Temporal Trends in the Prevalence of Diabetic Kidney Disease in the United States

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Context Diabetes is the leading cause of kidney disease in the developed world. Over time, the prevalence of diabetic kidney disease (DKD) may increase due to the expanding size of the diabetes population or decrease due to the implementation of diabetes therapies.

Objective To define temporal changes in DKD prevalence in the United States.

Design, Setting, and Participants Cross-sectional analyses of the Third National Health and Nutrition Examination Survey (NHANES III) from 1988-1994 (N=15 073), NHANES 1999-2004 (N=13 045), and NHANES 2005-2008 (N=9588). Participants with diabetes were defined by levels of hemoglobin A_{1c} of 6.5% or greater, use of glucose-lowering medications, or both (n=1431 in NHANES III; n=1443 in NHANES 1999-2004; n=1280 in NHANES 2005-2008).

Main Outcome Measures Diabetic kidney disease was defined as diabetes with albuminuria (ratio of urine albumin to creatinine ≥30 mg/g), impaired glomerular filtration rate (<60 mL/min/1.73 m^2 estimated using the Chronic Kidney Disease Epidemiology Collaboration formula), or both. Prevalence of albuminuria was adjusted to estimate persistent albuminuria.

Results The prevalence of DKD in the US population was 2.2% (95% confidence interval [CI], 1.8%-2.6%) in NHANES III, 2.8% (95% CI, 2.4%-3.1%) in NHANES 1999-2004, and 3.3% (95% CI, 2.8%-3.7%) in NHANES 2005-2008 ($P<.001$ for trend). The prevalence of DKD increased in direct proportion to the prevalence of diabetes, without a change in the prevalence of DKD among those with diabetes. Among persons with diabetes, use of glucose-lowering medications increased from 56.2% (95% CI, 52.1%-60.4%) in NHANES III to 74.2% (95% CI, 70.4%-78.0%) in NHANES 2005-2008 ($P<.001$); use of renin-angiotensin-aldosterone system inhibitors increased from 11.2% (95% CI, 9.0%-13.4%) to 40.6% (95% CI, 37.2%-43.9%), respectively ($P<.001$); the prevalence of impaired glomerular filtration rate increased from 14.9% (95% CI, 12.1%-17.8%) to 17.7% (95% CI, 15.2%-20.2%), respectively ($P=.03$); and the prevalence of albuminuria decreased from 27.3% (95% CI, 22.0%-32.7%) to 23.7% (95% CI, 19.3%-28.0%), respectively, but this was not statistically significant ($P=.07$).

Conclusions Prevalence of DKD in the United States increased from 1988 to 2008 in proportion to the prevalence of diabetes. Among persons with diabetes, prevalence of DKD was stable despite increased use of glucose-lowering medications and renin-angiotensin-aldosterone system inhibitors.

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Diabetic kidney disease (DKD) is a common and morbid complication of diabetes and the leading cause of chronic kidney disease in the developed world. Approximately 40% of persons with diabetes develop DKD, manifested as albuminuria, impaired glomerular filtration rate (GFR), or both.[1-4] Even mild degrees of albuminuria and decrease in GFR are associated with markedly increased risks of cardiovascular disease and death and higher health care costs.[5-7] In addition, DKD accounts for nearly half of all incident cases of end-stage renal disease (ESRD) in the United States.[7] Five-year survival for patients with ESRD is less than 40%; Medicare spending on the US ESRD program reached $26.8 billion in 2008.[7] Therefore, prevention of DKD is important to improve health outcomes of persons with diabetes and to reduce the societal burden of chronic kidney disease.

Two population trends could strongly influence DKD prevalence over time. First, the expanding size of the diabetes population could increase DKD prevalence. Second, widespread application of diabetes therapies could reduce DKD prevalence. From 1988 to 2006, the prevalence of diabetes among US adults aged 20 years or older increased from 7.4% to 9.6%.[8] Concurrently, clinical trials demonstrated that lowering blood glucose levels reduced the risk of developing albuminuria and other microvascular diabetes complications[9-11] and inhibitors of the renin-angiotensin-aldosterone system (RAAS)

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reduced albuminuria and the risk of progressive decrease in GFR,[12-15] leading to changes in the standards of care.[1,2]

In this study, we investigate trends in the prevalence of DKD in the United States over the past 2 decades and examine changes in disease manifestations among persons with diabetes.

METHODS

Study Population

The population-based National Health and Nutrition Examination Survey (NHANES) is a program of studies conducted by the National Center for Health Statistics to evaluate the health of noninstitutionalized adults and children in the United States.[16] The Third NHANES (NHANES III) took place from 1988-1994. Starting in 1999, NHANES became a continuous program with data compiled in 2-year blocks.

Health examinations including physical measurements and blood and urine collections are conducted in a mobile examination center. Each NHANES oversamples persons of black race, Hispanic ethnicity, or both. The current study includes participants in NHANES III, NHANES 1999-2004, and NHANES 2005-2008 who were aged 20 years or older, underwent a health examination in the NHANES mobile examination center, and had available data for medication use, levels of hemoglobin A_{1c}, serum creatinine concentrations, and urine albumin and creatinine concentrations.

All NHANES protocols were approved by the National Center for Health Statistics Research ethics review board (previously known as the NHANES institutional review board); all participants provided written informed consent.[16]

Diabetes Definition

Diabetes was defined as use of glucose-lowering medications (insulin or oral hypoglycemic medications), level of hemoglobin A_{1c} of 6.5% or greater, or both.[2,8] Level of hemoglobin A_{1c} of 6.5% or greater was recently recommended for diagnosis of diabetes by a broadly representative international expert committee and by the American Diabetes Association and is used in this study instead of fasting or postchallenge glucose to include NHANES participants who were not fasting or did not receive an oral glucose tolerance test.[2,17]

Level of hemoglobin A_{1c} was measured during all of the NHANES cycles using high-pressure liquid chromatography (coefficients of variation <3.0%).[16] Values in NHANES III and NHANES 1999-2004 were standardized to the Diabetes Control and Complications Trial laboratory. To account for change in hemoglobin A_{1c} assay location and platform, hemoglobin A_{1c} values from NHANES 2005-2008 were calibrated to values from earlier NHANES cycles using the equation: $Y = 0.4892 + 0.9277 \times X$.[8,16] We did not use self-reported history of diabetes to define diabetes to avoid bias by temporal changes in diabetes case definition and ascertainment.

DKD Definition

Diabetic kidney disease was defined as diabetes with the presence of albuminuria, impaired GFR, or both.[1,2] In each NHANES cycle, urine albumin and creatinine concentrations were measured in a random single-voided urine sample using a solid-phase fluorescent immunoassay and a Jaffe rate reaction, respectively. The ratio of urine albumin to creatinine was expressed in milligrams per gram with albuminuria defined as a level of 30 mg/g or greater.[1,2] Albuminuria is well-known to have substantial biological (intraindividual) variation, and current guidelines recommend that only persistent albuminuria be considered evidence of DKD.[1,2] Therefore, we used data from 45 participants with diabetes in NHANES III, ratio of urine albumin to creatinine of 30 mg/g or greater at their main examination, and a repeat urine sample approximately 2 weeks later to estimate the prevalence of persistent albuminuria from a single urine sample.[16] Of these 45 participants, 35 had persistent albuminuria (78%).

Serum creatinine concentrations were measured using the kinetic Jaffe rate method. Values from NHANES III and NHANES 1999-2000 were calibrated as previously described to account for laboratory drift in serum creatinine concentrations across NHANES cycles.[16,18-20] The GFR was estimated from calibrated serum creatinine concentrations using the Chronic Kidney Disease Epidemiology Collaboration equation.[21] Impaired GFR was defined as less than 60 mL/min/1.73 m^2.[1]

Other Clinical Characteristics

Age, sex, race/ethnicity, and duration of diabetes were assessed by questionnaire.[16] Type 1 diabetes was defined for descriptive purposes only using the following criteria: (1) diagnosis prior to age 30 years; (2) first insulin use within 2 years of diabetes diagnosis (allowing for reporting error); and (3) current insulin use. Medications taken during a 1-month period preceding the NHANES physical examination were assessed by in-person interview.[16] Body mass index was calculated as weight in kilograms divided by height in meters squared. Three or more consecutive blood pressure measurements separated by 30 seconds were made after 5 minutes of rest, with mean values used for analysis.

Statistical Methods

All statistical analyses were performed using Stata version 11.1 (StataCorp, College Station, Texas) and incorporated recommended NHANES weights to account for nonresponse bias and sampling.[16] For each of NHANES III, NHANES 1999-2004, and NHANES 2005-2008, we determined the prevalence of DKD in the US population and the distributions of clinical characteristics among the diabetes subpopulation using Stata's *svy* commands.

Diabetic kidney disease was evaluated in 4 mutually exclusive categories based on the presence or absence of albuminuria and impaired GFR. To estimate the prevalence of persistent albuminuria (78% of persons with ratio of urine albumin to creatinine ≥30 mg/g), 22% of participants with albuminuria alone were reclassified as having

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no DKD and 22% of participants with albuminuria and impaired GFR were reclassified as having only impaired GFR.

We also evaluated impaired GFR, persistent albuminuria, and any DKD as parallel outcomes. To estimate persistent albuminuria, we multiplied the prevalence of elevated ratio of urine albumin to creatinine by the estimated probability of persistence (0.78) and calculated corresponding 95% confidence intervals (CIs) for the product.[22] We estimated prevalence of any DKD as the sum of (1) the prevalence of impaired GFR and (2) the prevalence of normal GFR and elevated ratio of urine albumin to creatinine multiplied by the probability of persistence. We derived an ana-

Table 1. Characteristics of US Population With Diabetes

	NHANES 1988-1994 (n = 1431)		NHANES 1999-2004 (n = 1443)		NHANES 2005-2008 (n = 1280)	
	No.	Weighted Proportion (SE)[a]	No.	Weighted Proportion (SE)[a]	No.	Weighted Proportion (SE)[a]
US population, %[b]		6.0 (0.3)		7.8 (0.3)		9.4 (0.5)
Demographic variables						
Age, weighted mean (SD), y		59.7 (16.5)		58.8 (13.8)		59.1 (11.3)
Female sex, %	735	48.9 (2.1)	689	47.8 (1.4)	629	50.4 (1.9)
Race/ethnicity, %						
White (non-Hispanic)	478	68.7 (2.5)	556	63.6 (3.0)	496	62.9 (4.0)
Black (non-Hispanic)	457	16.9 (1.5)	338	14.8 (1.9)	373	17.2 (2.2)
Mexican American	451	6.6 (0.7)	430	8.1 (1.6)	257	8.7 (1.3)
Diabetes history						
Duration of diabetes, %[c]						
Previously undiagnosed	503	34.8 (1.9)	339	24.4 (1.5)	316	24.9 (2.0)
<5 y	306	25.8 (1.9)	315	25.3 (1.8)	266	22.3 (1.4)
5-<10 y	190	15.8 (1.9)	237	16.3 (1.1)	222	18.3 (1.5)
10-<20 y	243	14.7 (1.5)	267	16.6 (1.2)	275	21.6 (1.6)
≥20 y	157	8.4 (1.0)	258	16.5 (1.5)	175	11.7 (1.0)
Type 1 diabetes, %	18	5.8 (2.5)	17	2.4 (0.8)	28	4.6 (1.0)
Medication use						
Glucose-lowering medications, %	781	56.2 (2.1)	1053	70.4 (1.6)	937	74.2 (1.9)
Oral medications only	492	35.4 (1.9)	811	54.2 (1.6)	721	55.2 (1.9)
Insulin	289	20.8 (2.0)	222	16.2 (1.5)	216	19.0 (1.3)
RAAS inhibitors, %	160	11.2 (1.1)	514	34.3 (1.8)	544	40.6 (1.7)
ACE inhibitors	160	11.2 (1.1)	423	27.7 (1.4)	411	30.9 (1.4)
Angiotensin receptor blockers	0	0	101	7.3 (1.0)	145	10.2 (1.4)
Aldosterone antagonists	0	0	0	0	2	0.2 (0.2)
Lipid-lowering medications, %	74	8.9 (1.3)	419	34.0 (1.7)	642	50.2 (2.1)
Statins	28	3.6 (0.9)	372	29.6 (1.6)	531	40.5 (1.7)
Fibrates	40	4.8 (1.0)	53	4.6 (0.6)	68	6.4 (1.1)
Physical measurements, weighted mean (SD)						
Body mass index[d]		30.6 (6.7)		32.4 (7.4)		33.0 (7.4)
Systolic blood pressure, mm Hg		136.3 (19.7)		132.4 (21.4)		131.2 (20.1)
Diastolic blood pressure, mm Hg		76.2 (10.4)		70.1 (16.5)		69.3 (14.1)
Laboratory measurements						
Hemoglobin A_{1c}, %		8.1 (1.9)		7.7 (1.9)		7.3 (1.5)
Serum lipids, weighted mean (SD), mg/dL						
Total cholesterol		223.8 (53.3)		207.4 (56.0)		190.4 (44.6)
HDL cholesterol		44.1 (14.8)		46.3 (13.7)		47.5 (13.3)
LDL cholesterol		137.1 (39.4)		116.3 (35.2)		104.5 (36.4)
Triglycerides, weighted geometric mean (geometric SD), mg/dL		198.9 (2.2)		179.0 (1.9)		152.7 (1.6)

Abbreviations: ACE, angiotensin-converting enzyme; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NHANES, National Health and Nutrition Examination Survey; RAAS, renin-angiotensin-aldosterone system.
SI conversion factors: To convert HDL, LDL, and total cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113.
[a] Unless otherwise indicated.
[b] Values in this row reflect the proportion of the entire US population.
[c] The NHANES participants who were older than 80 years, whose age was truncated at 80 years in NHANES data files, and who reported an age of diabetes diagnosis after 80 years were included in a separate category not listed in this table; of those who fell into this category, there were 14 participants in NHANES 1988-1994, 21 in NHANES 1999-2004, and 18 in NHANES 2005-2008.
[d] Calculated as weight in kilograms divided by height in meters squared.

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lytical expression for the variance of any DKD prevalence using statistical results provided by Goodman.[22]

Binomial regression using a log link was used to estimate prevalence ratios and to test trends in DKD prevalence over time.[23] NHANES III, NHANES 1999-2004, and NHANES 2005-2008 were modeled primarily as nonordered independent variables. Tests for trend were performed using a continuous variable defined by the midpoint of each study period (in years).

In models examining any DKD as an outcome, participants with diabetes and albuminuria only were considered to have an outcome value of 0.78, which allowed for estimation of DKD prevalence ratios accounting for albuminuria misclassification. We used a multiple imputation approach to obtain 95% CIs for DKD prevalence ratios. For each imputation analysis, we used a different imputed persistence estimate obtained from a bootstrap sample to account for additional variability associated with estimation of persistence. The variance of the prevalence ratios was estimated by combining between- and within-imputation estimates.[24]

Models were adjusted for age (in categories), sex, and race/ethnicity. All hypothesis testing was 2-sided and *P* values of less than .05 were considered statistically significant.

RESULTS

Diabetes in the US Population

Of participants meeting our eligibility criteria from NHANES III (N=15 073), NHANES 1999-2004 (N=13 045), and NHANES 2005-2008 (N=9588), there were 1431, 1443, and 1280, respectively, who had diabetes (TABLE 1). The weighted national prevalence of diabetes was 6.0% (95% CI, 5.3%-6.7%) in NHANES III, 7.8% (95% CI, 7.1%-8.5%) in NHANES 1999-2004, and 9.4% (95% CI, 8.5%-10.4%) in NHANES 2005-2008.

DKD in the US Population

Prevalence of DKD in the US population was 2.2% in 1988-1994, 2.8% in 1999-2004, and 3.3% in 2005-2008 (TABLE 2; unadjusted $P<.001$ for trend). The demographically adjusted increase in DKD prevalence was 18% from 1988-1994 to 1999-2004 and 34% from 1988-1994 to 2005-2008 ($P=.003$ for trend).

Increases in DKD prevalence were largest for persons aged 65 years or older among whom DKD was most common. The estimated numbers of persons with DKD in the United States at any given point in time increased from 3.9 million (95% CI, 3.2-4.6 million) during 1988-1994 to 5.5 million (95% CI, 4.8-6.3 million) during 1999-2004 to 6.9 million (95% CI, 6.0-7.9 million) during 2005-2008 (FIGURE).

DKD Among Persons With Diabetes in the US Population

Among persons with diabetes, mean age, sex distribution, and the proportion of persons with type 1 diabetes were stable over the periods examined (Table 1). Larger proportions of participants described themselves as Mexican American and reported receiving a previous diagnosis of diabetes.

The proportion of persons with diabetes taking glucose-lowering medications increased from 56.2% (95% CI, 52.1%-60.4%) to 74.2% (95% CI, 70.4%-78.0%); mean hemoglobin A_{1c} values decreased from 8.1% to 7.3% (Table 1; $P<.001$ for trend). Use of RAAS inhibitors increased from 11.2% (95% CI, 9.0%-13.4%) to 40.6% (95% CI, 37.2%-43.9%) and mean systolic and diastolic blood pressures decreased from 136/76 mm Hg to 131/69 mm Hg ($P<.001$ for trend for each comparison). Use of lipid-lowering medications (primarily statins), increased from 8.9% (95% CI, 6.4%-11.4%) to 50.2% (95% CI, 46.1%-54.4%); mean low-density lipoprotein cholesterol levels decreased from 137 mg/dL to 105 mg/dL (to convert to mmol/L, multiply by 0.0259) ($P<.001$ for trend for each comparison).

Table 2. Prevalence of Diabetic Kidney Disease (DKD) in the US Population

	No. of NHANES Participants			Overall US Population: Prevalence of DKD (95% CI)			Persons With Diabetes: Prevalence of DKD (95% CI)		
	Total	Diabetes	DKD	Unadjusted, %	Adjusted Ratio[a]	*P* Value for Trend	Unadjusted, %	Adjusted Ratio[a]	*P* Value for Trend
Age ≥20 y									
1988-1994	15 073	1431	640	2.2 (1.8-2.6)	1 [Reference]		36.4 (31.2-41.6)	1 [Reference]	
1999-2004	13 045	1443	659	2.8 (2.4-3.1)	1.18 (0.99-1.42)	.003	35.2 (31.2-39.3)	0.99 (0.89-1.11)	.77
2005-2008	9588	1280	573	3.3 (2.8-3.7)	1.34 (1.11-1.61)		34.5 (30.5-38.5)	0.98 (0.87-1.10)	
Age 20-<65 y									
1988-1994	11 491	785	272	1.2 (0.9-1.6)	1 [Reference]		28.0 (21.6-34.4)	1 [Reference]	
1999-2004	9640	744	265	1.6 (1.3-1.9)	1.15 (0.88-1.51)	.19	26.9 (22.1-31.8)	0.97 (0.81-1.17)	.25
2005-2008	7263	705	249	1.8 (1.4-2.1)	1.19 (0.91-1.56)		24.6 (19.9-29.3)	0.89 (0.74-1.07)	
Age ≥65 y									
1988-1994	3582	646	368	7.1 (6.0-8.3)	1 [Reference]		49.5 (43.8-55.1)	1 [Reference]	
1999-2004	3405	649	394	8.6 (7.5-9.7)	1.20 (0.97-1.48)	.001	49.5 (44.9-54.1)	0.99 (0.89-1.12)	.77
2005-2008	2325	575	324	10.7 (9.3-12.2)	1.48 (1.19-1.83)		51.2 (45.7-56.7)	1.03 (0.89-1.18)	

Abbreviations: CI, confidence interval; NHANES, National Health and Nutrition Examination Survey.
[a] Adjusted for age, sex, and race/ethnicity.

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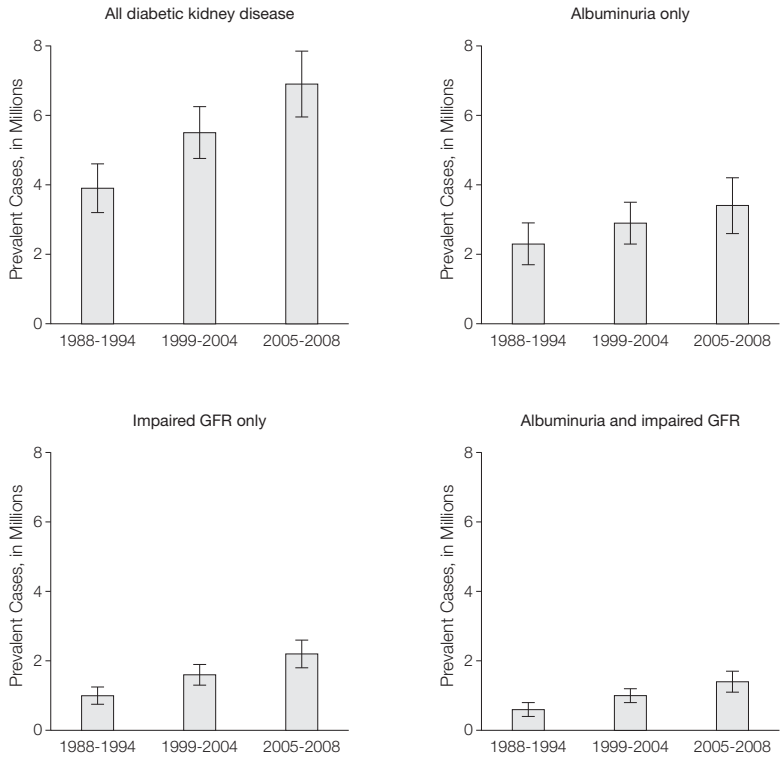
Figure. Prevalent Cases of Diabetic Kidney Disease in the United States



Prevalent cases are estimated numbers of persons in the US population and were calculated using National Health and Nutrition Examination Survey sample weighting. Error bars indicate 95% confidence intervals. GFR indicates glomerular filtration rate.

Among persons with diabetes, prevalence of any DKD was 36.4% in 1988-1994, 35.2% in 1999-2004, and 34.5% in 2005-2008 (Table 2). After adjustment for demographic factors, this represented no appreciable change over time (Table 2).

The prevalence of albuminuria (with or without impaired GFR) decreased from 27.3% in 1988-1994 to 24.9% in 1999-2004 to 23.7% in 2005-2008 (**Table 3**). After adjustment for demographic factors, the differences were not statistically significant (Table 3). In a subgroup analysis by age, the prevalence of albuminuria decreased only among persons younger than 65 years. The overall distribution of the ratio of urine albumin to creatinine (continuous variable) did not change appreciably (**Table 4**).

The prevalence of impaired GFR (with or without albuminuria) increased from 14.9% in 1988-1994 to 16.7% in 1999-2004 to 17.7% in 2005-2008, representing demographically adjusted increases in prevalence of 21% from 1999-2004 vs 1988-1994 and 29% from 2005-2008 vs 1988-1994 ($P = .03$ for trend; Table 3). After adjustment for demographic variables, the mean estimated GFR decreased by 3.9 mL/min/1.73 m^2 from 1988-1994 to 1999-2004 and from 1999-2004 to 2005-2008 (Table 4).

After adjustment for body mass index in addition to demographic factors, the prevalence ratios were 1 (reference) for 1988-1994, 0.98 (95% CI, 0.89-1.11) for 1999-2004, and 0.97 (95% CI, 0.87-1.10) for 2005-2008 for any DKD ($P = .77$ for trend); 1 (reference) for 1988-1994, 0.90 (95% CI, 0.78-1.04) for 1999-2004, and 0.84 (95% CI, 0.73-0.97) for 2005-2008 for albuminuria ($P = .03$ for trend); and 1 (reference) for 1988-1994, 1.21 (95% CI, 0.99-1.48) for 1999-2004, and 1.31 (95% CI, 1.04-1.65) for 2005-2008 for impaired GFR ($P = .02$ for trend). Prevalence of DKD did not change over time within any racial or ethnic group (eTable at http://www.jama.com).

COMMENT

We observed over the past 2 decades using national population-based data that the prevalence of DKD in the United States increased in direct proportion to the prevalence of diabetes itself. Among persons with diabetes, use of glucose-lowering medications and RAAS inhibitors increased markedly but there was no change in the prevalence of DKD. Specific clinical manifestations of DKD shifted with an increased prevalence of impaired GFR.

The increasing prevalence of DKD underscores its public health impact. Diabetes is the most common cause of chronic kidney disease, and DKD is the most common cause of ESRD in the United States. Absolute DKD prevalence estimates generated herein are conservative because the hemoglobin A_{1c}-based diabetes definition we used defines a smaller diabetes population than glucose-based definitions[8]; we estimated the prevalence of persistent albuminuria (as opposed to intermittent albuminuria); and we used an updated GFR estimating equation that defines a lower prevalence of impaired GFR than preceding equations.[21] Nonetheless, temporal trends reported herein suggest that DKD will continue to drive the prevalence of chronic kidney disease and ESRD for the foreseeable future.

Moreover, DKD carries with it substantial morbidity and mortality. Persons with diabetes are already at high risk for cardiovascular disease, and the additional development of DKD markedly amplifies their risk for cardiovascular disease and death.[5,6,25] Two recent studies comparing persons with type 1 diabetes with persons without diabetes sug-

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Table 3. Prevalence of Albuminuria and Impaired Glomerular Filtration Rate (GFR) Among Persons With Diabetes in the US Population

	Albuminuria				Impaired GFR			
		Prevalence (95% CI)				Prevalence (95% CI)		
	No.	Unadjusted, %	Adjusted Ratio[a]	*P* Value for Trend	No.	Unadjusted, %	Adjusted Ratio[a]	*P* Value for Trend
Age ≥20 y								
1988-1994	534	27.3 (22.0-32.7)	1 [Reference]		239	14.9 (12.1-17.8)	1 [Reference]	
1999-2004	531	24.9 (20.3-29.5)	0.92 (0.79-1.07)	.07	284	16.7 (14.6-18.9)	1.21 (0.99-1.48)	.03
2005-2008	447	23.7 (19.3-28.0)	0.87 (0.75-1.01)		262	17.7 (15.2-20.2)	1.29 (1.03-1.62)	
Age 20-<65 y								
1988-1994	256	26.1 (20.2-31.9)	1 [Reference]		48	4.5 (2.0-7.1)	1 [Reference]	
1999-2004	244	23.3 (18.4-28.2)	0.90 (0.72-1.11)	.05	46	5.8 (3.9-7.6)	1.42 (0.77-2.63)	.21
2005-2008	224	20.7 (16.3-25.1)	0.80 (0.65-0.99)		56	6.0 (3.9-8.2)	1.48 (0.78-2.79)	
Age ≥65 y								
1988-1994	278	29.3 (22.7-36.0)	1 [Reference]		191	31.2 (27.3-35.1)	1 [Reference]	
1999-2004	287	27.7 (22.3-33.1)	0.94 (0.76-1.15)	.62	238	35.5 (31.4-39.7)	1.14 (0.96-1.36)	.09
2005-2008	223	28.7 (23.5-33.8)	0.96 (0.79-1.16)		206	37.4 (31.5-43.3)	1.20 (0.96-1.49)	

Abbreviation: CI, confidence interval.
[a] Adjusted for age, sex, and race/ethnicity.

gest that virtually all excess mortality risk occurs in conjunction with the development of DKD.[26,27] Mean annual per-person cost of health care for Medicare recipients with DKD is $21 740 to $25 352.[7]

Among the diabetic population, use of glucose-lowering medications, RAAS inhibitors, and lipid-lowering medications increased markedly over the last 20 years, and intermediate therapeutic targets (hemoglobin A_{1c}, blood pressure, and low-density lipoprotein cholesterol) were substantially improved but this did not translate to a decreased prevalence of DKD. Trends in medication use reflect results of high-quality clinical trials published during this period in addition to epidemiological and health services work focused on education and implementation.

The Diabetes Control and Complications Trial and the UK Prospective Diabetes Study demonstrated that tight glucose control prevents the development of albuminuria in types 1 and 2 diabetes, respectively.[9-11] However, tight glucose control has not been proven to prevent decrease in GFR in randomized controlled trials. RAAS inhibitors reduce albuminuria, at least in part by hemodynamic effects reducing intraglomerular pressure.[28] Effects of RAAS inhibitors on GFR are more complex, with short-term reductions in GFR mediated by hemodynamic changes and long-term prevention of progressive reductions in GFR attributable to attenuation of progressive parenchymal injury.[12-15]

Table 4. Clinical Manifestations of Diabetic Kidney Disease Among Persons With Diabetes in the US Population[a]

	Unadjusted Mean (95% CI)	Adjusted Difference (95% CI)[b]
Ratio of urine albumin to creatinine, mg/g[c]		
1988-1994	20.8 (17.9 to 24.0)	0 [Reference]
1999-2004	19.9 (18.2 to 21.7)	–4.3 (–19.4 to 13.6)
2005-2008	20.3 (18.5 to 22.2)	–2.1 (–17.2 to 15.9)
Estimated GFR, mL/min/1.73 m^2		
1988-1994	85.8 (83.6 to 88.0)	0 [Reference]
1999-2004	83.4 (81.6 to 85.2)	–3.9 (–5.8 to –2.0)
2005-2008	83.4 (81.4 to 85.4)	–3.9 (–6.1 to –1.8)

Abbreviations: CI, confidence interval; GFR, glomerular filtration rate.
[a] All data are weighted to reflect the diabetic population of the United States.
[b] Adjusted for age, sex, and race/ethnicity. For ratio of urine albumin to creatinine, values are relative (expressed as % difference); for estimated GFR, values are absolute (expressed as difference in mL/min/1.73 m^2).
[c] Unadjusted mean values expressed as geometric means.

Thus, the suggestion of a trend toward declining prevalence of albuminuria observed in this study, at least among younger persons with diabetes, may be a direct result of improved glycemic control and RAAS inhibition. The increased prevalence of impaired GFR may be due to the hemodynamic effects of the RAAS inhibitors, including control of blood pressure to lower levels. However, RAAS inhibitors reduce GFR by approximately 4 mL/min/1.73 m^2 in clinical trials with high levels of adherence[29] so that a 30% increase in the prevalent use of RAAS inhibitors is unlikely to fully account for the 3.9 mL/min/1.73 m^2 decrease in estimated GFR observed herein. Therefore, it also is possible that implementation of diabetes treatments requires more time to demonstrate benefit, or that current diabetes therapies are failing to prevent decrease in GFR when applied on the population level.

Notably, most therapies targeting DKD have been developed while focusing on albuminuria reduction, potentially selecting for interventions that reduce albuminuria more than they preserve GFR.[30] Our results suggest that additional interventions are needed to prevent the development of diabetes and to target GFR loss once diabetes is diagnosed.

Characteristics of the diabetes population also may have changed in a man-

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ner that predisposes to DKD. Stable age and sex distributions in the diabetes population and multivariable modeling demonstrated that lack of decline in DKD prevalence is not due to demographic changes. Self-reported duration of diabetes increased over time, and longer disease duration could counterbalance concurrent changes favoring reduced DKD prevalence. Because diabetes diagnostic criteria and ascertainment changed during the study period, this possibility cannot be excluded. The diabetic population became more obese over the study period, and obesity is known to increase the risks of developing albuminuria and impaired GFR.[31-33] However, prevalence of DKD was stable, accounting for changes in body mass index.

Diabetic kidney disease was initially characterized as a disease manifesting as albuminuria followed by decrease in GFR.[34-36] However, a number of studies demonstrated that impaired GFR can occur without substantial albuminuria and that DKD can manifest solely as impaired GFR.[37-41] Our study suggests that the clinical pattern of DKD may be shifting over time, with more impaired GFR and the possibility of decreased albuminuria, which could be due to changes in diabetes treatment. Renal pathology underlying this shift and long-term implications of this shift on cardiovascular complications and ESRD remain to be determined. The increasingly frequent manifestation of impaired GFR (at least relative to albuminuria) supports current guidelines recommending screening for GFR in addition to albuminuria.[1,2]

Strengths of this study include the use of data with broad external validity, assessment of temporal trends over 20 years during which diabetes treatment changed substantially, examination of complementary albuminuria and GFR manifestations of DKD, and use of conservative and temporally unbiased definitions of diabetes and DKD.

This study also has limitations. NHANES does not include institutionalized persons, and persons who are ill with advanced DKD may be underrepresented. Despite careful effects to minimize assay drift, this may still affect the study results. Specifically, mean serum creatinine concentration was noted to increase over time among young, healthy NHANES participants (different participants at each cycle), suggesting that a subtle artificial decline in mean estimated GFR may persist despite calibration; measurement of urine albumin and creatinine also is not standardized.[20] Absolute estimates of persistent albuminuria prevalence were based in part on repeat measurements in a small group of NHANES III participants. This introduces uncertainty in albuminuria prevalence estimates (as reflected in the reported 95% CIs) but probably does not bias the analysis of temporal trends.

In conclusion, DKD has become more prevalent in the US population over the last 2 decades and will likely contribute increasingly to health care costs and mortality. Among persons with diabetes, clinical manifestations of DKD shifted to include more impaired GFR but the prevalence of any DKD did not change despite increased use of diabetes-related medications.

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Study concept and design: de Boer, Himmelfarb.
Acquisition of data: de Boer, Rue.
Analysis and interpretation of data: de Boer, Rue, Hall, Heagerty, Weiss, Himmelfarb.
Drafting of the manuscript: de Boer, Hall, Himmelfarb.
Critical revision of the manuscript for important intellectual content: de Boer, Rue, Hall, Heagerty, Weiss, Himmelfarb.
Statistical analysis: Rue, Hall, Heagerty.
Obtained funding: de Boer.
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Study supervision: de Boer, Weiss.
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