence among United States adults without diabetes; we also calculated these quantities using standardization to account for age, sex, and race/ethnicity. All prevalence estimates incorporated estimates of the persistence of the outcome as described above.

In subgroup analyses, we calculated age, sex, and race/ethnicity strata–specific estimates of prevalence; adjusted prevalence ratios; and adjusted differences through the use of interaction terms; we estimated stratum-specific population attributable risk through stratified analyses.

Results

A total of 15,675 adults participating in the NHANES from 2009 to 2014 were included in this analysis: 2279 with diabetes and 13,396 without diabetes. Compared with participants without diabetes, those with diabetes were older, more likely to be black or Mexican American, more likely to have a history of hypertension, and more likely to use antihypertensive medications in general and RAS inhibitors in particular (Table 1). Mean systolic BP was substantially higher among participants with versus without diabetes, and mean diastolic BP was only slightly lower. Among participants with diabetes, a diagnosis of diabetes was known by 71% of participants, 4.5% were considered to have type 1 diabetes, median duration of diagnosed diabetes was 5.0 years (including participants with undiagnosed diabetes as 0 years since diagnosis), 77% were using glucose-lowering medications, and mean hemoglobin A_{1c} was 7.4%.

Persistence of albuminuria was evaluated among 4995 participants, and persistence of reduced eGFR was evaluated among 2787 participants (Supplemental Table 2). Urine ACR was systematically lower on repeat testing compared with initial testing (Supplemental Figure 2). Estimates for persistence ranged from 42% (for urine ACR $\geq$30 mg/g among participants without diabetes) to 100% (for eGFR<30 ml/min per 1.73 m^2) and were higher for participants with versus without diabetes (except for eGFR<30 ml/min per 1.73 m^2).

For participants with versus without diabetes, the estimated prevalence of urine ACR $\geq$30 mg/g was 16% versus 3.0%, respectively; the estimated prevalence of urine ACR $\geq$300 mg/g was 4.6% versus 0.3%, respectively; the estimated prevalence of eGFR<60 ml/min per 1.73 m^2 was 12% versus 2.5%, respectively; and the estimated prevalence of eGFR<30 ml/min per 1.73 m^2 was 2.4% versus 0.4%, respectively (Table 2). The estimated prevalence of any CKD (urine ACR $\geq$30 mg/g, eGFR<60 ml/min per 1.73 m^2, or both) was 25% versus 5.3%, respectively. The prevalence of each CKD manifestation was progressively greater with a longer duration of diabetes (Figure 1). Prevalence ratios comparing participants with versus without diabetes were significantly greater than one for all five CKD outcomes.

The estimated difference in prevalence of any CKD comparing participants with versus without diabetes was 14.9% (95% CI, 12.3% to 17.6%) adjusting for demographic variables. This difference was 14.6% (95% CI, 11.3% to 17.8%) after further adjustment for components of BP. The estimated differences in prevalence between those with and without diabetes were 11.2% (95% CI, 9.4% to 13.0%) for urine ACR $\geq$30 mg/g, 3.9% (95% CI, 3.1% to 4.7%) for urine ACR $\geq$300 mg/g, 6.0% (95% CI, 3.1% to 9.0%) for eGFR<60 ml/min per 1.73 m^2, and 1.3% (95% CI, 0.3% to 2.4%) for eGFR<30 ml/min per 1.73 m^2 when adjusted for demographics only. In fully adjusted models, these differences in prevalence were 10.8%, 4.5%, 6.5%, and 1.8%, respectively.

Among all United States adults (with and without diabetes), the prevalence of any CKD was 7.3%, the prevalence of urine ACR $\geq$30 mg/g was 4.4%, the prevalence of urine ACR $\geq$300 mg/g was 0.8%, the prevalence of eGFR<60 ml/min per 1.73 m^2 was 3.5%, and the prevalence of eGFR<30 ml/min per 1.73 m^2 was 0.6% (Table 3). The prevalence values of these clinical CKD manifestations attributable to diabetes were 2.1%, 1.3%, 0.5%, 1.0%, and

Table 1. Characteristics of adults with and without diabetes in the United States from 2009 to 2014

Characteristic	No Diabetes Mellitus, *n*=13,396		Diabetes Mellitus, *n*=2279	
	N	Weighted Proportion (95% CI) or Mean (95% CI)	*N*	Weighted Proportion (95% CI) or Mean (95% CI)
Proportion of United States population		89.2 (88.6 to 89.9)		10.8 (10.1 to 11.4)
Demographic variables				
Age, yr		46 (45 to 47)		59 (58 to 60)
Women, %	6951	52 (51 to 53)	1093	48 (45 to 51)
Race/ethnicity, %				
White, non-Hispanic	6044	68 (64 to 73)	780	60 (55 to 64)
Black, non-Hispanic	2601	10 (8 to 12)	599	15 (12 to 19)
Mexican American	1839	8 (6 to 11)	398	10 (7 to 14)
Medical history				
History of hypertension, %	4036	28 (26 to 29)	1539	66 (64 to 69)
Duration of hypertension, yr		10.2 (9.7 to 10.6)		13.7 (12.8 to 14.5)
Duration of diabetes, yr[a]		0 (0 to 0)		5 (0 to 13)
Medication use				
Antihypertensive medications, %	3288	23 (21 to 24)	1626	70 (68 to 73)
RAS inhibitors, %	1983	14 (13 to 15)	1293	56 (53 to 59)
ACE inhibitors	1269	9 (8 to 10)	859	37 (34 to 39)
Angiotensin receptor blockers	661	4.4 (3.7 to 5.1)	440	20 (17 to 22)
BP, mm Hg				
Systolic BP		120.3 (119.7 to 120.8)		129.7 (128.5 to 130.9)
Diastolic BP		70.4 (69.7 to 71.0)		68.9 (67.9 to 69.9)

Diabetes is defined to be use of antidiabetic medications or a hemoglobin A_{1c} ≥6.5%. Cell contents are raw numbers of participants or weighted proportions or means (95% CI) of United States adults with or without diabetes mellitus with the indicated characteristic, as appropriate, except for row 3, which presents weighted proportions (95% CI) of all United States adults with and without diabetes mellitus. 95% CI, 95% confidence interval; RAS, renin-angiotensin system; ACE, angiotensin-converting enzyme.
[a]Median (interquartile range) duration of diabetes for United States adults with or without diabetes mellitus.

0.2%, respectively, or 28%, 31%, 58%, 29%, and 38% of the total population prevalence, respectively. When standardized to account for age, sex, and race/ethnicity, 24%, 28%, 54%, 21%, and 30%, respectively, of the total population prevalence were attributable to diabetes.

In subgroup analyses we examined estimates of prevalence, adjusted prevalence ratios, adjusted differences, and population-attributable risk across strata of age, sex, and race/ethnicity. For all CKD clinical manifestations, older adults had higher prevalences and adjusted differences compared with younger adults (Supplemental Table 3). In general, population-attributable risk differed most strikingly across strata of sex and race/ethnicity, and was sometimes substantially greater for males compared with females, and for blacks and Mexican Americans compared with whites (Supplemental Table 4).

Discussion

In 2009–2014, adults with diabetes in the United States had a substantially higher prevalence of CKD and each of its individual components compared with adults without diabetes. The prevalence of CKD and its components was progressively higher with longer diabetes duration. The excess risks of CKD, albuminuria, and reduced eGFR associated with diabetes were diminished somewhat with adjustment for demographics and several aspects of BP, but attenuation was modest, and the presence of diabetes remained associated with large differences in the prevalence of each CKD manifestation after adjustment. Specifically, diabetes was associated with a difference in absolute prevalence of any CKD of 14.6% independent of demographics and hypertension. Manifestations with the largest excess absolute risks were albuminuria (10.8%) and eGFR<60 ml/min per 1.73 m^2 (6.5%). Among people with diabetes, 51% of manifest CKD could be independently attributed to diabetes, with the highest attributable proportions for albuminuria (62%), macroalbuminuria (79%), and eGFR<30 ml/min per 1.73 m^2 (59%). Examining the overall population of United States adults, we estimated that 24% of all CKD could be attributed to diabetes independent of demographics.

These results suggest that, for persons with diabetes, albuminuria and reduced eGFR are not usually attributable simply to aging and hypertension, particularly when diabetes has been present for a long time. The excess risks of CKD attributable to diabetes could be due to direct causal effects of diabetes (*e.g.*, hyperglycemia-mediated diabetic glomerulopathy), other causal mechanisms related to diabetes (*e.g.*, metabolic derangements or vascular damage), treatments specific to diabetes or used more commonly among people with diabetes, or confounding by other characteristics more common in diabetes (*e.g.*, obesity,

Table 2. Associations of diabetes mellitus with CKD among adults in the United States

Parameter	Albuminuria ACR≥30 mg/g	Macroalbuminuria ACR≥300 mg/g	eGFR<60 ml/min per 1.73 m^2	eGFR<30 ml/min per 1.73 m^2	Any CKD
***N* with abnormality**					
No diabetes	1159	136	847	83	1774
Diabetes	690	177	482	65	943
Prevalence (95% CI), %					
No diabetes	3.0 (2.6 to 3.5)	0.3 (0.2 to 0.5)	2.5 (2.0 to 3.0)	0.4 (0.3 to 0.6)	5.3 (4.6 to 5.9)
Diabetes	16 (13 to 18)	4.6 (3.4 to 5.8)	12 (9 to 15)	2.4 (1.4 to 3.4)	25 (21 to 28)
Prevalence ratio (95% CI)					
Model 1	3.84 (3.21 to 4.59)	8.70 (5.78 to 13.10)	2.27 (1.65 to 3.10)	2.63 (1.41 to 4.89)	2.67 (2.26 to 3.15)
Model 2	2.66 (2.18 to 3.24)	4.85 (2.99 to 7.84)	1.91 (1.40 to 2.59)	2.45 (1.20 to 5.02)	2.05 (1.74 to 2.42)
Difference in prevalence (95% CI), %					
Model 1	11.2 (9.4 to 13.0)	3.9 (3.1 to 4.7)	6.0 (3.1 to 9.0)	1.3 (0.3 to 2.4)	14.9 (12.3 to 17.6)
Model 2	10.8 (8.7 to 12.9)	4.5 (3.5 to 5.5)	6.5 (2.8 to 10.3)	1.8 (0.2 to 3.4)	14.6 (11.3 to 17.8)
Attributable risk (95% CI), %					
Model 1	74 (69 to 79)	88 (84 to 93)	55 (41 to 47)	62 (39 to 85)	62 (56 to 69)
Model 2	62 (55 to 70)	79 (69 to 88)	47 (30 to 64)	59 (31 to 88)	51 (43 to 59)

Cell contents are raw numbers of participants, weighted proportions (95% CI) of United States adults with and without diabetes who have the indicated clinical manifestation, adjusted prevalence ratios, adjusted differences in prevalence, and risks of CKD attributable to diabetes. All estimates of prevalence take into account information on the persistence of albuminuria, reduced eGFR, or both. Any CKD was defined as a urine ACR ≥30 mg/g or eGFR<60 ml/min per 1.73 m^2. Model 1 was adjusted for demographics and included adjustment for age, age^2, sex, and race/ethnicity; model 2 additionally adjusted for use of renin-angiotensin system inhibitors, use of antihypertensive medications, history of hypertension, years of hypertension, and systolic BP. ACR, albumin-to-creatinine ratio; 95% CI, 95% confidence interval.

smoking, and genetic predisposition). It is not possible to discriminate these possibilities using survey data, although adjustment for RAS inhibitors does help to account for differences in use of this important class of medications. Nonetheless, kidney biopsy series of people with type 2 diabetes and albuminuria have shown proportions with typical lesions of diabetic glomerulopathy that are similar to or higher than the attributable risk proportions that we observed in our study (14–17). Again, similar to results from our study, typical lesions of diabetic glomerulopathy were observed in three of eight Australian patients with type 2 diabetes, normal urine albumin excretion, and reduced eGFR (18). Although differences in study populations and methods preclude definitive comparisons, these results suggest that much of the attributable risk that we observed in survey data may be due to direct effects of diabetes on the kidney. Differences (smaller attributable risk proportions in our study compared with proportions with diabetic glomerulopathy in research series) may be due to the broader range of CKD in our study (including milder forms) or the presence of normal urine albumin excretion and eGFR among participants with histologic diabetic glomerulopathy (which has been documented in autopsy series and research biopsies) (19–21). Our data lack specific histologic determination of CKD cause but are complementary to biopsy series, because they are representative of the patients seen in contemporary diabetes care.

We estimated that 24% of all CKD in the United States could be attributed to diabetes accounting for demographic characteristics, including 28% of urine ACR ≥300 mg/g and 21% of eGFR<60 ml/min per 1.73 m^2. These figures are estimates of the proportion of CKD in the United States population that might be alleviated if CKD attributable to diabetes was abolished (but some people with diabetes still developed CKD due to aging or other factors common to the general population). To the extent that the association of diabetes with CKD is not causal, these figures may overestimate population attributable risk. However, larger population proportions may have been attributable to diabetes if we used additional criteria to define a broader group of people with diabetes (*i.e.*, fasting glucose or oral glucose tolerance test data) (22).

Among people with diabetes and CKD in our study, a substantial minority had CKD that was not attributable to diabetes, and 53% of eGFR<60 ml/min per 1.73 m^2 was not attributable to diabetes when accounting for demographics and BP. Moreover, the underlying causes of the various CKD manifestations evaluated in this study are likely heterogeneous. Most current treatment recommendations for patients with diabetes and CKD (*i.e.*, lifestyle modification, appropriate glycemic control, lipid-lowering therapy, and BP control for the prevention of cardiovascular diseases and progression of CKD) are appropriate, regardless of the specific cause of CKD (7,8). However, the risks and benefits of these interventions may differ according to the underlying mechanism of CKD as may the risks and benefits of interventions shown more recently to improve renal outcomes in diabetes populations (23,24). Moreover, new therapies to prevent and treat diabetic CKD are on the basis of specific mechanisms of kidney injury (25,26). Clinical trials of these new therapies will be most effective when they are targeted to populations likely to respond to the intervention under evaluation. The direction of

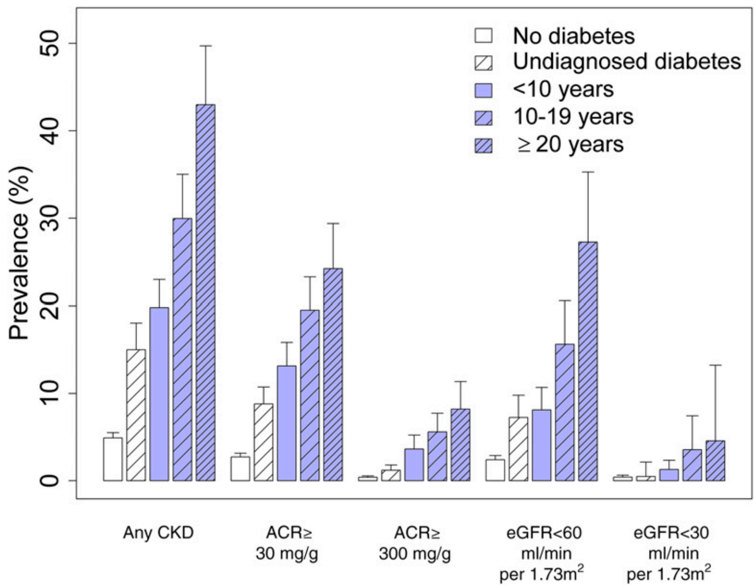

Figure 1. | Prevalence of CKD among adults in the United States from 2009 to 2014 is higher with presence and longer duration of diabetes. Any CKD was defined as a urine albumin-to-creatinine ratio (ACR) ≥30 mg/g or eGFR<60 ml/min per 1.73 m^2. All prevalence values are unadjusted values that incorporate estimates of persistence. Error bars represent the upper bound of 95% confidence intervals.

"precision medicine" to evaluate human kidney tissue and validate prognostic, predictive, and actionable biomarkers is an important step toward differentiation of clinically relevant CKD subtypes.

Strengths of our study include the evaluation of a large, contemporary sample of people with and without diabetes that is representative of the United States population; the incorporation of data on repeat measurements to estimate persistent CKD; and the evaluation of absolute prevalence, differences in prevalence, and attributable risks to quantify the public health effect of diabetes and CKD. Limitations include the lack of kidney tissue to definitively identify causes of CKD, potential incomplete adjustment for BP duration and severity, the inability to determine in detail which specific diabetes-related factors and nondiabetes-related factors were associated with CKD, and the possibility that some risk attributable to diabetes is actually due to residual confounding by other factors that may cause both diabetes and CKD. With regard to BP, we were able to include a number of variables addressing duration and severity, and the inclusion of these variables could be considered overadjustment, because diabetes may contribute to CKD in part through hypertension. Because this study was cross-sectional, prevalence estimates reflect a combination of CKD incidence and duration. Our data do not inform which patients with diabetes and CKD should be evaluated for other causes of kidney damage (for example, by referral to a nephrologist or kidney biopsy).

In conclusion, diabetes is strongly associated with both albuminuria and reduced eGFR independent of age, sex,

Table 3. Extent to which CKD can be attributed to diabetes among adults in the United States

Parameter, %	Albuminuria ACR≥30 mg/g	Macroalbuminuria ACR≥300 mg/g	eGFR<60 ml/min per 1.73 m^2	eGFR<30 ml/min per 1.73 m^2	Any CKD
Prevalence among all United States adults	4.4 (3.9 to 4.9)	0.8 (0.6 to 1.0)	3.5 (2.9 to 4.0)	0.6 (0.5 to 0.7)	7.3 (6.6 to 8.0)
Prevalence among United States adults without diabetes	3.1 (2.7 to 3.6)	0.4 (0.2 to 0.5)	2.7 (2.2 to 3.3)	0.4 (0.3 to 0.5)	5.6 (4.9 to 6.2)
Prevalence attributable to diabetes	1.2 (1.0 to 1.5)	0.4 (0.3 to 0.6)	0.7 (0.4 to 1.1)	0.2 (0.1 to 0.3)	1.7 (1.4 to 2.1)
Proportion attributable to diabetes	28 (22 to 34)	54 (43 to 67)	21 (12 to 31)	30 (19 to 41)	24 (19 to 29)

Estimates and 95% confidence intervals are on the basis of 500 bootstrap samples and incorporate bootstrap estimates of persistence. Estimates for prevalence among United States adults without diabetes are standardized for age, sex, and race/ethnicity to United States population. Prevalence attributable to diabetes is defined as the difference in prevalence among all United States adults and United States adults without diabetes; proportion attributable to diabetes is defined as 100 times the ratio of the prevalence attributable to diabetes to the prevalence among all United States adults. ACR, albumin-to-creatinine ratio.

race, ethnicity, and BP. Our data suggest that a large portion of CKD in the United States is attributable to diabetes. To reduce the public health burden of CKD, what is needed is an enhanced understanding of the molecular pathways through which diabetes causes CKD, new methods of identifying these pathways, and the development and evaluation of new interventions to prevent and treat CKD in persons with diabetes.

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Disclosures

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Supplementary material for:

Diabetes and chronic kidney disease in the US population, 2009-2014

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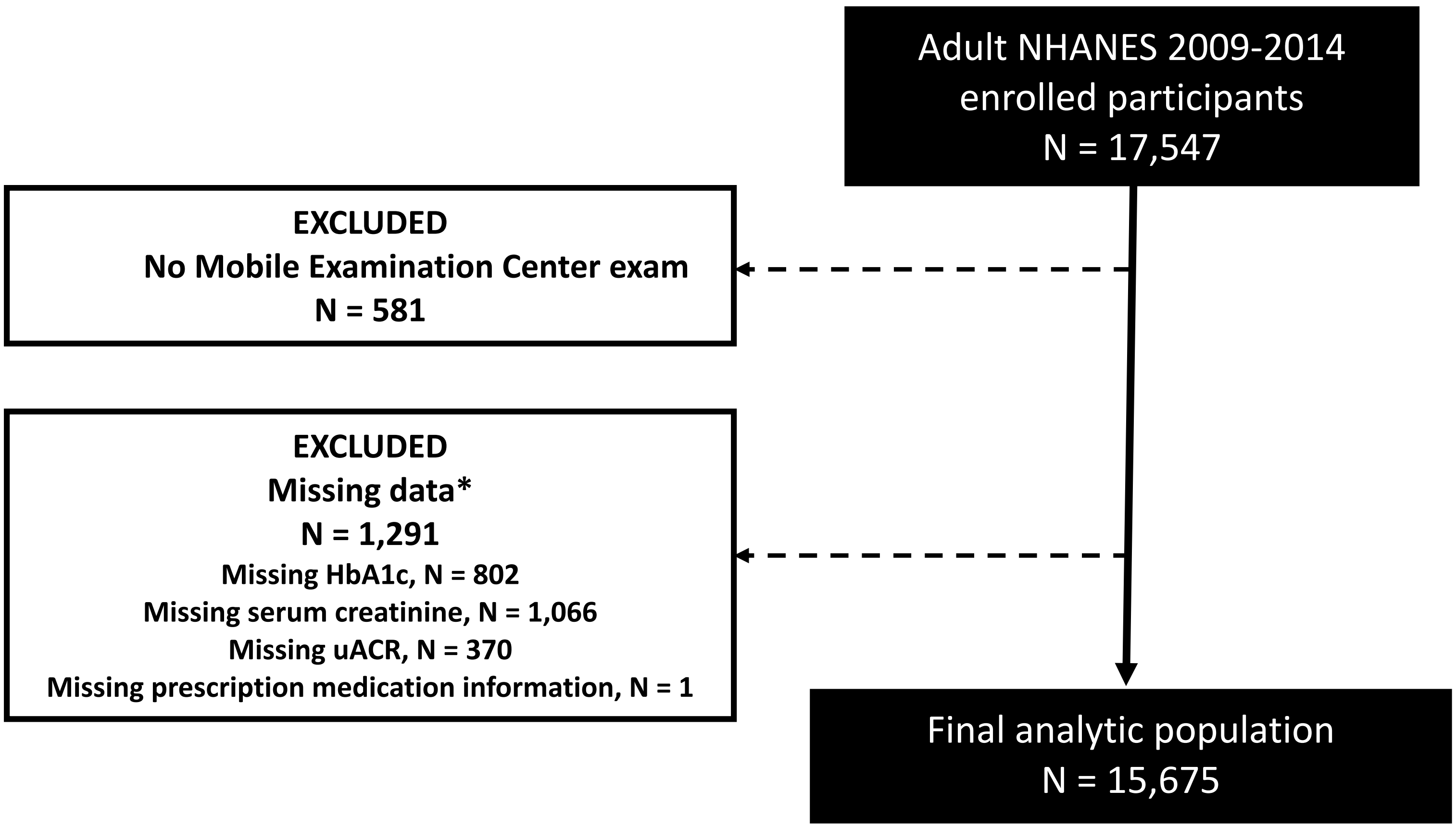
Supplemental Figure 1. Flow diagram of selection of final analytic population



ACR = albumin-creatinine ratio
*Participants were required to have complete information for listed data elements in order to be included in final analytic population; some participants had multiple missing measurements.

Supplemental Table 1. Characteristics of adult 2009-2014 NHANES participants included and excluded from analysis population

	All adult 2009-2014 NHANES participants (N = 17,547)		Excluded from analysis population (N = 1,872)		Included in analytic population (N = 15,675)	
	N	Weighted proportion (95% CI) or mean (95% CI)	N	Weighted proportion (95% CI) or mean (95% CI)	N	Weighted proportion (95% CI) or mean (95% CI)
Demographic variables						
Age, weighted mean, y		47.3 (46.6, 48.0)		48.8 (46.9, 50.6)		47.2 (46.5, 47.9)
Female sex, %	9,043	52 (51, 53)	999	57 (53, 61)	8,044	52 (51, 52)
Race/ethnicity, %						
White (non-Hispanic)	7,489	67 (63, 71)	665	55 (49, 61)	6,824	68 (63, 72)
Black (non-Hispanic)	3,754	11 (10, 13)	554	22 (18, 26)	3,200	11 (9, 13)
Mexican-American	2,447	9 (6, 11)	210	8 (5, 10)	2,237	9 (6, 11)
Medical history						
History of hypertension	6,340	32 (31, 33)	765	39 (35, 43)	5,575	32 (30, 33)
Duration of hypertension, y		11.1 (10.6, 11.5)		12.9 (11.5, 14.3)		10.9 (10.5, 11.4)
Medication use						
Antihypertensive medications, %	5,622	28 (27, 30)	708	35 (32, 39)	4,914	28 (26, 29)
RAS inhibitors, %	3,693	19 (17, 20)	417	20 (17, 23)	3,276	18 (17, 20)
ACE inhibitors	2,374	12 (11, 13)	246	11 (9, 14)	2,128	12 (11, 13)
Angiotensin receptor blockers	1,266	6.2 (5.5, 6.9)	165	8.9 (6.5, 11.3)	1,101	6.0 (5.4, 6.7)
Blood pressure						
Systolic blood pressure, mmHg		121.5 (120.9, 122.1)		125.3 (123.2, 127.4)		121.3 (120.7, 121.9)
Diastolic blood pressure, mmHg		70.2 (69.6, 70.8)		69.6 (68.7, 70.5)		70.2 (69.6, 70.9)

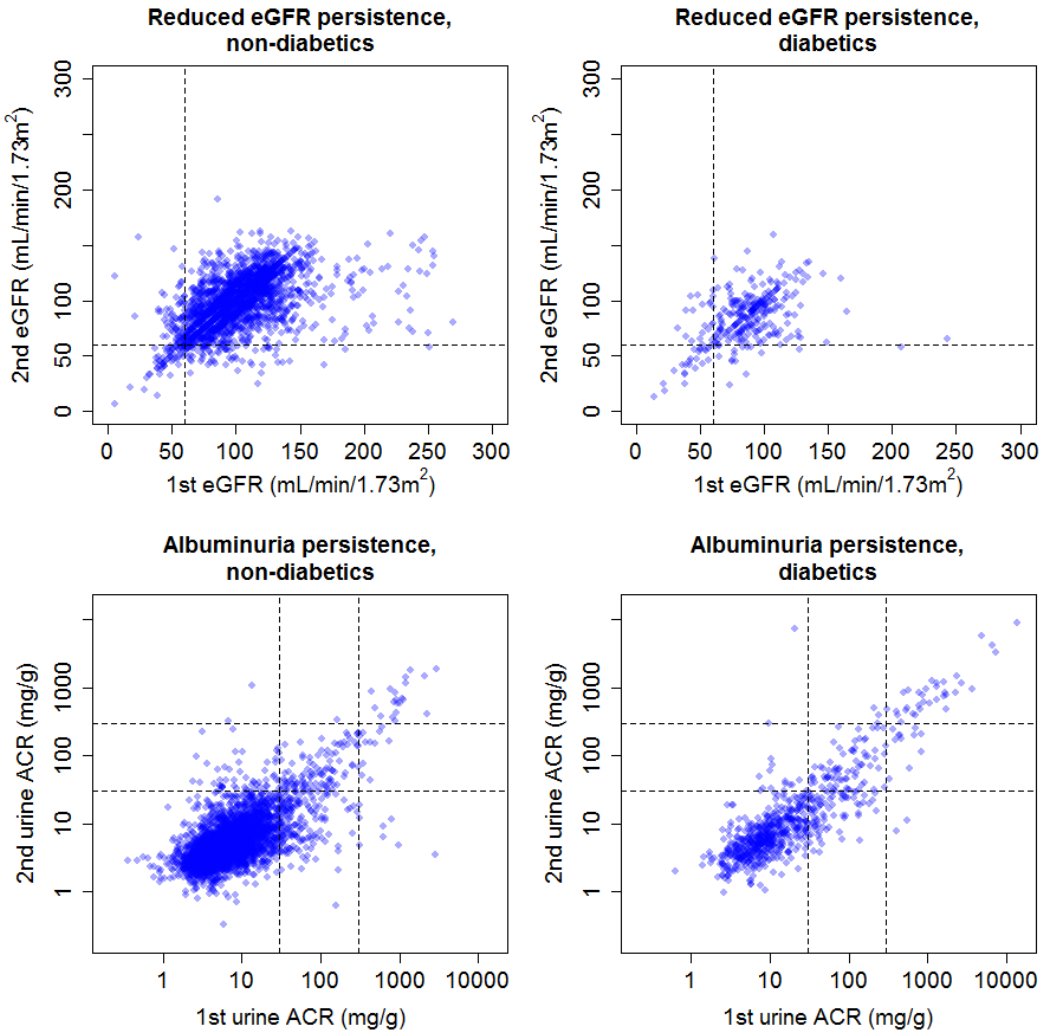
Diabetes is defined to be use of antidiabetic medications or a HbA1c ≥ 6.5%.
Cell contents are raw numbers of participants, or weighted proportion or mean (95% CI) of US adults included or excluded from analytic population with the indicated characteristic, as appropriate.
Abbreviations: RAS = renin angiotensin system; ACE = angiotensin-converting-enzyme.

Supplemental Table 2. Persistence of clinical manifestations of chronic kidney disease, by diabetes status.

	Number with abnormality during main NHANES examination*	Number with persistent abnormality during repeat testing	Proportion with persistent abnormality
Albuminuria (ACR≥ 30 mg/g)			
No diabetes	320	134	0.42
Diabetes	205	121	0.59
Macroalbuminuria (ACR ≥ 300 mg/g)			
No diabetes	40	20	0.50
Diabetes	47	34	0.72
Estimated GFR < 60 mL/min/1.73 m^2			
No diabetes	136	63	0.46
Diabetes	42	25	0.60
Estimated GFR < 30 mL/min/1.73 m^2			
No diabetes	6	6	1.00
Diabetes	3	3	1.00
Any chronic kidney disease			
No diabetes	N/A	N/A	0.47
Diabetes	N/A	N/A	0.65

*Only participants who underwent two measurements of urine ACR (or eGFR) were included in this analysis; no participants had two measurements of both urine ACR and serum. 4,268 non-diabetic and 727 diabetics NHANES 2009-2010 participants were used for evaluation of urine albumin-creatinine ratio (ACR); 2,483 non-diabetic and 304 diabetic NHANES III (1988-1994) participants were used for evaluation of estimated glomerular filtration rate (eGFR). Proportion with persistent abnormality is defined as the proportion of participants in each category with abnormal values whose values were also abnormal on repeat testing.

Supplemental Figure 2. Persistence of albuminuria and low GFR, by diabetes status.



For estimated glomerular filtration rate (GFR) plots, dashed lines indicate the threshold for low eGFR (<60 mL/min/1.73m^2). In albuminuria plots, dashed lines indicate thresholds for microalbuminuria (ACR ≥30 mg/g) and macroalbuminuria (ACR ≥300 mg/g), and units are mg albumin per gram creatinine. The first urine albumin-creatinine ratio (ACR) measurement was made from spot urine samples collected during the Mobile Examination Center examination at any time of day, while the second urine ACR measurement was made from spot urine samples collected at home as a first-morning void.

Supplemental Table 3. Associations of diabetes mellitus with chronic kidney disease among adults in the United States, by age, sex, and race/ethnicity strata.

	N with abnormality		Unadjusted prevalence (%) (95% CI)		Adjusted prevalence ratio (95% CI)	Adjusted difference in prevalence (%) (95% CI)	Adjusted attributable risk (%) (95% CI)
	No diabetes	Diabetes	No diabetes	Diabetes	Model 1	Model 1	Model 1
Albuminuria (ACR≥ 30 mg/g)							
Age							
< 65 years	683	339	2.1 (1.8, 2.4)	13 (11, 15)	5.32 (4.47, 6.33)	11 (9, 12)	81 (78, 84)
≥ 65 years	456	339	6.2 (5.2, 7.3)	17 (14, 20)	2.96 (2.46, 3.56)	11 (9, 13)	66 (60, 72)
Sex							
Female	647	299	3.2 (2.7, 3.7)	14 (12, 17)	3.38 (2.80, 4.07)	10 (8, 12)	70 (65, 76)
Male	492	379	2.2 (1.8, 2.6)	15 (13, 18)	5.13 (4.25, 6.19)	12 (10, 14)	80 (77, 84)
Race/ethnicity							
White	507	233	2.6 (2.1, 3.0)	14 (11, 16)	4.23 (3.52, 5.09)	10 (9, 12)	76 (72, 81)
Black	241	181	3.4 (2.8, 4.0)	17 (14, 19)	3.62 (3.00, 4.36)	12 (10, 14)	72 (67, 77)
Mexican-American	147	137	3.0 (2.3, 3.6)	18 (14, 22)	4.59 (3.80, 5.55)	14 (12, 16)	78 (74, 82)
Estimated GFR < 60 mL/min/1.73 m^2							
Age							
< 65 years	170	117	0.7 (0.5, 0.9)	5.4 (3.5, 7.3)	3.62 (2.74, 4.78)	3.8 (2.5, 5.1)	72 (64, 80)
≥ 65 years	695	378	11 (9, 14)	23 (18, 29)	2.14 (1.58, 2.88)	12 (6, 17)	53 (38, 68)
Sex							
Female	469	243	2.7 (2.2, 3.3)	13 (9, 16)	2.35 (1.75, 3.17)	6.8 (4.0, 9.7)	57 (44, 70)
Male	396	252	2.0 (1.6, 2.5)	12 (9, 15)	2.42 (1.79, 3.26)	6.3 (3.6, 8.9)	58 (45, 71)
Race/ethnicity							
White	605	209	3.0 (2.4, 3.6)	14 (10, 18)	2.28 (1.69, 3.08)	7.3 (4.2, 10.3)	56 (42, 70)
Black	114	134	1.4 (1.0, 1.7)	12 (9, 16)	2.99 (2.20, 4.06)	7.6 (4.9, 10.4)	66 (55, 77)
Mexican-American	51	58	0.8 (0.5, 1.1)	6.4 (4.1, 8.7)	2.33 (1.70, 3.18)	2.8 (1.4, 4.3)	57 (42, 71)
Any chronic kidney disease							
Age							
< 65 years	808	398	2.8 (2.4, 3.1)	17 (15, 20)	4.35 (3.81, 4.97)	13 (11, 15)	77 (74, 80)
≥ 65 years	972	546	16 (14, 18)	35 (31, 40)	2.19 (1.84, 2.61)	19 (14, 23)	54 (46, 62)
Sex							

Female	1,002	448	5.7 (5.0, 6.4)	24 (21, 28)	2.53 (2.15, 2.98)	14 (12, 17)	60 (54, 67)
Male	778	496	4.1 (3.5, 4.6)	24 (21, 27)	3.14 (2.66, 3.70)	16 (13, 18)	68 (63, 73)
Race/ethnicity							
White	970	347	5.3 (4.6, 5.9)	24 (21, 28)	2.76 (2.33, 3.28)	15 (12, 18)	64 (58, 70)
Black	324	259	4.6 (3.9, 5.3)	26 (22, 30)	2.79 (2.39, 3.26)	17 (15, 20)	64 (58, 70)
Mexican-American	174	160	3.6 (2.9, 4.3)	22 (18, 26)	2.99 (2.57, 3.47)	15 (13, 17)	67 (61, 72)

Cell contents are raw numbers of participants, weighted proportion (95% CI) of US adults with and without diabetes who have the indicated clinical manifestation, adjusted prevalence ratios, adjusted differences in prevalence, and risk of CKD attributable to diabetes. All estimates of prevalence take into account information on the persistence of albuminuria, reduced eGFR, or both. Any chronic kidney disease was defined as a urine albumin to creatinine ratio (ACR) ≥30 mg/g or estimated glomerular filtration rate (GFR) <60 mL/min/1.73m^2. Model 1 was adjusted for demographics and included adjustment for age, age^2, sex, race/ethnicity, and an interaction between the clinical manifestation and the stratum of interest.

Supplemental Table 4. Extent to which chronic kidney disease can be attributed to diabetes among adults in the United States, by age, sex, and race/ethnicity strata.

	Prevalence among all US adults	Prevalence among US adults without diabetes	Prevalence attributable to diabetes	Proportion attributable to diabetes
Albuminuria (ACR ≥ 30 mg/g)				
Age				
< 65 years	3.3 (2.9, 3.7)	2.4 (2.0, 2.8)	0.9 (0.7, 1.1)	27 (22, 33)
≥ 65 years	9.2 (8.2, 10.3)	6.4 (5.4, 7.5)	2.8 (2.0, 3.5)	30 (23, 38)
Sex				
Female	4.6 (4.0, 5.1)	3.6 (3.1, 4.2)	0.9 (0.7, 1.2)	21 (15, 26)
Male	4.1 (3.6, 4.7)	2.6 (2.1, 3.0)	1.6 (1.2, 1.9)	38 (31, 45)
Race/ethnicity				
White	3.9 (3.4, 4.4)	3.0 (2.5, 3.5)	0.9 (0.7, 1.2)	24 (18, 30)
Black	6.0 (5.2, 6.7)	4.0 (3.3, 4.6)	2.0 (1.5, 2.5)	34 (26, 41)
Mexican-American	5.3 (4.5, 6.1)	3.3 (2.6, 4.0)	2.0 (1.4, 2.5)	38 (29, 47)
Macroalbuminuria (ACR ≥ 300 mg/g)				
Age				
< 65 years	0.6 (0.4, 0.7)	0.3 (0.2, 0.4)	0.3 (0.2, 0.4)	55 (42, 69)
≥ 65 years	1.8 (1.4, 2.3)	0.8 (0.5, 1.2)	1.0 (0.6, 1.4)	55 (39, 71)
Sex				
Female	0.7 (0.5, 0.8)	0.4 (0.2, 0.5)	0.3 (0.2, 0.4)	43 (27, 59)
Male	0.9 (0.7, 1.2)	0.3 (0.2, 0.5)	0.6 (0.4, 0.8)	64 (51, 77)
Race/ethnicity				
White	0.6 (0.4, 0.8)	0.3 (0.1, 0.4)	0.3 (0.2, 0.5)	57 (41, 73)
Black	1.5 (1.0, 2.0)	0.6 (0.3, 0.9)	0.9 (0.5, 1.2)	57 (41, 74)
Mexican-American	1.2 (0.8, 1.6)	0.5 (0.2, 0.9)	0.7 (0.3, 1.0)	55 (35, 76)
Estimated GFR < 60 mL/min/1.73 m^2				
Age				
< 65 years	1.1 (0.9, 1.4)	0.8 (0.6, 1.0)	0.3 (0.2, 0.4)	27 (16, 38)
≥ 65 years	15 (12, 17)	12 (9, 14)	3.0 (1.4, 4.6)	21 (10, 31)
Sex				
Female	3.9 (3.2, 4.5)	3.0 (2.4, 3.7)	0.8 (0.4, 1.2)	21 (12, 31)
Male	3.1 (2.5, 3.7)	2.4 (1.8, 2.9)	0.7 (0.3, 1.1)	23 (12, 35)
Race/ethnicity				

White	4.1 (3.4, 4.7)	3.3 (2.6, 4.0)	0.8 (0.4, 1.2)	19 (9, 28)
Black	3.1 (2.5, 3.8)	2.0 (1.5, 2.5)	1.1 (0.6, 1.7)	35 (21, 49)
Mexican-American	1.3 (1.0, 1.7)	0.8 (0.5, 1.1)	0.6 (0.3, 0.9)	42 (24, 59)
Any chronic kidney disease				
Age				
< 65 years	4.3 (3.8, 4.7)	3.3 (2.9, 3.8)	0.9 (0.7, 1.2)	22 (16, 28)
≥ 65 years	22 (19, 24)	16 (14, 18)	5.7 (4.2, 7.1)	26 (20, 32)
Sex				
Female	7.9 (7.1, 8.7)	6.4 (5.6, 7.2)	1.5 (1.1, 1.9)	19 (14, 24)
Male	6.7 (6.0, 7.4)	4.6 (4.0, 5.3)	2.0 (1.6, 2.5)	31 (25, 37)
Race/ethnicity				
White	7.5 (6.7, 8.3)	5.9 (5.2, 6.7)	1.6 (1.2, 2.0)	21 (16, 26)
Black	8.4 (7.5, 9.4)	5.8 (5.0, 6.7)	2.6 (1.9, 3.3)	31 (24, 38)
Mexican-American	6.3 (5.4, 7.2)	4.2 (3.4, 4.9)	2.1 (1.4, 2.8)	34 (25, 43)

Estimates and confidence intervals are based on 500 bootstrap samples, and incorporate bootstrap estimates of persistence. Estimates for prevalence among US adults without diabetes are standardized for age, sex, and race/ethnicity to US population, as appropriate, within each stratum. Prevalence attributable to diabetes is defined as the difference in prevalence among all US adults and US adults without diabetes; proportion attributable to diabetes is defined as the ratio of the prevalence attributable to diabetes to the prevalence among all US adults. Abbreviations: ACR = albumin-creatinine ratio; GFR = glomerular filtration rate.