Prevalence of Chronic Kidney Disease in the United States

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Context The prevalence and incidence of kidney failure treated by dialysis and transplantation in the United States have increased from 1988 to 2004. Whether there have been changes in the prevalence of earlier stages of chronic kidney disease (CKD) during this period is uncertain.

Objective To update the estimated prevalence of CKD in the United States.

Design, Setting, and Participants Cross-sectional analysis of the most recent National Health and Nutrition Examination Surveys (NHANES 1988-1994 and NHANES 1999-2004), a nationally representative sample of noninstitutionalized adults aged 20 years or older in 1988-1994 (n=15 488) and 1999-2004 (n=13 233).

Main Outcome Measures Chronic kidney disease prevalence was determined based on persistent albuminuria and decreased estimated glomerular filtration rate (GFR). Persistence of microalbuminuria (>30 mg/g) was estimated from repeat visit data in NHANES 1988-1994. The GFR was estimated using the abbreviated Modification of Diet in Renal Disease Study equation reexpressed to standard serum creatinine.

Results The prevalence of both albuminuria and decreased GFR increased from 1988-1994 to 1999-2004. The prevalence of CKD stages 1 to 4 increased from 10.0% (95% confidence interval [CI], 9.2%-10.9%) in 1988-1994 to 13.1% (95% CI, 12.0%-14.1%) in 1999-2004 with a prevalence ratio of 1.3 (95% CI, 1.2-1.4). The prevalence estimates of CKD stages in 1988-1994 and 1999-2004, respectively, were 1.7% (95% CI, 1.3%-2.2%) and 1.8% (95% CI, 1.4%-2.3%) for stage 1; 2.7% (95% CI, 2.2%-3.2%) and 3.2% (95% CI, 2.6%-3.9%) for stage 2; 5.4% (95% CI, 4.9%-6.0%) and 7.7% (95% CI, 7.0%-8.4%) for stage 3; and 0.21% (95% CI, 0.15%-0.27%) and 0.35% (0.25%-0.45%) for stage 4. A higher prevalence of diagnosed diabetes and hypertension and higher body mass index explained the entire increase in prevalence of albuminuria but only part of the increase in the prevalence of decreased GFR. Estimation of GFR from serum creatinine has limited precision and a change in mean serum creatinine accounted for some of the increased prevalence of CKD.

Conclusions The prevalence of CKD in the United States in 1999-2004 is higher than it was in 1988-1994. This increase is partly explained by the increasing prevalence of diabetes and hypertension and raises concerns about future increased incidence of kidney failure and other complications of CKD.

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CHRONIC KIDNEY DISEASE (CKD) is now recognized as a common condition that elevates the risk of cardiovascular disease as well as kidney failure and other complications.[1-3] The number of patients with kidney failure treated by dialysis and transplantation (the end stage of CKD) has increased dramatically in the United States from 209 000 in 1991 to 472 000 in 2004.[4] The age-, sex-, and race-adjusted incidence of end-stage renal disease increased by 43% during the decade following 1991.[4] Estimation of the prevalence of earlier stages of CKD in the US population and ascertainment of trends over time is central to disease management and prevention planning, particularly given the increase in the prevalence of obesity, diabetes,[5,6] and hypertension,[7,8] the leading risk factors for CKD.[5]

Earlier stages of CKD are defined based on the combination of kidney damage (most often quantified using albuminuria) and decreased kidney function (quantified as glomerular filtration rate [GFR] estimated from the serum creatinine concentration).[2] The National Health and Nutrition Examination Surveys (NHANES) have provided a rigorous basis for estimating CKD prevalence. These large nationally representative surveys conducted by the National Center of Health Statistics (NCHS) include a laboratory assessment of albuminuria and serum creatinine allowing for identification and staging of CKD regardless of the participant or their physician's awareness

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of the condition. Initial prevalence estimates for CKD stages in NHANES 1988-1994 in adults have provided a benchmark for kidney disease studies, prevention efforts, and health care planning.[1,9] Later studies have compared NHANES 1988-1994 estimates with NHANES 1999-2000 data and found an increased prevalence of albuminuria but no significant increase in the overall prevalence of CKD. The precision of these trend estimates was constrained by the relatively small sample size of the 1999-2000 survey[10] and limited data to establish consistent calibration of the creatinine assays over time. A recent study calibrating serum creatinine in all NHANES surveys from 1988 to 2004 permits a more rigorous examination of the trends in the prevalence of CKD using standardized creatinine.[11] Estimation of GFR from serum creatinine is the recommended approach for CKD staging at this time and increasing evidence shows a strong association with risk even when applied to the general population.[3,12-15]

We compare the prevalence of CKD in NHANES 1988-1994 with NHANES 1999-2004 and describe the distribution of CKD stages and severity. The effect of the increasing prevalence of diabetes and changes in hypertension and obesity are examined as explanatory variables for changes in CKD prevalence in the general US adult population.

METHODS

Study Population

The NHANES are cross-sectional, multistage, stratified, clustered probability samples of the US civilian noninstitutionalized population conducted by the NCHS, a branch of the Centers for Disease Control and Prevention.[16] The NHANES analyzed were conducted from 1988-1994 in 2 phases (1988-1991 and 1991-1994) and from 1999-2004 in 3 phases (1999-2000, 2001-2002, and 2003-2004), and the data from the 2 phases and 3 phases, respectively, were combined herein following NCHS recommendations.[17,18] The protocols for conduct of NHANES were approved by the NCHS institutional review board and informed consent was obtained from all participants.[19,20]

In all NHANES, certain subgroups of the population were oversampled including Mexican Americans, non-Hispanic blacks, and elderly persons to ensure adequate sample sizes of these groups. Individuals participated in an interview conducted at home and also in an extensive physical examination performed at a mobile examination center, which included blood and urine collection. We limited the study population to persons examined in a mobile examination center who were aged 20 years or older and who were not missing serum creatinine measurements: 15 488 in NHANES 1988-1994 (7471 in 1988-1991 and 8017 in 1991-1994) and 13 233 in NHANES 1999-2004 (4101 in 1999-2000, 4684 in 2001-2002, and 4448 in 2003-2004).

Measures of Kidney Function and Kidney Damage

Serum creatinine was measured using a kinetic rate Jaffe method. To appropriately estimate GFR, all serum creatinine measurements were recalibrated to standardized creatinine measurements obtained at the Cleveland Clinic Research Laboratory (Cleveland, Ohio) as detailed recently.[11] Briefly, frozen serum samples (approximately 200 specimens from NHANES 1988-1994 and each later 2-year survey [1999-2000, 2001-2002, and 2003-2004]) were thawed and reassayed for serum creatinine in 2006. Regression models were developed to correct serum creatinine values in NHANES 1988-1994 and 1999-2000 (standard creatinine = $-0.184 + 0.960 \times$ NHANES 1988-1994 uncalibrated serum creatinine and standard creatinine = $0.147 + 1.013 \times$ NHANES 1999-2000 uncalibrated serum creatinine). No correction was needed for the 2001-2002 and 2003-2004 surveys.

The GFR was estimated using the abbreviated Modification of Diet in Renal Disease (MDRD) Study formula. This formula was developed based on 1628 participants in which serum creatinine, age, sex, and race were related to GFR measured using urinary clearance of ^{125}I-iothalamate.[21] The formula initially used serum creatinine measured by a kinetic rate Jaffe method but was later reexpressed to use standard creatinine[22] as follows: GFR = $175 \times$ (standardized serum creatinine)$^{-1.154} \times$ (age)$^{-0.203} \times 0.742$ (if the individual is female) or $\times 1.212$ (if the individual is black). Estimated GFR is reported in mL/min/1.73 m^2 and race is either black or not black. Values that exceeded 200 mL/min/1.73 m^2 were truncated at that level and individuals were classified using standard criteria.[1] Individuals with estimated GFR below 15 mL/min/1.73 m^2 (CKD stage 5) were excluded because estimates of this stage are likely to be unreliable due to the small number of individuals and the likelihood that many of these individuals are ill or receiving dialysis and would have a low response rate.

A random spot urine sample was obtained from participants examined at a mobile examination center using a clean-catch technique and sterile containers. Frozen nonhematuric specimens were analyzed. Urine albumin and creatinine concentrations were measured in the same laboratory during all surveys. Albumin was measured by solid phase fluorescence immunoassay and urine creatinine was measured by the modified kinetic Jaffe method using a Synchron AS/Astra Analyzer (Beckman Coulter, Fullerton, California). Urinary albumin-to-creatinine ratio was computed and is reported in milligrams per gram. Albuminuria is defined as an albumin-to-creatinine ratio of 30 mg/g or higher, with microalbuminuria defined as an albumin-to-creatinine ratio of 30 mg/g to 299 mg/g, and macroalbuminuria defined as an albumin-to-creatinine ratio of 300 mg/g or higher.

Persistent albuminuria was defined as kidney damage (CKD stages 1-2). Repeated measurements obtained approximately 2 weeks after the original examination in a subset of 1241 participants in NHANES 1988-1994 were used to estimate the persistence of mi-

croalbuminuria as described previously.[1,9,10] Briefly, the proportion of individuals with persistent albuminuria was calculated as the proportion with albuminuria at a single visit × 50.9% for those with microalbuminuria and an estimated GFR of more than 90 mL/min/1.73 m^2; 75.0% for those with microalbuminuria and an estimated GFR of 60 to 89 mL/min/1.73 m^2; and 100% for those with macroalbuminuria regardless of estimated GFR. These same persistence estimates were applied to both surveys and all age, sex, and race groups thereby influencing only the prevalence of CKD stages 1 and 2 but not trends over time or associations with other factors. Standard errors (SEs) incorporate sampling variation in the persistence estimates above. All albuminuria analyses excluded women who were pregnant or menstruating.

The CKD stages were categorized based on the classification system established by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative.[1] The CKD stages are defined as follows: stage 1, persistent albuminuria with an estimated GFR higher than 90 mL/min/1.73 m^2; stage 2, persistent albuminuria with an estimated GFR of 60 to 89 mL/min/1.73 m^2; stage 3, a GFR of 30 to 59 mL/min/1.73 m^2; and stage 4, a GFR of 15 to 29 mL/min/1.73 m^2. NHANES 1999-2004 participants were asked if they were aware they had "weak or failing kidneys" and the responses were tabulated by the presence of markers of CKD.

Assessment of Demographics and Risk Factors for Kidney Disease

NHANES included measurement of height and weight, which was used for the calculation of body mass index (BMI; calculated as weight in kilograms divided by height in meters squared). Information on age, sex, race/ethnicity (categorized as non-Hispanic white, non-Hispanic black, Mexican American, or all other) and smoking was based on self-report during the interview portion of the survey. Smoking status was determined using answers to the questions: "Have you smoked at least 100 cigarettes in your life?" and "Do you now smoke cigarettes?" Hypertension and diabetes were defined by a physician diagnosis that was self-reported by the participant because CKD is most strongly related to these conditions. Fasting glucose (available for only half of the participants) and measured blood pressure were not used in the primary analysis but yielded similar results in sensitivity analyses (data not shown).

Statistical Analyses

Analyses were performed incorporating the sampling weights to obtain unbiased estimates from the complex NHANES sampling design using Stata version 8.2 (StataCorp, College Station, Texas). The SEs for all estimates were obtained using the Taylor series (linearization) method following NHANES recommended procedures and weights.[16-18] Estimates and SEs were obtained for each survey period. Comparisons across surveys and 95% confidence interval (CI) estimates for CKD stages incorporating persistence data on microalbuminuria were made using bootstrap methods implemented in Stata. Adjustment was conducted using the direct method for age and logistic regression for multiple variables. Estimates from this study are nationally representative of the noninstitutionalized US population of adults aged 20 years or older. Prevalence estimates were applied to the 2000 US census to obtain estimates of the number of individuals with CKD in the United States in the year 2000. In hypothesis testing, a P value of less than .05 was the level of significance used in this study.

A sensitivity analysis (conservative trends analysis) was conducted by adjusting serum creatinine so its mean level in a young healthy subgroup was identical between the 1988-1994 and 1999-2004 surveys. The goal of this analysis was to determine if differences in mean serum creatinine across surveys (potentially indicating a residual laboratory calibration difference) might explain some or all of the changes in the prevalence of CKD. Among 8728 participants aged 20 to 39 years without diagnosed hypertension or diabetes, the weighted mean standardized serum creatinine levels were 0.04 mg/dL (to convert to µmol/L, multiply by 88.4) lower in 1988-1994 than in 1999-2004 ($P < .001$). In the conservative trends analysis, this value was added to the 1988-1994 data to make the mean value in the young healthy group identical across surveys. The later surveys were chosen as the reference group because their creatinine assay yielded unbiased results compared with reference methods.[11]

RESULTS

NHANES 1988-1994 included 15 488 participants and NHANES 1999-2004 included 13 233 participants aged 20 years or older examined at the mobile examination center with an estimated GFR of at least 15 mL/min/1.73 m^2. During the period between the surveys, the US population became older and included a smaller proportion of non-Hispanic whites (TABLE 1). The shift in age distribution was less pronounced in individuals older than 60 years in which CKD is more common. At the same time, the prevalence of self-reported diabetes and hypertension increased as did the mean BMI and proportion of the population that is overweight and obese, which are all risk factors for CKD.

Mean albuminuria increased across the surveys but mean albumin-to-creatinine ratio was not different among young healthy individuals (12.2 mg/g in 1988-1994 and 12.3 mg/g in 1999-2004). The mean serum creatinine concentration was higher in 1999-2004 compared with 1988-1994, corresponding to a lower mean estimated GFR in 1999-2004. The conservative trends analysis, which added 0.04 mg/dL to the serum creatinine concentration in NHANES 1988-1994, resulted in nearly identical mean serum creatinine concentrations and mean estimated GFRs across surveys.

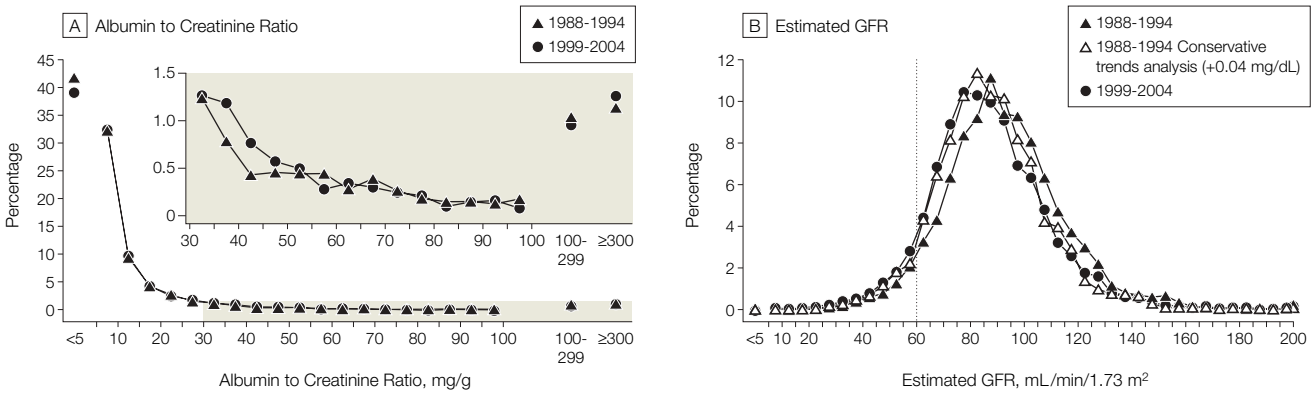
FIGURE 1 shows the distribution of albuminuria (panel A) and estimated

Table 1. Population Characteristics of US Adults Aged 20 Years or Older Based on NHANES 1988-1994 and NHANES 1999-2004[a]

	NHANES 1988-1994 (n = 15 488)			NHANES 1999-2004 (n = 13 233)		
	No. of Participants	% (SE)	Mean (SE); Median (IQR)	No. of Participants	% (SE)	Mean (SE); Median (IQR)
Age, y	15 488		44.8 (0.5)	13 233		46.2 (0.3)
Age group, y						
20-39	6367	45.7 (1.0)		4714	39.4 (0.8)	
40-59	4194	31.7 (0.6)		3921	38.3 (0.7)	
60-69	2174	11.4 (0.5)		2015	10.5 (0.4)	
≥70	2753	11.2 (0.7)		2583	11.9 (0.4)	
Sex						
Female	8214	52.2 (0.5)		6925	51.8 (0.4)	
Male	7274	47.9 (0.5)		6308	48.2 (0.4)	
Race/ethnicity						
Non-Hispanic white	6450	76.9 (1.3)		6764	72.6 (1.7)	
Non-Hispanic black	4168	10.3 (0.6)		2477	10.5 (1.0)	
Mexican American	4250	5.1 (0.4)		3009	7.3 (0.9)	
Other	620	7.7 (0.8)		983	9.6 (1.2)	
Diabetes, self-report	1266	5.4 (0.3)		1278	6.8 (0.3)	
Hypertension, diagnosed	4211	23.8 (0.7)		4120	27.1 (0.8)	
Body mass index[b]	15 453		26.6 (0.1)	12 857		28.1 (0.1)
<25	6073	44.5 (0.9)		4083	34.4 (0.6)	
25-29.99	5435	33.1 (0.6)		4640	34.8 (0.7)	
≥30	3945	22.3 (0.7)		4134	30.8 (0.7)	
Urine albumin, mg/dL[c]	14 319		26.5 (1.7); 6.2 (2.7-12.8)	12 216		32.5 (2.1); 7.1 (3.7-14.1)
Urine creatinine, mg/dL[c]	14 319		129.0 (1.4); 117.6 (63.3-78.7)	12 216		129.7 (1.6); 118.0 (65.0-178.0)
Albuminuria (ACR), mg/g[c]	14 319		25.4 (1.7); 5.6 (3.5-10.1)	12 216		28.6 (2.3); 5.9 (3.9-11.0)
Standard serum creatinine, mg/dL	15 488		0.843 (0.003)	13 233		0.888 (0.003)
Estimated GFR, mL/min/1.73 m^2	15 488		92.7 (0.5)	13 233		87.4 (0.4)
Conservative trends analysis						
Serum creatinine, mg/dL	15 488		0.884 (0.003)	NA		NA
Estimated GFR, mL/min/1.73 m^2	15 488		87.5 (0.5)	NA		NA

Abbreviations: ACR, albumin to creatinine ratio; GFR, glomerular filtration rate; IQR, interquartile range; NA, data not available; NHANES, National Health and Nutrition Examination Surveys.
SI conversion factor: To convert creatinine to µmol/L, multiply values by 88.4.
[a] Examined individuals excluding persons with an estimated GFR of less than 15.
[b] Calculated as weight in kilograms divided by height in meters squared.
[c] Only a total of 14 319 participants were available for these analyses because these data required a urine analysis and excluded pregnant or menstruating women.

Figure 1. Albumin to Creatinine Ratio and Estimated Glomerular Filtration Rate (GFR) in NHANES 1988-1994 and 1999-2004



The inset in panel A shows the higher range of albuminuria in greater detail. Panel B includes data on GFR estimated from a conservative trends analysis in which 0.04 mg/dL was added to serum creatinine to eliminate the difference in mean GFR between surveys. The vertical line in panel B demarcates an estimated GFR of 60 mL/min/1.73 m^2, which defines decreased GFR. For both panels, the statistical testing is done for the overall mean and for meaningful categories (ie, estimated GFR <60 and albumin to creatinine ratio ≥30). NHANES indicates National Health and Nutrition Examination Surveys.

GFR (panel B) in the 2 surveys. The distribution of albumin to creatinine ratio is skewed in both surveys. There is a somewhat higher prevalence of albuminuria during 1999-2004 compared with 1988-1994 in the ranges of 35 to 49 mg/g and 300 mg/g or higher (panel A). The distribution of estimated GFR is more symmetric with a higher prevalence of values below 60 mL/min/1.73 m^2 in 1999-2004 than in 1988-1994. The conservative trends analysis aligns the mean estimated GFR across surveys with implications for subsequent sensitivity analyses.

The proportion of the US population with mild, moderate, or severely reduced estimated GFR increased from 1988-1994 to 1999-2004 (TABLE 2). The combined prevalence estimate for 1999-2004 had similar precision to the 1988-1994 estimate while prevalence estimates from each of the three 2-year surveys had relatively wide 95% CIs. Moderately reduced GFR increased in prevalence from 5.4% to 7.7% ($P<.001$) and the prevalence of severely reduced GFR increased from 0.21% to 0.35% ($P=.02$; Table 2). Similarly, the proportion of the overall population with microalbuminuria on a single occasion increased from 7.1% to 8.2% ($P=.01$). The prevalence of macroalbuminuria increased somewhat from 1.1% to 1.3% but this difference was well within the limits of random variation ($P=.37$). Subdividing the prevalence of albuminuria by different levels of estimated GFR showed that the prevalence of microalbuminuria increased significantly among individuals with normal estimated GFR while all other subgroups showed no significant increase or decrease in albuminuria.

The prevalence estimate for each stage of CKD was higher in 1999-2004 than in 1988-1994 with the difference being statistically significant for CKD stages 2 through 4 and overall (TABLE 3). Stratified analyses by sex and race showed similar trends. The overall prevalence of CKD among men was 8.2% in 1988-1994 and 11.1% in 1999-2004. Among women, the prevalences were 12.1% and 15.0%, respectively. By ethnicity, the change was from 10.5% to 13.8% among non-Hispanic whites, 10.2% to 11.7% among non-Hispanic blacks, and from 6.3% to 8.0% among Mexican Americans. The age-adjusted prevalence odds ratios (ORs) for an estimated GFR of less than 60 mL/min/

Table 2. Prevalence of Kidney Function and Albuminuria Categories in US Adults Aged 20 Years or Older Based on NHANES 1988-1994 and NHANES 1999-2004[a]

	NHANES 1988-1994		NHANES 1999-2004		
	No. of Participants	% (SE)	No. of Participants	% (SE)	*P* Value
Kidney function (GFR), mL/min/1.73 m^2					
Normal (≥90)	8600	51.9 (1.1)	5891	40.7 (1.0)	<.001
Mildly reduced (60-89)	5751	42.4 (1.0)	5946	51.2 (0.8)	<.001
Moderately reduced (30-59)	1088	5.4 (0.3)	1316	7.7 (0.3)	<.001
Severely reduced (15-29)	49	0.21 (0.03)	80	0.35 (0.05)	.02
Albuminuria (ACR), mg/g[b]					
Overall					
Normal	12 655	91.8 (0.4)	10 636	90.5 (0.3)	.01
Microalbuminuria	1353	7.1 (0.4)	1315	8.2 (0.3)	.01
Macroalbuminuria	311	1.1 (0.1)	265	1.3 (0.1)	.37
GFR ≥90 mL/min/1.73 m^2					
Normal	7182	94.1 (0.5)	4594	92.1 (0.5)	.003
Microalbuminuria	532	5.3 (0.5)	435	7.2 (0.5)	.004
Macroalbuminuria	76	0.6 (0.1)	49	0.7 (0.1)	.53
GFR 60-89 mL/min/1.73 m^2					
Normal	4778	91.8 (0.5)	5143	91.8 (0.4)	.96
Microalbuminuria	568	7.2 (0.4)	588	7.4 (0.4)	.69
Macroalbuminuria	117	1.0 (0.1)	83	0.8 (0.1)	.29
GFR 30-59 mL/min/1.73 m^2					
Normal	682	72.2 (1.9)	877	75.6 (1.6)	.18
Microalbuminuria	243	22.0 (1.8)	270	18.3 (1.3)	.10
Macroalbuminuria	96	5.8 (0.8)	104	6.1 (0.7)	.82
GFR 15-29 mL/min/1.73 m^2					
Normal	13	37.5 (12.5)	22	34.0 (7.9)	.81
Microalbuminuria	10	19.9 (8.6)	22	23.7 (6.1)	.72
Macroalbuminuria	22	42.6 (8.8)	29	42.4 (8.2)	.98

Abbreviations: ACR, albumin to creatinine ratio; GFR, glomerular filtration rate; NHANES, National Health and Nutrition Examination Surveys.
[a] Age-adjusted prevalence estimates for microalbuminuria and macroalbuminuria in 1988-1994 adjusted to the 1999-2004 age distribution in Table 1 are 7.2% and 1.2%, respectively.
[b] Women who were pregnant or in menses were excluded. Normal was defined as an ACR of less than 30; microalbuminuria, an ACR of 30 to 299; and macroalbuminuria, an ACR of 300 or greater.

1.73 m^2 were all between 1.4 and 1.5 and statistically significant in men, women, non-Hispanic whites and blacks, and Mexican Americans with a somewhat weaker association in the smaller number of individuals of other ethnicity.

Trends over time were also similar within age categories, indicating the trends were not due to age differences in the population (FIGURE 2). In both NHANES surveys, the prevalence of CKD increased with age with stages 1 and 2 increasing from 2% to 3% at age 20 to 39 years to 9% to 10% after the age of 70 years. The prevalence of stage 1 alone did not increase with age because an increasing prevalence of albuminuria was offset by a decreasing proportion of individuals with a GFR of 90 mL/min/1.73 m^2 or higher. The prevalences for stage 3 and 4 combined were 0.2% in 1988-1994 and 0.7% in 1999-2004 at aged 20 to 39 years compared with 27.8% in 1988-1994 and 37.8% in 1999-2004 after the age of 70 years. The dramatic increase in prevalence is consistent with the known decline of measured GFR with age.[23] At each age, the prevalence of decreased GFR was higher in the 1999-2004 survey than in the 1988-1994 survey ($P < .05$ for ages 20-39, 40-59, and ≥70 years).

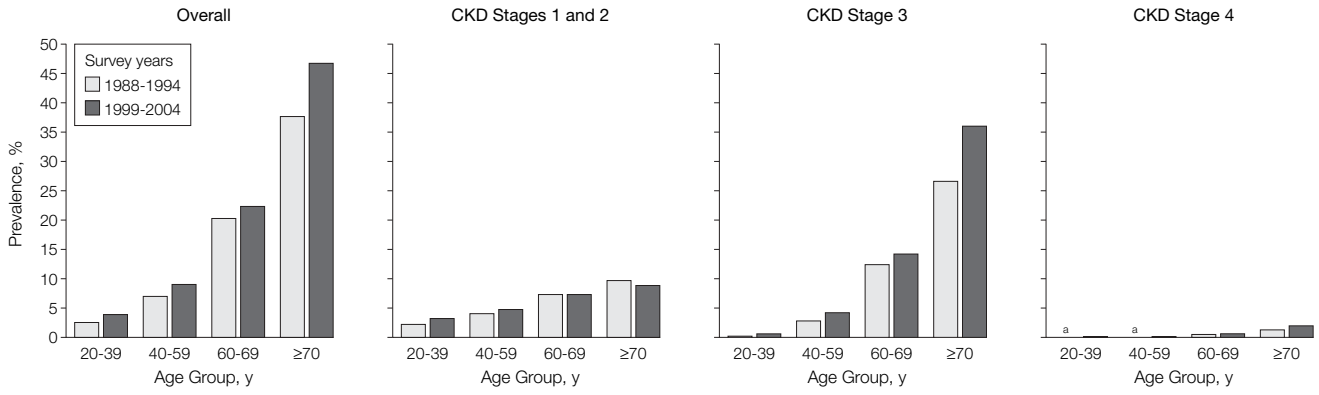
Differences in prevalence of decreased GFR and albuminuria between 1988-1994 and 1999-2004 remain substantial after adjustment for changes in the age, sex, and race/ethnic composition of the US population during this period (TABLE 4). The higher prevalence of diagnosed diabetes, hypertension, and higher BMI explained some of the higher prevalence. For albuminuria trends, the higher prevalence was partly explained by the older age and high proportion of minority groups (OR declined from 1.18 to 1.12 after adjustment). Further adjustment for the higher prevalence of diagnosed diabetes and hypertension and higher BMI explained practically all of the difference (OR declined to 1.03). In the fully adjusted models, the prevalence of albuminuria was strongly associated with diagnosed diabetes (OR, 3.58; 95% CI, 3.12-4.12) and hypertension (OR, 1.70; 95% CI, 1.10-1.92) as well as older age and all race/ethnicity groups other than non-Hispanic whites ($P < .001$) but not higher BMI ($P = .12$). The prevalence OR of estimated GFR of less than 60 mL/min/1.73 m^2 in 1999-2004 compared with 1988-1994 was 1.47. Age adjustment had little impact, likely because the increase in the number of older individuals was offset by a

Table 3. Prevalence of Chronic Kidney Disease (CKD) Stages in US Adults Aged 20 Years or Older Based on NHANES 1988-1994 and NHANES 1999-2004

CKD Stage[a]	Prevalence, % (95% CI)		Prevalence Ratio for NHANES 1999-2004 to 1988-1994 (95% CI)	Estimated No. of US Adults in 2000, No. in Millions (95% CI)
	NHANES 1988-1994	NHANES 1999-2004		
1	1.71 (1.28-2.18)	1.78 (1.35-2.25)	1.05 (0.85-1.30)	3.6 (2.7-4.5)
2	2.70 (2.17-3.24)	3.24 (2.61-3.88)	1.21 (1.03-1.41)	6.5 (5.2-7.8)
3	5.42 (4.89-5.95)	7.69 (7.02-8.36)	1.42 (1.25-1.62)	15.5 (14.1-16.8)
4	0.21 (0.15-0.27)	0.35 (0.25-0.45)	1.70 (1.11-2.51)	0.7 (0.5-0.9)
5	NA	NA	NA	NA
Total	10.03 (9.16-10.91)	13.07 (12.04-14.10)	1.30 (1.19-1.43)	26.3 (24.2-28.3)

Abbreviations: CI, confidence interval; NA, data not included because patients with CKD stage 5 were excluded; NHANES, National Health and Nutrition Examination Surveys.
[a] Defined based on standard criteria[1]: stage 1, persistent albuminuria with glomerular filtration rate (GFR) higher than 90 mL/min/1.73 m^2; stage 2, persistent albuminuria with GFR of 60 to 89 mL/min/1.73 m^2; stage 3, GFR of 30 to 59 mL/min/1.73 m^2; stage 4, GFR of 15 to 29 mL/min/1.73 m^2. The age-adjusted prevalence rates for CKD stages 1, 2, 3, and 4 in 1988-1994 adjusted to the 1999-2004 age distribution in Table 1 are 1.7%, 2.8%, 5.6%, and 0.2%, respectively, for a total of 10.3%.

Figure 2. Prevalence of Chronic Kidney Disease (CKD) Stages by Age Group in NHANES 1988-1994 and 1999-2004



NHANES indicates National Health and Nutrition Examination Surveys.
[a] There were no cases in 1988-1994.

similar increase in the number of younger individuals, allowing the percentage of individuals aged 60 years or older to remain relatively unchanged (Table 1). The prevalence OR increased further to 1.53 after adjustment for age, sex, and race due to the lower prevalence of decreased GFR among minority groups. The OR decreased to 1.43 with additional adjustment for diagnosed diabetes, hypertension, and BMI. In the fully adjusted model, the prevalence of low GFR was strongly associated with diagnosed diabetes (OR, 1.54; 95% CI, 1.28-1.80) and hypertension (OR, 1.98; 95% CI, 1.73-2.67) as well as higher BMI (OR, 1.08; 95% CI, 1.02-1.15 per 5-unit increment of BMI) and older age but was lower among males, non-Hispanic blacks, and Mexican Americans compared with non-Hispanic whites ($P < .001$).

The conservative trends analysis showed that the difference in mean serum creatinine concentration between surveys accounts for much but possibly not all of the higher prevalence of lower GFR in 1999-2004. In this analysis, the prevalence of CKD in 1988-1994 was higher (1.5 for stage 1, 2.8 for stage 2, 6.7 for stage 3, and 0.23 for stage 4 for a total of 11.3). The prevalence OR of estimated GFR less than 60 mL/min/1.73 m^2 was 1.17 (95% CI, 1.02-1.34). After full adjustment in the conservative trends analysis, the prevalence OR of decreased GFR between surveys was 1.08 (95% CI, 0.94-1.24), indicating that the differences in mean serum creatinine concentration, demographics, diagnosed diabetes, hypertension, and BMI between surveys explain nearly all of the difference in prevalence of low GFR between 1988-1994 and 1999-2004 ($P = .27$).

The proportion of individuals who reported being aware they had weak or failing kidneys in 1999-2004 (not asked in 1988-1994) was low. In CKD stage 3, 11.6% (SE, 2.0%) of men and only 5.5% (SE, 0.8%) of women reported being aware of having weak or failing kidneys. Even among men with CKD stage 3 and elevated albuminuria, awareness of weak or failing kidneys was only 22.8% (SE, 3.9%). In stage 4, there was no longer a sex difference but the percentage was still only 42% (SE, 8%). Awareness rates increased among women between 1999-2000 and 2003-2004 but rates were low in all survey periods.

COMMENT

Analysis of survey data from a representative sample of the US population shows that the prevalence rate of CKD is high. Estimates from 1999-2004 are higher than those in 1988-1994, which reflected an increase in microalbuminuria as well as an increase in the prevalence of moderately and severely reduced estimated GFR. Overall, the prevalence rate of CKD increased from 10.0% (95% CI, 9.1-10.9) to 13.1% (95% CI, 12.0-14.1). This increase was only slightly explained by the aging of the US population because the age-adjusted prevalence estimate of CKD stages 1 through 4 only increased to 10.3% when the 1988-1994 prevalence was adjusted to the 1999-2004 age structure. The increased prevalence of diagnosed diabetes and hypertension and obesity explained some of the increase in prevalence. In contrast, these factors explained the entire increase in the prevalence of albuminuria. Awareness of CKD remains very low, even among individuals with both reduced kidney function and albuminuria. The estimated number of individuals with CKD increased even more dramatically because of the growth in the US population aged 20 years or older from 178 million in 1990 to 197 million in 2000.

The increase in prevalence of CKD is partly explained by the increase in a number of CKD risk factors, including an aging US population and an increase in the proportion of individuals with obesity, diagnosed diabetes, and hypertension.[5,24,25] The proportion of

Table 4. Logistic Regression of Albuminuria and Decreased Estimated Glomerular Filtration Rate (GFR) Comparing NHANES 1999-2004 With NHANES 1988-1994 Before and After Adjustment

	Trends		Conservative Trends Analysis[a]	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Albuminuria in NHANES 1999-2004 vs 1988-1994				
Unadjusted	1.18 (1.03-1.34)	.01		
Adjusted for age	1.15 (1.00-1.32)	.05		
Sex and race[b]	1.12 (0.99-1.28)	.08		
Diagnosed diabetes and hypertension[b]	1.06 (0.93-1.21)	.39		
Body mass index[b]	1.03 (0.90-1.18)	.63		
Estimated GFR <60 mL/min/1.73 m^2 in NHANES 1999-2004 vs 1988-1994				
Unadjusted	1.47 (1.27-1.69)	<.001	1.17 (1.02-1.34)	.03
Adjusted for age	1.50 (1.31-1.73)	<.001	1.13 (0.99-1.30)	.07
Sex and race[b]	1.53 (1.33-1.76)	<.001	1.15 (1.00-1.32)	.05
Diagnosed diabetes and hypertension[b]	1.45 (1.27-1.67)	<.001	1.10 (0.96-1.26)	.17
Body mass index[b]	1.43 (1.24-1.63)	<.001	1.08 (0.94-1.24)	.29

Abbreviations: CI, confidence interval; NHANES, National Health and Nutrition Examination Surveys; OR, odds ratio.
[a] Serum creatinine among young healthy participants (aged 20-39 years without diabetes and hypertension) was adjusted to be identical across surveys by adding 0.04 mg/dL to serum creatinine in NHANES 1988-1994.
[b] Indicates addition of variables to the model in the previous row.

minority populations has also increased although the prevalence of CKD in these populations in NHANES is not higher than that in non-Hispanic whites. This lower CKD prevalence among ethnic minorities compared with whites is in contrast to the higher dialysis rates in these groups and remains unexplained. One explanation could be that the MDRD Study equation performs differently in various ethnic and racial groups. Mexican Americans and Native Americans in particular were not represented in the MDRD Study in which the equation was developed. Nonetheless, the MDRD Study equation was validated in 5504 individuals and showed little bias among blacks.[26] An underestimate in whites and women may explain some of the higher prevalence in these groups. It has been hypothesized that the lower prevalence of CKD among blacks could be due to hyperfiltration and faster progression through CKD stage 3.[10,27] However, differential errors in GFR estimation cannot be ruled out. Studies measuring GFR in population-based samples of individuals of different ethnicities and ages are needed. Adjustment for all risk factors explained nearly the entire increase in the prevalence of albuminuria but only a fraction of the increase in the prevalence of low estimated GFR (Table 4). This is partly explained by the stronger association of diabetes with albuminuria compared with low GFR. In addition, albuminuria and low GFR show opposite associations with non-Hispanic black and Mexican American race/ethnicity.

The CKD prevalence estimates reported herein are higher than those reported previously. For 1988-1994, the prevalence based on the recent calibration to standard serum creatinine concentration is 10.0% compared with a prevalence of 8.8% reported previously using the same criteria. This difference is the result of a difference between the initial calibration of serum creatinine concentration to the MDRD Study Beckman Synchron CX3 method for assaying creatinine and the most recent calibration to the Roche Enzymatic method.[28] The new calibration resulted in higher values in the 1988-1994 and 1999-2000 surveys (0.05 and 0.10 mg/dL, respectively, at 1.0 mg/dL).[11] The previous calibration of the 1999-2000 survey was conducted during a single month of the survey rather than a random sample of specimens from throughout the survey period. Thus, only recently has there been data from a panel of masked frozen specimens from each survey analyzed at a single laboratory to provide a direct comparison of serum creatinine concentration across all of the surveys. The high correlation between the original creatinine measures and the assays performed for calibration (r=0.98 for 1988-1994, r=0.98 for 1999-2000, r=0.98 for 2001-2002, and r=0.99 for 2003-2004) lends support to our ability to make reliable comparisons. The prevalence estimates presented herein differ from those in a recent brief report,[29] which also analyzed NHANES data, for 3 main reasons: we estimated CKD stage 1 or 2 based on persistent albuminuria rather than counting all individuals with microalbuminuria; we used the MDRD Study equation expressed in standard creatinine because it corresponds to the calibration of NHANES serum creatinine concentration to standard creatinine; and we also estimated the effect of a conservative trends analysis, which indicates much of the change in the prevalence of CKD is related to a subtle but influential difference in the estimate mean serum creatinine concentration of the population.

Despite an updated laboratory calibration traceable to criterion standard reference methods using a random sample of specimens from each NHANES survey, small residual differences in laboratory measurements across surveys cannot be ruled out. Increased muscle mass or increased protein intake could also have increased the mean serum creatinine concentration. Laboratory or non–kidney-related effects on serum creatinine concentration were of particular concern because there was a higher mean standard serum creatinine concentration in the 1999-2004 survey compared with the 1988-1994 survey, even among young participants without diagnosed diabetes or hypertension. The persistence of the increase in CKD prevalence from 1988-1994 to 1999-2004 even after equalizing the mean serum creatinine concentration in a conservative trends analysis supports the conclusion that the increase in CKD prevalence is real. However, CKD prevalence estimates are sensitive to small differences in serum creatinine concentration and the magnitude of the increase in prevalence could be smaller than that suggested by a simple comparison across surveys.

The new data on trends in CKD provide a larger context for trends in kidney failure treated by dialysis and transplantation. The age- and sex-adjusted incidence of end-stage renal disease in the United States increased 42% between 1991 and 2001. During this time, there has been a consistent slowing in the rate of growth of treated kidney failure rates from greater than 10% per year in the 1980s to a decrease of 1.1% between 2002 and 2004. However, the 2004 rate of 339 per million is still far higher than the Healthy People 2010 goal of 217 per million population.[4] Furthermore, models of the treated kidney failure epidemic suggest that even with adjusted rates leveling off, the growing prevalence of diabetes and the aging of the population will result in a progressive increase in the number of patients treated for kidney failure. It is estimated that by 2015 there will be 136 000 patients with incident end-stage renal disease per year and 712 000 patients with prevalent disease.[30] Our analysis suggests that the increasing prevalence of diabetes is already leading to a measurable increase in the earlier stages of CKD (stages 1-4).

Interpretation of the high prevalence of CKD in the US population should take into account its wide spectrum of disease severity, etiology, and comorbid conditions. Within CKD stages 1 and 2, persistent microalbuminuria outnumbers macroalbuminuria approximately 9 to 1. Although al-

buminuria is the strongest risk factor for CKD progression, it is also associated with an increased risk of cardiovascular morbidity and mortality.[13] Chronic kidney disease stages 3 and 4 are marked by complications of reduced GFR. Chronic kidney disease stage 3 outnumbers CKD stage 4 approximately 20 to 1; within stage 3, the upper half of estimated GFR outnumbers the lower half by 3 to 1. In one study,[13] CKD stage 4 was associated with a 17.6% risk of progression to kidney failure and a 45.7% mortality risk during a mean follow-up of 3 years. By contrast, in CKD stage 3, the risk for progression to kidney failure was 1.1% but the mortality risk was 24.3% compared with 0.07% and 10.2%, respectively, in patients without CKD. Better data are needed to allow physicians to combine information on estimated GFR, albuminuria, and other clinical characteristics to predict kidney disease progression, complications of reduced GFR and cardiovascular disease, as well as to establish the balance of risks and benefits for the treatment of different patient subgroups with CKD.

This study has a number of limitations including reliance on estimation of GFR, rather than direct measurement using injection of an exogenous marker. Equations for estimating GFR have limited precision compared with measured GFR. Imprecision and bias are greater at higher GFR, limiting the accuracy of classification in the mildly decreased GFR group.[26,31] In addition, systematic differences between the measured and estimated GFR may be influenced by the population in which the equation is applied.[31,32] Such a bias might contribute to racial/ethnic differences in prevalence estimates, but any systematic difference would apply to all of the NHANES surveys and would be unlikely to affect the trends reported herein. The persistence of albuminuria was estimated based on limited data and assumed to be the same across surveys, age, and other subgroups. The data are not sufficient to test this assumption. However, by assuming the same persistence in the different surveys, the trends observed cannot be the result of changes in estimated persistence rate of microalbuminuria. Differential nonresponse, particularly lower response among sicker individuals, could have biased the present prevalence estimates. This bias may be most plausible for the more advanced stages of CKD and thus, the prevalence of CKD stage 4 may be underestimated among individuals who volunteered to participate in NHANES. In addition, both NHANES surveys only sampled noninstitutionalized adults. Chronic kidney disease prevalence in nursing homes and its trends over time is unknown but likely to be high. In 2000, 1.6 million (4.5%) adults older than age 65 years were in nursing homes.[33]

In conclusion, survey data suggest that the prevalence of CKD in the United States is high and has increased between 1988-1994 and 1999-2004, from 10% to 13%, while awareness of kidney disease among the general public remains very low. The increasing prevalence of diagnosed diabetes and hypertension has contributed to this increase, which may propagate to higher rates of complications and kidney failure requiring dialysis or transplantation. Earlier stages accounted for most of the individuals with CKD. Because individuals with early stages of CKD have a higher risk of cardiovascular disease morbidity and mortality than their risk of progression to kidney failure, cardiovascular risk factor management in this group is critical. The high prevalence of CKD overall, and particularly among older individuals and persons with hypertension and diabetes, suggests that CKD needs to be a central part of future public health planning.

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Acquisition of data: Coresh, Selvin, Manzi, Stevens, Eggers, Van Lente.
Analysis and interpretation of data: Coresh, Selvin, Stevens, Manzi, Kusek, Eggers, Levey.
Drafting of the manuscript: Coresh, Selvin.
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Medicine is the only profession that labors incessantly to destroy the reason for its existence.
—James Bryce (1838-1922)