Supplementary Appendix

Supplement to: Tuttle KR, Jones CR, Daratha KB, et al. Incidence of chronic kidney disease among adults with diabetes, 2015–2020. N Engl J Med 2022;387:1430-1. DOI: 10.1056/NEJMc2207018

This appendix has been provided by the authors to give readers additional information about the work.

Supplementary Appendix

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Background

National surveillance data indicate 15% of the United States (US) adult population had chronic kidney disease (CKD) in 2015–2018.[1] The burden of CKD is particularly high among persons with diabetes, occurring in approximately 40% of those with type 2 diabetes and 30% of those with type 1 diabetes.[2] Contemporary data for CKD incidence in diabetes is timely and important with the emergence of highly effective new therapies for prevention and treatment, such as sodium glucose co-transporter 2 inhibitors, glucagon-like peptide-1 receptor agonists, and a non-steroidal mineralocorticoid receptor antagonist.[3-9] The study aim was to estimate contemporary CKD incidence in diabetes by demographic characteristics based on real-world data from community, academic, and safety-net healthcare delivery sites with diverse patient populations.

Data Source

Electronic health record (EHR) data from two healthcare systems, Providence and the University of California Los Angeles (UCLA) Health, were used to create the Center for Kidney Disease Research, Education, and Hope (CURE-CKD) registry with demographics, encounters, administrative codes, laboratory tests, and prescription medication.[10] Data from Providence were obtained from sites in 5 western states (Washington, Montana, Oregon, Alaska, and California). The Providence and UCLA Health Institutional Review Boards approved CURE-CKD with a determination that written informed consent was not required for this limited dataset.

Study Population

Adults ≥20 years old with diabetes between January 1, 2015 and December 31, 2020 were the study population (n=654,459; **Fig. S1**). Race and ethnic identity were extracted from the EHR. Identification algorithms for diabetes and CKD have been published.[10] Diabetes was identified by a high glycated hemoglobin level (HbA1c ≥6.5%) or sustained elevation of blood glucose levels (either two random blood glucose concentrations ≥200 mg/dL or two fasting blood

glucose concentrations ≥126 mg/dL between one day and two years apart). In those without high HbA1c or blood glucose levels, prescriptions for a glucose-lowering medication (excluding metformin prescribed for polycystic ovarian syndrome) or administrative codes identified diabetes (**Table S1**). Prescription medication data were collected at the time of diabetes identification. Incident CKD was defined by two laboratory tests ≥90 days apart: estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2, urine albumin/creatinine ratio (UACR) ≥30 mg/g, urine protein/creatinine ratio (UPCR) ≥150 mg/g, or by an administrative code (**Table S2**). Persons with diabetes not meeting the criteria for CKD over a ≥1-year observation window were considered CKD free at baseline. Incident CKD was determined by the second confirmatory abnormal laboratory value or the first CKD code after baseline. The 2021 Chronic Kidney Disease-Epidemiology (CKD-EPI) creatinine equation was used for eGFR.[11]

Statistical Analyses

CKD Incidence was computed for January 1, 2015–December 31, 2020 and in three 2-year time periods (January 1, 2015–December 31, 2016, January 1, 2017–December 31, 2018, and January 1, 2019–December 31, 2020). For each, at-risk person-time extended from the date of the first encounter with diabetes to the encounter when incident CKD occurred, or in those who did not develop CKD, to the last encounter within the same time period. Persons were included in each time period in which they had at least two encounters (**Fig. S1**). Incidence rates were computed as the number of new cases of CKD/1,000 person-years at risk. Overall CKD incidence was standardized to the 2010 US Census Bureau population by age, race and ethnicity, and sex. Rates stratified by demographics (age, race and ethnicity, sex) were adjusted for the remaining two variables. CKD incidence was also computed in a sensitivity analysis including only persons with diabetes and normal laboratory tests for CKD at baseline due to missingness of these tests

(36.1%). Incidence estimates were computed using the SAS procedure PROC STDRATE. Other analyses were completed using SAS Enterprise Guide 7.1.

Characteristics of the Study Population

Among racial and ethnic groups, the most common identity was White followed by persons who identified as Asian, Hispanic/Latino(a), and Black (**Table S3**). Identification as American Indian/Alaska Native and Native Hawaiian/Pacific Islander was ≤1%. HbA1c was 6.4±1.4% and systolic blood pressure was 129±16 mm Hg at baseline.

CKD Incidence by Demographics and Time Trends

CKD incidence was higher among older age groups compared to the 20–39 year old reference group (**Fig. S2**). Except for the Asian group, higher CKD incidence was observed among non-White groups versus the White group. CKD incidence was lower in females than males.

CKD incidence in diabetes trended downward across time periods overall and when stratified by age, race and ethnicity, and sex (**Table S4**). In a sensitivity analysis of those with normal baseline laboratory tests for CKD (n=65,854 in 2015–2016, n=123,253 in 2017–2018, and n=140,861 in 2019–2020), overall CKD incidence was 71.2 cases/1,000 person-years (95% CI 65.8–76.6) in 2015–2016, 70.2 cases/1,000 person-years (95% CI 67.6–72.8) in 2017–2018, and 65.4 cases/1,000 person-years (95% CI 63.1–67.7).

Summary, Context, Strengths, and Limitations

Among adults with diabetes treated at two US healthcare systems, CKD incidence was higher in American Indian/Alaska Native, Black, Hispanic/Latino(a), and Native Hawaiian/Pacific Islander groups compared to the White group during 2015–2020. Conversely, a lower rate of incident CKD was observed in the Asian group. CKD incidence was progressively higher with

older age and males experienced incident CKD more often than females with diabetes. Overall CKD incidence declined between 2015 and 2020 with similar trends across demographic groups.

Prior CKD incidence estimates for diabetes were derived from studies that used an outcome of kidney failure[12,13], were remote in time, conducted in small or homogenous groups, or embedded within clinical trials of treatments that affect CKD.[14-18] Therefore, those estimates do not necessarily reflect the CKD risks of larger, more diverse populations treated in contemporary US practice. By using the 2021 CKD-EPI equation that does not include a race term, we identified CKD by eGFR consistently across race groups.[11] Additionally, the laboratory criteria for CKD used in previous studies varied widely and rarely required persistence.

Strengths of CURE-CKD include a large study population, sequential years of follow-up, and curated patient-level data. Still, EHR data are inherently limited by retrospective and missing data. For example, laboratory tests for CKD were missing in about one-third of persons with diabetes at baseline. Diabetes could not be classified by type or duration due to misclassification and missingness. To address these limitations, diabetes was identified by laboratory tests and prescriptions for glucose-lowering medications in addition to administrative codes.[10] A sensitivity analysis of a subset of patients with normal baseline CKD laboratory tests also found comparable CKD incidence estimates over time, supporting the primary analysis. Finally, CURE-CKD had higher numbers in Asian/Pacific Islander and White groups and fewer in Black or Hispanic/Latino(a) groups compared to the general US population with diabetes (**Table S5**).

Disclosures

The findings and conclusions are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC). This work was supported by CDC project number 75D301-21-P-12254.

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Figure S1. Flow diagram for study population with diabetes who developed incident CKD.

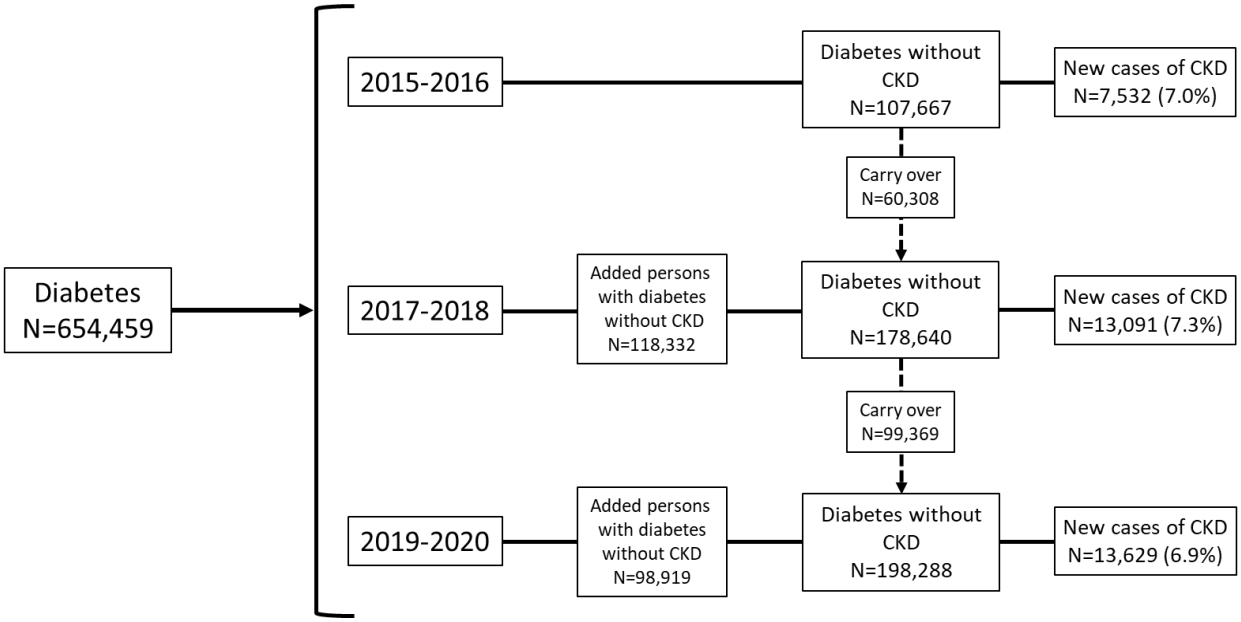

Figure S2. CKD incidence with 95% CIs in diabetes over time. A. Overall CKD incidence standardized to the 2010 US Census Bureau population by age, race and ethnicity, and sex. B. Age-specific, adjusted for sex and race and ethnicity. C. Race and ethnicity-specific, adjusted for sex and age. D. Sex-specific, adjusted for age and race and ethnicity. (AI/AN – American Indian/Alaskan Native; NH/PI – Native Hawaiian/Pacific Islander)

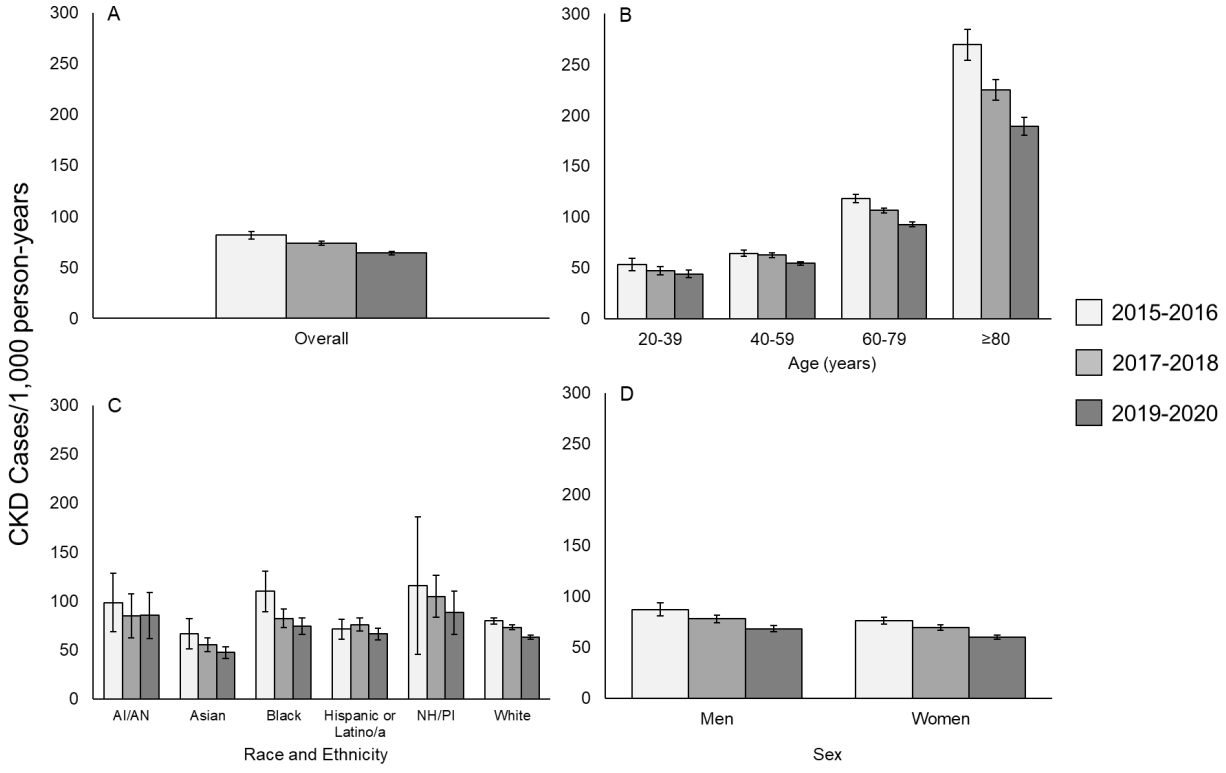

Table S1. ICD-9 and 10 codes series for identification of diabetes.

ICD Code
ICD 9
249
250
251.3
357.2
362.0, .01-.07
366.41
648.0, .00-.04
V58.67
ICD 10
E08
E09
E10
E11
E13
E89.1
O24
P70.2
R73.9
T38.3
Z79.4
Z86.31

ICD-International Classification of Diseases.

Table S2. ICD-9 and 10 code series for identification of CKD.

ICD Code Series
ICD 9
249.4, 40-.41
250.4, 40-.43
285.21
403
404
405.01, .11, .91
446.21, .4
580
581
582
583
584
585
586
587
588
589
593
599
634.3, 30-.32
635.3. 30-.32
636.3, .30-.32
637.3, .30-.32
638.3
639.3
642.1, .11-.14
646.2, .20-.24
669.3, 30, .32, .34
710.0-.2
753
791.0
866
958.5
996.73, 81
V42.0
V45.1, .11-.12
V56
ICD 10
E08.2, .21-.22, .29
E09.2, .21-.22, .29
E10.2, 21-.22, .29
E11.2, .21-.22, .29
E13.2, .21-.22, .29
D63.1
I12
I13
I15.0-.1
M32.14-.15
M35.04, 0A

N00
N01
N02
N03
N04
N05
N06
N07
N08
N10
N11
N12
N13
N14
N15
N16
N17
N18
N19
N20.0, .2
N23
N25
N26
N27
N28.0, .1, .8, .81, .83, .89, .9
N29
O03.32, .82
O04.82
O07.32
O08.4
O10.2, .21, .211-.213, .219, .22-.23, .3, .31, .311-.313, .319, .32, .33
O12.1, .10-.15, .2, .20-.25
O23.0, .00-.03
O26.83, .831-.833, .839
O90.4
Q60
Q61
Q62.0, .1, .10-.12, .3, .31-.32 .39
Q63
R31
R80
S37.0, .00, .001, .001A, .001D, .001S, .002, .002A, .002D, .002S, .009, .009A, .009D, .009S, .09, .091, .091A, .091D, .091S, .092, .092A, .092D, .092S, .099, .099A, .099D, .099S
T79.5, .5XXA, .5XXD, .5XXS
T86.1, .10-.13, .19
Z48.22
Z49
Z91.15
Z94.0
Z99.2

ICD-International Classification of Diseases

Table S3. Characteristics of persons with diabetes and without CKD at baseline by time period.

	2015–2020 N=353,565	2015–2016 N=107,667	2017–2018 N=178,640	2019–2020 N=198,288
Demographic Characteristics				
Sex, n (%)				
Female	195,318 (55.2)	59,984 (55.7)	97,318 (54.5)	106,590 (53.8)
Male	158,247 (44.8)	47,683 (44.3)	81,322 (45.5)	91,698 (46.2)
Age, years, n (%)				
20-39	38,173 (10.8)	13,132 (12.2)	20,209 (11.3)	21,776 (11.0)
40-59	111,479 (31.5)	36,784 (34.2)	61,338 (34.3)	66,520 (33.5)
60-79	166,539 (47.1)	48,509 (45.1)	83,086 (46.5)	94,714 (47.8)
80+	37,374 (10.6)	9,242 (8.6)	14,007 (7.8)	15,278 (7.7)
Age, years, mean, SD	61, 15	59, 15	60, 15	60, 15
Race and ethnicity, n (%)				
American Indian/Alaska Native	3,249 (0.9)	1,120 (1.0)	1,604 (0.9)	1,636 (0.8)
Asian	34,731 (9.8)	9,693 (9.0)	18,575 (10.4)	21,032 (10.6)
Black	16,190 (4.6)	5,101 (4.7)	8,611 (4.8)	9,118 (4.6)
Hispanic/Latino(a)	18,026 (5.1)	4,852 (4.5)	8,883 (5.0)	11,237 (5.7)
Native Hawaiian/Pacific Islander	2,657 (0.8)	824 (0.8)	1,396 (0.8)	1,616 (0.8)
White	241,293 (68.2)	75,838 (70.4)	120,210 (67.3)	131,881 (66.5)
Other[a]	37,419 (10.6)	10,239 (9.5)	19,361 (10.8)	21,768 (11.0)
Baseline Clinical Characteristics				
eGFR, mL/min/1.73m^2				
n (%)	188,473 (53.3)	56,510 (52.5)	98,178 (55.0)	107,720 (54.3)
mean, SD	90.7, 17.9	90.5, 18.2	91.4, 17.1	91.9, 16.5
SBP, mm Hg				
n (%)	231,816 (65.6)	66,507 (61.8)	119,056 (66.6)	131,453 (66.3)
mean, SD	129, 16	129, 16	129, 16	129, 16
HbA1c, %				
n (%)	113,254 (32.0)	34,098 (31.7)	61,192 (34.3)	67,464 (34.0)
mean, SD	6.4, 1.4	6.5, 1.4	6.6, 1.5	6.6, 1.5
UACR, mg/g				
n (%)	14,179 (4.0)	4,552 (4.2)	9,950 (5.6)	9,777 (4.9)
median (IQR)	8.0 (4.3-17.5)	8.7 (4.9-18.7)	7.4 (4.1-15.3)	7.2 (4.1-14.7)
Medications, n (%)				
ACE inhibitor or ARB	116,430 (32.9)	36,992 (34.4)	60,104 (33.6)	66,444 (33.5)
MRA	8,347 (2.4)	2,419 (2.2)	3,864 (2.2)	4,405 (2.2)
NSAID	117,806 (33.3)	31,125 (28.9)	54,819 (30.7)	64,796 (32.7)
PPI	83,995 (23.8)	26,220 (24.4)	40,807 (22.8)	44,314 (22.3)
Metformin	83,221 (23.5)	28,313 (26.3)	43,837 (24.5)	48,395 (24.4)
Insulin	44,709 (12.6)	13,762 (12.8)	21,582 (12.1)	25,537 (12.9)
Sulfonylurea	16,864 (4.8)	6,749 (6.3)	9,292 (5.2)	9,627 (4.9)
DPP-4 inhibitor	7,303 (2.1)	2,544 (2.4)	3,945 (2.2)	4,459 (2.2)
GLP-1 receptor agonist	4,136 (1.2)	971 (0.9)	1,895 (1.1)	2,826 (1.4)
SGLT2 inhibitor	4,115 (1.2)	926 (0.9)	1,852 (1.0)	3,036 (1.5)

CKD-chronic kidney disease; N-overall sample size; n-by group sample size; SD-standard deviation; eGFR-estimated glomerular filtration rate; SBP-systolic blood pressure; Hb-hemoglobin; UACR-urine albumin/creatinine ratio; IQR-interquartile range; ACE-angiotensin-converting enzyme; ARB-angiotensin II receptor blocker; NSAID-nonsteroidal anti-inflammatory drug; PPI-proton-pump inhibitor; MRA-mineralocorticoid receptor antagonist; DPP-dipeptidyl peptidase; GLP-glucagon-like peptide; SGLT-sodium-glucose co-transporter.

[a]includes persons who did not identify with main US Census Bureau categories.

Table S4. CKD incidence among persons with diabetes by demographics and time period.

CKD incidence (95% confidence interval)	2015–2016	2017–2018	2019–2020
Overall[*]			
New cases of CKD (n)	7,532	13,091	13,629
Person-years	74,871	143,627	170,039
Incidence rate/1,000 person-years	81.6 (78.0-85.2)	73.7 (71.5-75.8)	64.0 (62.2-65.9)
Sex-specific[†]			
Male			
New cases of CKD (n) and 95% CIs	3,723	6,798	7,097
Person-years	32,302	64,414	77,858
Incidence rate/1,000 person-years	87.3 (80.8-93.8)	78.0 (74.5-81.6)	68.3 (65.2-71.3)
Female			
New cases of CKD (n)	3,809	6,293	6,532
Person-years	42,569	79,213	92,181
Incidence rate/1,000 person-years	76.2 (72.7-79.7)	69.6 (67.1-72.1)	60.1 (57.9-62.3)
Age-specific[‡]			
20-39 years			
New cases of CKD (n)	421	682	705
Person-years	8,640	15,158	16,775
Incidence rate/1,000 person-years	53.1 (46.9-59.4)	47.1 (43.0-51.2)	44.1 (40.3-47.8)
40-59 years			
New cases of CKD (n)	1,633	3,130	3,096
Person-years	26,236	50,804	58,161
Incidence rate/1,000 person-years	64.4 (61.1-67.8)	62.5 (60.2-64.9)	54.3 (52.3-56.4)
60-79 years			
New cases of CKD (n)	3,935	7,075	7,638
Person-years	34,135	67,880	83,559
Incidence rate/1,000 person-years	118.4 (114.4-122.3)	106.4 (103.8-109.1)	92.8 (90.5-95.0)
80+ years			
New cases of CKD (n)	1,543	2,204	2,190
Person-years	5,860	9,786	11,544
Incidence rate/1,000 person-years	269.6 (254.5-284.7)	225.3 (215.0-235.6)	189.3 (180.5-198.1)
Race and ethnicity-specific[§]			
American Indian/Alaska Native			
New cases of CKD (n)	88	117	126
Person-years	758	1,219	1,298
Incidence rate/1,000 person-years	98.5 (68.5-128.6)	85.1 (62.6-107.6)	85.2 (61.5-108.9)
Asian			
New cases of CKD (n)	538	1,064	1,153
Person-years	6,685	15,039	18,246
Incidence rate/1,000 person-years	66.6 (51.2-81.9)	55.2 (48.3-62.1)	47.3 (41.5-53.1)
Black			
New cases of CKD (n)	398	700	707
Person-years	3,500	7,089	7,783
Incidence rate/1,000 person-years	109.8 (88.8-130.7)	82.2 (72.9-91.5)	74.3 (65.8-82.7)
Hispanic/Latino(a)			
New cases of CKD (n)	717	1,647	1,828
Person-years	7,475	16,556	22,282
Incidence rate/1,000 person-years	71.2 (61.0-81.3)	75.8 (69.1-82.5)	66.4 (60.5-72.3)
Native Hawaiian/Pacific Islander			
New cases of CKD (n)	51	140	135
Person-years	555	1,058	1,250
Incidence rate/1,000 person-years	115.9 (45.7-186.1)	104.5 (83.1-126.0)	88.0 (65.7-110.3)
White			

New cases of CKD (n)	5,499	9,002	9,260
Person-years	53,624	98,048	114,075
Incidence rate/1,000 person-years	79.8 (76.7-83.0)	73.0 (70.6-75.3)	63.1 (61.2-65.0)

CKD-chronic kidney disease; CI-confidence interval. *adjusted by age, race and ethnicity, and sex to the 2010 US Census Bureau; †adjusted by age, race and ethnicity; ‡adjusted by sex, race and ethnicity; §adjusted by age and sex

Table S5. Summary table of representativeness by demographics among adults ≥20 years with diabetes in CURE-CKD and in the US general population.

	CURE-CKD	US population*	Comments
			The CURE-CKD study population is derived from clinical populations in two large US healthcare systems, whereas US national data is obtained by community-based surveys. CURE-CKD excluded persons with diabetes who had prevalent CKD. The US national data report is a general summary without exclusion by comorbidities, and thus, is expected to contain some persons with prevalent CKD.
Demographics			
Sex (%)			
Female	55.2	48.8	The greater proportion of females in CURE-CKD likely reflects the sex distribution of persons with diabetes who access healthcare systems compared to the general population with diabetes.
Male	44.8	51.2	
Age, years (%)			
20-44	16.2	14.9	In contrast to the general population with diabetes, the overall age distribution in CURE-CKD was shifted toward more people with age ≥65 years and fewer people in the 45-64 year age range, but the mean age was similar.
45-64	38.8	47.3	
≥65	45.0	39.2	
Age, years (mean)	61.0	60.5	
Race and Ethnicity (%)			
American Indian/Alaska Native	0.9	0.9	The CURE-CKD population with diabetes has more persons in the Asian/Pacific Islander and White groups than the US general population with diabetes. Conversely, the proportions who identify as Black or Hispanic or Latino(a) are lower. The Other category is not represented in the Diabetes in America Report. The race and ethnic distribution in CURE-CKD may represent regional differences as well as differences between those who access healthcare and the US general population. To align with the US National Data Report, the data source for the most recent Diabetes in America Report, Asian and Pacific Islander groups were combined here, which differs from the US Census Bureau classification used in the main study analyses. Race and ethnic identities were self-reported in the US National Data Report and derived from electronic health records in CURE-CKD.
Asian/Pacific Islander	10.6	4.0	
Black	4.6	15.6	
Hispanic or Latino(a)	5.1	14.7	
White	68.2	64.8	
Other†	10.6	-	

*Diabetes in America 3rd edition. National Institute of Diabetes and Digestive and Kidney Diseases; 2018 PMID: 33651524.

†Persons who did not identify with main US Census Bureau categories.

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