CKD Surveillance Using Laboratory Data From the Population-Based National Health and Nutrition Examination Survey (NHANES)

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Surveillance for chronic kidney disease (CKD) using nationally representative samples of the US population is central in providing information about the magnitude and trends in CKD burden that will guide disease management and prevention planning for clinicians and public health authorities. We used a cross-sectional study design to estimate the change in prevalence of CKD over time by using National Health and Nutrition Examination Survey (NHANES) data. NHANES III (1988-1994) included 15,488 participants and NHANES rounds 1999-2004 included 13,233 participants older than 20 years with serum creatinine measurements who were examined in a mobile examination center. Early stages of CKD were defined by glomerular filtration rate (GFR) estimated by using the Modification of Diet in Renal Disease (MDRD) Study equation and urinary albumin-creatinine ratio following the classification system established by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative. Moderately decreased GFR increased in prevalence from 5.4% to 7.7% ($P < 0.001$) and severely decreased GFR increased from 0.21% to 0.35% ($P = 0.02$) from 1988-1994 to 1999-2004. Within CKD stage 3, 18.6% $\pm$ 1.6% (SE) of individuals should be referred to a nephrologist following a proposed set of criteria for referral; referral rates were highest for individuals with diabetes and lower in whites compared with other race-ethnicity groups. These survey data suggest that the prevalence of CKD has increased between 1988-1994 and 1999-2004. Surveillance for early stages of CKD (stages 1 to 4) should monitor these and other trends.

Am J Kidney Dis 53(S3):S46-S55.

INDEX WORDS: Surveillance; kidney; National Health and Nutrition Examination Survey (NHANES); national surveys; glomerular filtration rate (GFR).

Chronic kidney disease (CKD) has become a global public health problem and is a common condition in the United States.[1,2] CKD is associated with a wide range of complications in addition to the risk of progression to kidney failure or end-stage renal disease (ESRD) requiring dialysis or transplantation and being a marker of high cardiovascular disease risk.[3] From 1991 to 2001, the incidence of treated ESRD adjusted for age, race, and sex increased by 43%, and in 2004, there were approximately 472,000 patients with treated ESRD, the final stage of CKD.[4] In the last 2 decades, prevalences of obesity, diabetes, and hypertension have also increased.[5-8] Given the increase in incidence of ESRD and prevalence of major CKD risk factors, it is important to track trends over time in the prevalence of all stages of CKD.

Surveillance for CKD is central in providing information about the magnitude and trends in burden of CKD that will guide disease management and prevention planning for both clinicians and public health authorities. Surveillance, defined as "the continuing scrutiny of all aspects of occurrence and spread of a disease that are pertinent to effective control,"[9] can take many forms and can focus on diagnosed or undiagnosed disease. For kidney disease, surveillance can monitor high-risk subgroups for incident CKD to take clinical action or quantify changes in the incidence or prevalence of CKD in populations to guide public health activities. In contrast to patients with treated ESRD, for whom both prevalence and incidence trends are available, incidence data for patients with CKD are more limited and trends in incidence are largely unavailable. Here, we focus on quantifying the total prevalence of CKD, including both diagnosed and undiagnosed disease, in the US population. This requires a representative sample of the population and the means to determine whether individuals in the sample have CKD regardless of previous diagnosis. Unlike ESRD, marked by clinical symptoms indicating a need for renal

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0272-6386/09/5303-0106$36.00/0

doi:10.1053/j.ajkd.2008.07.054

replacement therapy, earlier stages of CKD are mostly asymptomatic. Thus, the diagnosis of CKD relies on laboratory values of markers for kidney damage, quantified by persistent albuminuria and decreased kidney function classified as glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2.[1] GFR can be measured directly by using urine and serum concentrations of such exogenous substances as inulin, iodine-125–iothalamate, or iohexol.[10] However, estimating GFR from serum creatinine level is the presently recommended method for CKD staging and is more feasible in the large studies that are required for accurate estimation of total CKD burden in the United States.[1,2]

The National Health and Nutrition Examination Surveys (NHANES) conducted by the National Center for Health Statistics (NCHS) represent an ideal sample for estimating the total burden of CKD and have been used extensively for estimating CKD prevalence in the broader US population. We summarize data from a recent publication updating trends data from 1988 to 2004[11] and expand on the characteristics of subgroups within CKD stage 3, which contains the largest number of individuals compared with any other CKD stage. The NHANES include laboratory measurement of both albuminuria and serum creatinine, thus allowing for the staging of CKD in a nationally representative sample regardless of the participants' awareness or history of diagnosis of CKD. Surveillance requires the ability to evaluate estimates of incidence or prevalence from current data against similar estimates from similar past data. As such, initial estimates of the prevalence of CKD stages from NHANES III (1988-1994) have provided a benchmark for kidney disease studies, prevention efforts, and health care planning.[2,12] Studies have compared estimates from NHANES 1999-2000 with the baseline estimates provided by NHANES III, finding an increased prevalence of albuminuria, but no significant increase in overall prevalence of CKD. The precision of these trend estimates was constrained by the relatively small sample size of the 1999-2000 survey and may have been biased because of limited data to establish consistent calibration of the creatinine assays over time.[12] Proper assay calibration is necessary when comparing estimates derived from laboratory data to ensure correct and unbiased comparisons, especially when assays are performed years apart and/or in different laboratories. A recent study calibrating serum creatinine levels in all NHANES from 1988 to 2004 permitted a more rigorous examination, with less bias, of the trends in the prevalence of CKD using standardized creatinine.[13]

We compare the prevalence of CKD in 1988-1994 with 1999-2004 and describe the distribution of CKD stages and severity. In particular, CKD stage 3 is described in detail, and the impact of proposed criteria for referral to a nephrologist is explored. The impact 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

The methods used here have been published in detail recently.[11] Briefly, the NHANES are cross-sectional multistage stratified clustered probability samples of the US civilian noninstitutionalized population conducted by the NCHS.[14] We analyzed data from NHANES III and combined NHANES 1999-2000, 2001-2002, and 2003-2004 (NHANES 1999-2004) following NCHS recommendations.[15,16] All surveys oversampled certain subgroups of the US population, including non-Hispanic blacks, Mexican Americans, and the elderly, to obtain adequate sample sizes for these groups in subsequent analyses.

Urinary albumin and creatinine concentrations were assayed in the same laboratory for all surveys. Urinary albumin-creatinine ratio (ACR; in milligrams per gram) was computed and forms the basis for the definition of albuminuria. Microalbuminuria is defined as ACR of 30 to less than 300 mg/g, and macroalbuminuria is defined as ACR of 300 mg/g or greater. All albuminuria analyses excluded women who were pregnant or in menses. Serum creatinine was measured by using a kinetic rate Jaffé method. All serum creatinine measurements were recalibrated to standardized creatinine measurements obtained at the Cleveland Clinic Research Laboratory (Cleveland, OH).[13] This recalibration is necessary for appropriate estimation of GFR and accurate assessment of trends in prevalence over time using the different NHANES.

GFR was estimated from recalibrated serum creatinine by using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation.[17] The MDRD Study equation originally was developed using serum creatinine measured by means of a kinetic rate Jaffé method; here, we use the isotope dilution mass spectrometry–traceable MDRD Study equation that uses standardized creatinine[18]: GFR $= 175 \times$ (standardized serum creatinine)$^{-1.154} \times$ (age)$^{-0.203} \times 0.742$ (if the individual is a woman) $\times$ 1.212 (if the individual is black). Estimated GFR (eGFR) is reported in milliliters per minute per 1.73 m^2. GFR, estimated from standardized serum creatinine level, and ACR were used to define early

stages of CKD according to the classification system established by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI)[2] as follows: stage 1, persistent albuminuria with eGFR of 90 mL/min/1.73 m^2 or greater; stage 2, persistent albuminuria with eGFR of 60 to 89 mL/min/1.73 m^2; stage 3, eGFR of 30 to 59 mL/min/1.73 m^2; and stage 4, eGFR of 15 to 29 mL/min/1.73 m^2.

Estimation of the proportion of individuals with CKD stage 3 eligible for referral to a nephrologist followed the criteria proposed in the KDOQI hypertension guidelines.[19] Using these guidelines, all individuals with eGFR less than 30 mL/min/1.73 m^2 would be recommended for referral. Individuals with eGFR of 30 mL/min/1.73 m^2 or greater would be referred based on any of the following indications of increased risk of CKD progression: (1) presence of macroalbuminuria, (2) type 2 diabetes with microalbuminuria, (3) diabetic retinopathy, (4) hyperkalemia (serum potassium $>$ 5.5 mEq/L), and (5) resistant hypertension. For this analysis, resistant hypertension was defined as systolic blood pressure greater than 130 mm Hg or diastolic blood pressure greater than 80 mm Hg while using 3 or more antihypertensive medications. This analysis excluded women who were pregnant or in menses and was limited to NHANES III because this was the only survey with data for retinopathy.

Given the complex survey design and oversampling of certain subgroups, statistical analyses were performed using sampling weights to obtain unbiased estimates of CKD prevalence using Stata, version 8.2 (StataCorp, College Station, TX). SEs for all estimates were obtained by using the Taylor series (linearization) method following NHANES-recommended procedures and weights.[14-16] Multivariable logistic regression was used to compare albuminuria and eGFR less than 60 mL/min/1.73 m^2 in NHANES 1999-2004 with NHANES III. Demographic variables (age, sex, and race), body mass index (BMI), and diagnosed diabetes and hypertension were entered in the model to assess the amount by which changes in these CKD risk factors would account for any increase in CKD prevalence. Information about age, sex, race/ethnicity, and smoking was based on self-report during the survey interview. Hypertension and diabetes were defined by self-report of physician diagnosis. Height and weight were measured during NHANES examinations and used to calculate BMI (kg/m^2). A sensitivity analysis (conservative trends analysis) was performed by adding 0.04 mg/dL to serum creatinine levels in NHANES III so that the mean level in a young healthy subgroup was identical to NHANES 1999-2004. The aim of this analysis is to determine whether a difference in mean serum creatinine levels between the surveys, potentially caused by residual laboratory calibration difference, might account for the changes in prevalence of CKD.

RESULTS

NHANES III included 15,488 participants and NHANES rounds 1999-2004 included 13,233 participants older than 20 years with serum creatinine measurements. 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 at older than 60 years, at which time CKD is more common. At the same time, the prevalence of self-reported diabetes and hypertension increased, as did mean BMI and proportion of the population that is overweight and obese, all risk factors for CKD. Mean albuminuria increased across the surveys, but mean ACR was not different in young healthy individuals (12.2 mg/g in 1988-1994 and 12.3 mg/g in 1999-2004). Mean serum creatinine level was higher in 1999-2004 compared with 1988-1994, corresponding to a lower mean eGFR in 1999-2004. The conservative trends analysis that added 0.04 mg/dL to the serum creatinine level in NHANES III resulted in nearly identical mean serum creatinine levels and mean eGFRs across surveys.

The proportion of the US population with mild, moderate, or severely decreased eGFRs increased from 1988-1994 to 1999-2004. The combined prevalence estimate for 1999-2004 had precision similar to the 1988-1994 estimate, whereas prevalence estimates from each of the three 2-year surveys had relatively wide confidence intervals (CIs; Fig 1). Moderately decreased GFRs increased in prevalence from 5.4% to 7.7% ($P < 0.001$), and severely decreased GFRs increased from 0.21% to 0.35% ($P = 0.02$). Similarly, the proportion of the overall population with microalbuminuria on a single occasion increased from 7.1% to 8.2% ($P = 0.01$). The prevalence of macroalbuminuria increased from 1.1% to 1.3%, but this difference was well within the limits of random variation ($P = 0.4$). Subdividing the prevalence of albuminuria by different levels of eGFR showed that the prevalence of microalbuminuria increased significantly in individuals with normal eGFR, whereas all other subgroups showed no significant increase or decrease in albuminuria.[11]

The prevalence estimate for each stage of CKD was higher in 1999-2004 than in 1988-1994, and the difference was statistically significant for CKD stages 2 to 4 and overall (Table 2). Stratified analyses by sex and race showed similar trends. The overall prevalences of CKD in 1988-1994 and 1999-2004 in men were 8.2% and 11.1%. In women, they were 12.1% and 15.0%. By ethnicity, the change was from 10.5% to 13.8% in non-Hispanic whites, 10.2% to 11.7%

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

	NHANES 1988-1994			NHANES 1999-2004		
	No. of Participants	Mean or %	SE	No. of Participants	Mean or %	SE
Mean age (y)	15,488	44.8	0.5	13,233	46.2	0.3
Age group (y)						
20-39 (%)	6,367	45.7	1.0	4,714	39.4	0.8
40-59 (%)	4,194	31.7	0.6	3,921	38.3	0.7
60-69 (%)	2,174	11.4	0.5	2,015	10.5	0.4
≥70 (%)	2,753	11.2	0.7	2,583	11.9	0.4
Sex						
Women (%)	8,214	52.2	0.5	6,925	51.8	0.4
Men (%)	7,274	47.9	0.5	6,308	48.2	0.4
Race						
Non-Hispanic white (%)	6,450	76.9	1.3	6,764	72.6	1.7
Non-Hispanic black (%)	4,168	10.3	0.6	2,477	10.5	1.0
Mexican American (%)	4,250	5.1	0.4	3,009	7.3	0.9
Other (%)	620	7.7	0.8	983	9.6	1.2
Diabetes, self-report (%)	1,266	5.4	0.3	1,278	6.8	0.3
Hypertension, diagnosed (%)	4,211	23.8	0.7	4,120	27.1	0.8
Mean BMI (kg/m^2)	15,453	26.6	0.1	12,857	28.1	0.1
BMI group (kg/m^2)						
<25 (%)	6,073	44.5	0.9	4,083	34.4	0.6
25-29.99 (%)	5,435	33.1	0.6	4,640	34.8	0.7
≥30 (%)	3,945	22.3	0.7	4,134	30.8	0.7
Kidney function (GFR; mL/min/1.73 m^2)						
Normal, ≥90 (%)	8,600	51.9	1.1	5,891	40.7*	1.0
Mildly reduced, 60-89 (%)	5,751	42.4	1.0	5,946	51.2*	0.8
Moderately reduced, 30-59 (%)	1,088	5.4	0.3	13,16	7.7*	0.3
Severely reduced, 15-29 (%)	49	0.21	0.03	80	0.35†	0.05
Albuminuria (ACR), mg/g‡						
Normal, ACR <30 (%)	12,655	91.8	0.4	10,636	90.5†	0.3
Microalbuminuria, ACR 30-299 (%)	1,353	7.1	0.4	1,315	8.2†	0.3
Macroalbuminuria, ACR ≥ 300 (%)	311	1.1	0.1	265	1.3	0.1

Note: 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. Conversion factors for units: ACR in mg/g to mg/mmol, ×0.113; GFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, ×0.01667.

Abbreviations: ACR, albumin-creatinine ratio; BMI, body mass index; GFR, glomerular filtration rate; NHANES, National Health and Nutrition Examination Survey.

*$P < 0.001$ compared with 1988-1994.

†$P < 0.05$ compared with 1988-1994.

‡Women who were pregnant or in menses were excluded.

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in non-Hispanic blacks, and 6.3% to 8.0% in Mexican Americans. After age adjustment, prevalence odds ratios (ORs) for eGFR less than 60 mL/min/1.73 m^2 between 1999-2004 and 1988-1994 were of similar magnitude (1.4 to 1.5) and statistically significant in men, women, non-Hispanic whites, non-Hispanic blacks, and Mexican Americans. The association was weaker in the smaller number of individuals of other ethnicity. Trends over time also were similar within age categories, indicating the trends were not caused by age differences in the population (data not shown[11]).

Differences in prevalences 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 3). The greater prevalence of diagnosed diabetes, hypertension, and greater BMI explained some of the greater prevalence. For albuminuria trends, the greater prevalence was partly

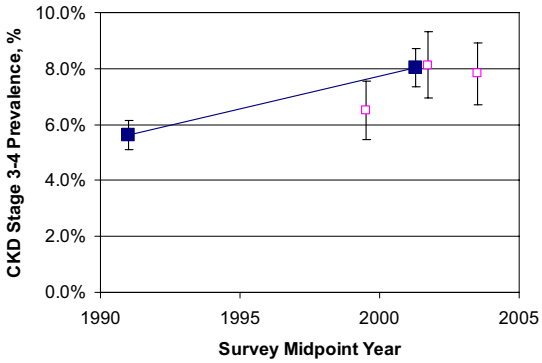

Figure 1. Trends in the prevalence of chronic kidney disease (CKD) stages 3 and 4 between National Health and Nutrition Examination Surveys (NHANES) 1988-1994 and 1999-2004 (full squares), as well as the 3-component surveys for the later NHANES (empty squares for 1999-2000, 2001-2002, and 2003-2004). Error bars denote 95% confidence intervals.

explained by the older age and high proportion of minority groups (OR decreased from 1.18 to 1.12 after adjustment). Further adjustment for the greater prevalence of diagnosed diabetes and hypertension and greater BMI explained practically all the difference (OR decreased 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 to 4.12) and hypertension (OR, 1.70; 95% CI, 1.1 to 1.92), as well as older age, and all race-ethnicity groups other than non-Hispanic white ($P < 0.001$), but not greater BMI ($P = 0.1$). The prevalence OR of estimated GFR 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 number of older individuals was offset by a similar increase in number of younger individuals, leading the percentage of individuals 60 years and older to remain relatively unchanged (Table 1). The prevalence OR increased further to 1.53 after adjustment for age, sex, and race because of the lower prevalence of decreased GFR in minority groups. The OR decreased to 1.43 with additional adjustment for diagnosed diabetes and hypertension and BMI. In the fully adjusted model, the prevalence of low GFR was associated strongly with diagnosed diabetes (OR, 1.54; 95% CI, 1.28 to 1.80) and hypertension (OR, 1.98; 95% CI, 1.73 to 2.67), as well as greater BMI (OR, 1.08; 95% CI, 1.02 to 1.15 per 5 kg/m^2) and older age, but was lower in men, non-Hispanic blacks, and Mexican Americans compared with non-Hispanic whites ($P < 0.001$).

The conservative trends analysis showed that the difference in mean serum creatinine levels between surveys accounts for much, but possibly not all, of the greater prevalence of lower GFRs in 1999-2004. In this analysis, the prevalence of CKD in 1988-1994 was greater (1.5%, 2.8%, 6.7%, and 0.23% for CKD stages 1 to 4, for a

Table 2. Prevalence of CKD Stages in US Adults Aged 20 Years or Older Based on NHANES 1988-1994 and NHANES 1999-2004

	NHANES 1988-2004	NHANES 1999-1994	Prevalence Ratio 1999-2004/1988-1994	Estimated Number in United States in 2000
CKD Stage	Prevalence, % (95% CI)	Prevalence, % (95% CI)	Ratio (95% CI)	No. in Millions (95% CI)
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	10.0 (9.2-10.9)	13.1 (12.4-14.1)	1.30 (1.19-1.43)	26.3 (24.2-28.3)

Note: CKD stages are defined based on standard criteria[1] as follows: stage 1, persistent albuminuria with GFR greater 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; and stage 4, GFR of 15 to 29 mL/min/1.73 m^2. The age-adjusted prevalence rates for CKD stages 1 to 4 in 1988-1994 adjusted to the 1999-2004 age distribution in Table 1 are 1.7%, 2.8%, 5.6%, and 0.2% for a total of 10.3%. Conversion factor: GFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, $\times 0.01667$.

Abbreviations: CKD, chronic kidney disease; CI, confidence interval; GFR, glomerular filtration rate; NHANES, National Health and Nutrition Examination Survey; NA, not available.

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Table 3. Logistic Regression of Albuminuria and Decreased Estimated GFR Comparing 1999-2004 With 1988-1994 Before and After Adjustment

	Trends			Conservative Trends Analysis*		
	OR	95% CI	*P*	OR	95% CI	*P*
Albuminuria in 1999-2004 *v* 1988-1994						
Unadjusted	1.18	1.03-1.34	0.01			
Adjusted for age	1.15	1.00-1.32	0.05			
Plus sex and race	1.12	0.99-1.28	0.08			
Plus diagnosed diabetes and hypertension	1.06	0.93-1.21	0.4			
Plus body mass index	1.03	0.90-1.18	0.6			
Estimated GFR $<$ 60 in 1999-2004 *v* 1988-1994						
Unadjusted	1.47	1.27-1.69	0.000	1.17	1.02-1.34	0.03
Adjusted for age	1.50	1.31-1.73	0.000	1.13	0.99-1.30	0.07
Plus sex and race	1.53	1.33-1.76	0.000	1.15	1.00-1.32	0.05
Plus diagnosed diabetes and hypertension	1.45	1.27-1.67	0.000	1.10	0.96-1.26	0.2
Plus body mass index	1.43	1.24-1.63	0.000	1.08	0.94-1.24	0.3

Note: Plus indicates the addition of variables to the model in the previous row. GFR expressed in mL/min/1.73 m^2; factor for conversion to mL/s/1.73 m^2, $\times$0.01667.

Abbreviations: CI, confidence interval; GFR, glomerular filtration rate; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio.

*Serum creatinine levels in young healthy participants (age 20 to 39 years without diabetes and hypertension) were adjusted to be identical across surveys by adding 0.04 mg/dL to serum creatinine levels in NHANES 1988-1994.

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total of 11.3%). The prevalence OR of eGFR less than 60 mL/min/1.73 m^2 comparing 1999-2004 with 1988-1994 was 1.17 (95% CI, 1.02 to 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 to 1.24), indicating that the differences in mean serum creatinine levels, demographics, diagnosed diabetes, hypertension, and BMI between surveys explain nearly all the difference in prevalence of low GFR between 1988-1994 and 1999-2004 ($P = 0.3$).

Because CKD stage 3 includes a large number of individuals, we examined the distribution of individuals in this stage across different characteristics (Table 4). As expected, the majority of individuals had a greater eGFR (45 to 59 mL/min/1.73 m^2 included 78.8% of all individuals with CKD stage 3, adding percentages across sex, age, and albuminuria categories). In addition, 61.5% of all individuals with CKD stage 3 had an eGFR of 45 to 59 mL/min/1.73 m^2 with no evidence of albuminuria. Table 4 also lists the distribution of albuminuria, with 25.7% of CKD stage 3 individuals with and 74.3% without albuminuria, and age, in which 22.1%, 22.7%, and 55.2% were aged 59 or younger, 60 to 69, and 70 years and older, respectively. A total of 16.6% of individuals with CKD stage 3 had previously diagnosed diabetes, and slightly less than half these had evidence of albuminuria (7.5% of all individuals with stage 3).

An analysis estimating the proportion of individuals with CKD stage 3 who would be eligible for referral to a nephrologist using 1 proposed referral recommendation suggested that 18.6% of individuals should be referred to a nephrologist, whereas the other 81.4% could be managed by their internists (Table 5). Under this scenario, the largest proportion of referrals in patients with CKD stage 3 was caused by macroalbuminuria, type 2 diabetes with the presence of albuminuria, or diabetic retinopathy. Independently of other criteria for referral, macroalbuminuria accounted for 20.5% $\pm$ 4.0% of referrals; type 2 diabetes with albuminuria, 32.9% $\pm$ 5.6%; and diabetic retinopathy, 23.1% $\pm$ 4.5%. Hyperkalemia (0.5% $\pm$ 0.3%) and resistant hypertension (11.5% $\pm$ 4.2%) accounted for less, and 11.5% of individuals would be referred for more than 1 criterion. The suggested referral rate was lower for whites than other groups because of a lower rate of albuminuria and diabetes (Table 6). However, retinopathy data are limited to NHANES III, making many of the specific referral groups relatively small and estimated rates imprecise.

Table 4. Distribution of Individuals With Chronic Kidney Disease Stage 3 by Estimated GFR Less Than 45 mL/min/1.73 m^2, Age, Sex, Presence of Albuminuria, and Diabetes: Combined NHANES 1988-1994 and 1999-2004

	Sex				Diagnosed Diabetes					
	Women		Men		Yes		No		Total	
	%	SE	%	SE	%	SE	%	SE	%	SE
Age < 60 y										
GFR 45-59 mL/min/1.73 m^2										
Normal, ACR < 30 mg/g	10.6	1.1	6.1	1.0	1.2*	0.4	15.5	1.5	16.7	1.6
Albuminuria, ACR ≥ 30 mg/g	1.7	0.3	1.5*	0.5	0.8*	0.4	2.4*	0.5	3.2	0.6
GFR 30-44 mL/min/1.73 m^2										
Normal, ACR < 30 mg/g	0.9*	0.3	0.2*	0.1	0.3*	0.2	0.8*	0.3	1.1*	0.4
Albuminuria, ACR ≥ 30	0.5*	0.3	0.7*	0.2	0.5*	0.2	0.7*	0.2	1.2*	0.3
Age 60-69 y										
GFR 45-59 mL/min/1.73 m^2										
Normal, ACR < 30 mg/g	9.6	0.8	5.9	0.6	2.5	0.4	13.0	0.8	15.6	0.9
Albuminuria, ACR ≥ 30 mg/g	2.3*	0.5	1.3*	0.3	1.4*	0.4	2.2	0.4	3.6	0.6
GFR 30-44 mL/min/1.73 m^2										
Normal, ACR < 30 mg/g	1.2	0.2	0.9*	0.3	0.3*	0.1	1.8*	0.4	2.1	0.3
Albuminuria, ACR ≥ 30 mg/g	0.7*	0.2	0.7*	0.2	0.7*	0.2	0.8*	0.2	1.4*	0.3
Age ≥70 y										
GFR 45-59 mL/min/1.73 m^2										
Normal, ACR < 30 mg/g	19.0	1.2	10.4	0.6	3.4	0.4	26.0	1.2	29.4	1.2
Albuminuria, ACR ≥ 30 mg/g	5.7	0.5	4.7	0.5	2.6	0.4	7.8	0.7	10.4	0.7
GFR 30-44 mL/min/1.73 m^2										
Normal, ACR < 30 mg/g	6.6	0.7	2.8	0.3	1.4*	0.4	8.1	0.6	9.5	0.7
Albuminuria, ACR ≥ 30 mg/g	3.6	0.5	2.3	0.3	1.5	0.3	4.3	0.5	5.9	0.6
Total	62.4	1.3	37.6	1.3	16.6	1.2	83.4	1.2	100	

Note: Percentages were calculated using survey weights and add up to 100% across all cells in the main columns (N = 272 individuals with CKD stage 3). Women who were pregnant or in menses were excluded. Conversion factors for units: ACR in mg/g to mg/mmol, ×0.113; GFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, ×0.01667.

Abbreviations: GFR, glomerular filtration rate; ACR, albumin-creatinine ratio; NHANES, National Health and Nutrition Examination Survey.

*Estimates with low precision (SE > 20% of estimate).

DISCUSSION

In summary, the NHANES provide an excellent source for tracking trends in the total prevalence of CKD, including diagnosed and undiagnosed cases. The most recent data suggest an increasing prevalence of all stages of CKD, which is at least partly explained by an increase in prevalences of obesity, diagnosed diabetes, and treated hypertension. Estimating the magnitude of the increase is sensitive to small differences in mean values of serum creatinine across surveys. Thus, continued efforts to standardize serum creatinine and assess drift in calibration over time are central to any surveillance activity.

Surveillance for CKD should acknowledge that stages 1 to 5 differ markedly in their severity, as well as prevalence. The most severe stages 4 and 5 have the lowest prevalence. However, because they have the greatest rates of complications and medical costs, tracking them is vital. Given their low prevalence (~0.3% each), individuals with these stages are not well represented in population-based surveys. It also is a concern that these individuals may have clinical symptoms and may be less likely to volunteer or come to an examination. Thus, alternative methods of surveillance for CKD stages 4 and 5 should be considered. We should look beyond the established surveillance for treated ESRD, which combines the presence of kidney failure with the patient being offered and deciding to accept renal replacement therapy. Large health care organization and laboratory chains could be a useful way to track individuals with severe CKD, although inferences will be complicated by the nonrandom nature of participation in these systems. Data from the Department of Veterans Affairs for 2.6 million veterans aged 18 to 100 years with at

Table 5. Proportion of Individuals With CKD Stage 3 and Whether They Meet Proposed Criteria for Referral to a Nephrologist by Age, Sex, Race, and Diabetes Status: NHANES 1988-1994

	CKD Stage 3		Meet a Proposed Set of Criteria for Referral to a Nephrologist		
	No. of Participants	%	No. of Participants	%	SE
Overall	1,021	100.0	217	18.6	1.6
Age (y)					
<60	119	18.5	30	16.9	3.5
60-69	235	27.1	67	21.5	3.6
≥70	667	54.4	120	17.6	2.0
Sex					
Women	567	62.8	113	18.3	2.2
Men	454	37.2	104	19.0	2.9
Race					
White	708	87.2	112	16.9	1.6
Black	174	6.4	57	32.9	3.7
Hispanic	106	1.4	41	35.2	5.8
Other	33	5.0	7	23.6*	12.4
Diabetes					
No	833	84.8	100	10.4	1.5
Yes	187	15.2	117	64.6	5.1

Note: Proposed criteria[19] for referral include ACR greater than 300 mg/g, type 2 diabetes with ACR greater than 30 mg/g, diabetic retinopathy, hyperkalemia, or resistant hypertension. Only NHANES 1988-1994 data were used because of availability of data for retinopathy. Women who were pregnant or in menses were excluded.

Abbreviations: ACR, albumin-creatinine ratio; CKD, chronic kidney disease; NHANES, National Health and Nutrition Examination Survey.

*Estimates with low precision (SE > 20% of estimate).

least 1 outpatient serum creatinine measurement indicated that 5,300 (0.2%) had an eGFR less than 15 mL/min/1.73 m^2 without being on dialysis therapy, whereas 14,637 (0.6%) were treated for ESRD.[20] The time spent in stage 5 CKD without treatment is relatively short because the annual ESRD incidence is 70% to 80% for veterans younger than 65 years and 29% after age 85

Table 6. Proportion of Individuals With CKD Stage 3 According to Proposed Criteria for Referral to a Nephrologist by Race: NHANES 1988-1994

	White			Black			Mexican American		
	No. of Participants	%	SE	No. of Participants	%	SE	No. of Participants	%	SE
Not Referred	596	83.1	1.65	117	67.1	3.7	65	64.8	5.8
Referred	112	16.9	1.65	57	32.9	3.7	41	35.2	5.8
Reason for referral:									
Macroalbuminuria	28	3.3*	0.7	11	7.6*	2.8	11	11.9*	4.5
Diabetes with microalbuminuria	34	5.1*	1.3	21	11.9	2.3	9	6.7*	3.2
Retinopathy	23	4.4*	1.1	12	6.7*	1.7	5	4.2*	1.8
Hyperkalemia	2	0.1*	0.1	0	0.0	0.0	0	0.0	0.0
Resistant hypertension	12	2.3*	1.0	4	2.2*	1.1	0	0.0	0.0
Diabetes with microalbuminuria & retinopathy	10	1.7*	0.4	5	3.0*	1.4	11	6.3*	2.1
Macroalbuminuria & retinopathy	2	0.1*	0.1	2	0.9*	0.6	1	1.1*	1.1
Multiple other	1	0.1*	0.1	2	0.6*	0.5	4	5.0*	3.4

Note: Only NHANES 1988-1994 used due to availability of data for retinopathy. Women who were pregnant or in menses were excluded.

Abbreviations: CKD, chronic kidney disease; NHANES, National Health and Nutrition Examination Survey.

*Estimates with low precision (SE > 20% of estimate).

years. Conversely, mortality rates increased from 3% at younger than 44 years to 49% after the age of 85 years.[21]

Population-based surveys can be very useful for patients with CKD stages 1 to 3 and, with large surveys, CKD stage 4. However, within these stages, it would be useful to also track the distribution of albuminuria and other markers of severity and likelihood of complications and progression. For example, although the prevalence of CKD stage 3 based on NHANES 1988-1994 and 1999-2004 increased from 5.4% to 7.7%, the estimated proportion of these individuals with albuminuria decreased somewhat. Thus, the proportion of the population with both moderately decreased GFR and albuminuria increased from 1.5% to 1.9% (calculated from Table 2 of Coresh et al[11]).

It is useful to evaluate criteria for potential action, as well as the evidence for these criteria. We evaluated a set of proposed criteria for referral to a nephrologist that suggest that although all patients with CKD stages 4 and 5 ($n \approx 1.1$ million) should see a nephrologist, only 18.6% of individuals with stage 3 ($n \approx 2.9$ million) should be referred. Concerning individuals with eGFR greater than 60 mL/min/1.73 m^2 and albuminuria, 30.8% ($n \approx 3.0$ million) should be referred, a majority of these because of the presence of macroalbuminuria (69.2% $\pm$ 2.3%), although these estimates do not incorporate persistence data. Additional studies evaluating the evidence for such criteria and the impact of such referral are needed. However, initial estimates can be useful to assess the potential impact of recommendations, policies, or ad hoc practice patterns.

In summary, laboratory evaluation combined with rigorous survey methods is central to the surveillance of CKD. Although a flattening in the age-adjusted rates of treated ESRD is reassuring, it is counteracted by an aging population and longer survival on dialysis therapy, which increase the number of individuals treated for ESRD. It is important to also track patients with untreated kidney failure (CKD stage 5), as well as those with undiagnosed CKD. The most recent data suggest that the obesity epidemic is leading to an increase in the prevalence of albuminuria and decreased kidney function (CKD stages 1 to 4). Surveillance of these trends in the future is important to better understand this population at risk of a wide range of complications. Surveillance efforts also should focus on defining meaningful subgroups of patients with CKD by their need for services (referral to specialists), risk of different complications, and potential benefit from different therapies.

ACKNOWLEDGEMENTS

This report reproduces much of the information presented previously in the report Prevalence of Chronic Kidney Disease in the United States. JAMA 298:2038-2047, 2007.[11]

Support: The project is funded by Grants UO1 DK 053869, UO1 DK 067651, and UO1 DK 35073 from the National Institute of Diabetes, Digestive and Kidney Disease. Dr Castro was supported by National Institutes of Health/National Heart, Lung, and Blood Institute Grant T32HL007024.

Financial Disclosure: None.

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