

# Cystatin C Levels in U.S. Adults, 1988–1994 Versus 1999–2002: NHANES

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**Background and objectives:** Creatinine-based estimates of GFR suggest an evolving epidemic of chronic kidney disease (CKD) in U.S. adults that is inadequately explained by conventional, modifiable risk factors. Cystatin C has recently emerged as a promising measure of GFR. To enable further insights into the evolution of CKD in the U.S. population, this study aimed to examine cystatin C levels in U.S. adults.

**Design, setting, participants, and measurements:** Stored serum samples, measured in 2006, were used to compare cystatin C levels among adult participants in the National Health and Nutrition Examination Survey (NHANES) in two time periods, 1988–1994 (n = 6877) and 1999–2002 (n = 4563).

**Results:** Mean cystatin C levels (0.9 versus 0.9 mg/L,  $P = 0.65$ ) and urinary albumin-creatinine ratios were similar (5.8 versus 5.9 mg/g,  $P = 0.19$ ) in the 2 study eras. In contrast, standardized serum creatinine (0.8 versus 0.9 mg/dl,  $P < 0.0001$ ) was higher and estimated GFR (93.2 versus 87.6 ml/min/1.73 m<sup>2</sup>,  $P < 0.001$ ) was lower in 1999–2002. Similar discrepancies in population trends (when cystatin C and creatinine-based methods were used to define GFR) were present when categories of kidney function were considered, and when adjustment was made for demography and comorbid illness.

**Conclusions:** The disparity between temporal trends when kidney function is assessed with different measurements suggests that estimating trends in disease burden remains an open question.

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Chronic kidney disease (CKD) may be important from a public health perspective; it is common, and associated with cardiovascular disease, end-stage kidney disease, death risks in community settings, and substantial health care expenditure (1–5). In the last decade, incidence of end-stage kidney disease treated with renal replacement therapy has increased substantially (5,6), as has the population-wide burden of treatable CKD risk factors, principally hypertension (7), obesity, and diabetes (8,9). However, trends in the burden of CKD are unlikely to be accurately inferred from trends in incidence of end-stage kidney disease. For example, in one notable study comparing 1976–1980 and 1988–1994, CKD prevalence did not keep pace with incidence of end-stage kidney disease treated with renal replacement therapy (10).

Precise estimates of disease trends are desirable for disease management at a public health level. In this regard, recent observations have generated concern that kidney function in representative U.S. adults may be declining without adequate explanation (11). These twin observations (increasing disease burden; inability to explain this burden with easily identifiable, modifiable risk factors) may be a cause for concern from a public health perspective.

Cystatin C is a low-molecular-weight protein with attractive properties as a measure of GFR, including near-constant production rates and free filtration by the glomerulus (12); in addition, cystatin C levels appear to be independent of sex and race, and the contribution of lean-body mass to cystatin C appears to be less than one-tenth that of true GFR in healthy adults (13).

Cystatin C levels were measured in a large, systematically sampled group of National Health and Nutrition Examination Survey (NHANES) participants from 1988–1994 and 1999–2002, enabling further insights into the evolution of CKD in the U.S. population.

## Materials and Methods

### Objectives

The objectives of this study were to compare representative U.S. adult participants in NHANES 1988–1994 and 1999–2002 with respect to mean cystatin C levels, the primary objective, and serum creatinine levels, GFR values estimated from serum creatinine (eGFR<sub>creatinine</sub>) and cystatin C (eGFR<sub>cystatin C</sub>), urinary albumin-creatinine ratios (ACR), and stages of kidney function.

### Study Population

NHANES surveys are cross-sectional, multistage, stratified, clustered probability samples of noninstitutionalized U.S. civilian population (14). NHANES III was performed in 2 phases (1988–1991 and 1991–1994); since 1999, NHANES has been performed continuously in 2-yr cycles. For the current study, data from the 1988–1991 and 1991–1994 cycles were combined to define an earlier study population, and data from 1999–2000 and 2001–2002 were combined to form a later popula-

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tion, a strategy recommended by the National Center for Health Statistics (15,16).

NHANES intentionally oversampled certain population subgroups, including the elderly, Mexican Americans, and non-Hispanic African Americans. Participants were interviewed at home, and physical examinations and blood and urine collections were performed in mobile examination centers.

### Measurements and Definitions

Selection factors and measurement techniques for cystatin C and serum creatinine are shown in Figure 1. Cystatin C levels were measured in stored serum samples for all participants aged  $\geq 60$  yr; for participants aged 12 to 59 yr, cystatin C levels were measured in a random sample of 25%, in all men with standardized serum creatinine levels  $> 1.2$  mg/dl, and in all women with levels  $> 1.0$  mg/dl. For the current study, we limited the population to participants aged  $\geq 20$  yr in whom cystatin C levels were measured. Cystatin C levels were measured by a particle-enhanced immunonephelometric assay (N Latex Cystatin C; Dade Behring, Deerfield, IL). This assay has a range of 0.23 to 7.25 mg/L, and interassay coefficients of 5.05% and 4.87% at cystatin C levels of 0.97 and 1.90 mg/L, respectively (17).

Serum creatinine was measured throughout by the kinetic alkaline picrate method. Between 1988 and 1994, measurements were performed at the White Sands Research Center (Coulston Foundation) laboratory (Alamogordo, NM) with a Roche/Hitachi 737 analyzer (Roche Diagnostics, Indianapolis, IN). In 1999, 2000, and 2001, measurements were performed at the Coulston Foundation laboratory with a Roche Hitachi 917 analyzer. In 2002, 2003, and 2004, measurements were performed at the Collaborative Laboratory Services laboratory (Ottumwa, IA) with a Beckman Coulter Synchron LX20 (Beckman Coulter, Fullerton, CA). For this study, serum creatinine measurements were realigned to standardized creatinine measurements obtained at the Cleveland Clinic Research Laboratory (Cleveland, OH). For creatinine standardization, 4 random samples of 200 stored surplus specimens were obtained from study participants aged  $\geq 60$  yr in NHANES 1988–1994, 1999–2000, 2001–2002, and 2003–2004; creatinine was measured with a Roche coupled enzymatic assay (creatininase, creatinase, sarcosine oxidase; kits no. 1775677 and 1775766) on a Roche P Module instrument (18). College of American Pathologists Creatinine Accuracy

Calibration Verification/Linearity Survey LN24 samples were used to confirm that calibration of the Roche enzymatic method was traceable to methods based on liquid chromatography-isotope dilution gas chromatography mass spectrometry. Ultimately, standardized creatinine values (in mg/dl) were calculated from actual creatinine, as follows:

$$\text{Standardized creatinine}_{1988-1994} = 0.960$$

$$\times (\text{measured creatinine}_{1988-1994}) - 0.184$$

$$\text{Standardized creatinine}_{1999-2000} = 1.013$$

$$\times (\text{measured creatinine}_{1999-2000}) + 0.147$$

$$\text{Standardized creatinine}_{2001-2002} = \text{measured creatinine}_{2001-2002}$$

The abbreviated Modification of Diet in Renal Disease (MDRD) Study formula was used to estimate GFR from standardized creatinine as follows:  $\text{eGFR}_{\text{creatinine}} (\text{ml}/\text{min}/1.73 \text{ m}^2) = 175 \times (\text{standardized serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times 0.742 (\text{women}) \times 1.212 (\text{African Americans})$  (19,20). The following formula was used to calculate eGFR from cystatin C levels:  $\text{eGFR}_{\text{cystatin C}} (\text{ml}/\text{min}/1.73 \text{ m}^2) = 76.7 \times \text{cystatin C}^{-1.19}$  (21). Urinary albumin and creatinine concentrations were measured at the University of Minnesota (Minneapolis, MN) from random urine spot samples by the modified kinetic Jaffe method with a Synchron AS/Astra Analyzer (Beckman Coulter). The National Kidney Foundation Kidney Disease Outcomes Quality Initiative classification system (1) was used to define categories of kidney function, except that GFR levels 30 to 59 ml/min/1.73 m<sup>2</sup> were subdivided into two categories (22): 30 to 44 and 45 to 59 ml/min/1.73 m<sup>2</sup>, and, because of small numbers, GFR values  $< 15$  ml/min/1.73 m<sup>2</sup> were subsumed into the  $< 30$  category.

Current smokers were defined by affirmative answers to the questions, “Do you now smoke cigarettes?” and “Have you smoked at least 100 cigarettes in your life?” Diabetes and hypertension were defined by self-report.

### Analysis

NHANES-recommended analytical procedures were followed and SUDAAN software (Research Triangle Institute, Research Triangle

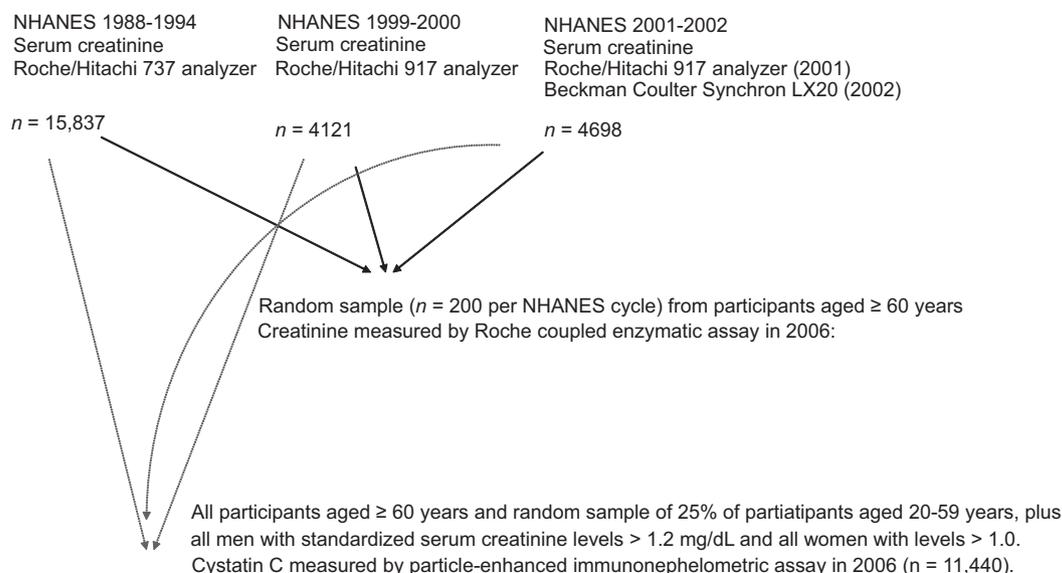


Figure 1. Selection factors and measurement techniques for cystatin C and serum creatinine.

Park, NC) was used to incorporate the sampling weights implicit in this complex sample survey design (15,23). As recommended by NHANES, we used specific weights that accounted for the probability of having a cystatin C measurement, namely WTCYPEX6 for NHANES 1988–1994 and WTSCY4YR for NHANES 1999–2002. ANOVA and  $\chi^2$  tests were used for unadjusted comparisons of 1988–1994 and 1999–2002 participants. Multiple logistic regression was used for multivariate comparisons of kidney function categories. An alpha level less than 0.05 was considered statistically significant.

Three sensitivity analyses were applied to comparative trends in kidney function. Serum creatinine values for 1988–1994 and 1999–2002 were compared in a reference population aged < 40 yr without diabetes or hypertension; because serum creatinine values were 0.06 mg/dl higher ( $P < 0.001$ ) in 1999–2002, all creatinine-based comparisons were repeated with 0.06 subtracted from 1999–2002 levels. Second, eGFR trends were compared in subgroups defined by age, sex, and race. Finally, all analyses were repeated with eGFR<sub>cystatin C</sub> defined by Equation 2 in the study by Stevens *et al.* (21); findings with Equation 2 were similar to those with Equation 1 and are not presented here.

### Results

Participants with cystatin C measurements were very similar to their parent populations in both study eras (Table 1). In the study population of adult participants with cystatin C measurements, discriminating characteristics ( $P < 0.05$  versus 1988–1994) of 1999–2002 participants were as follows: nonwhite race

(28.3% versus 23.4%), presence of diabetes (6.7% versus 5.0%), smoking (20.5% versus 28.7%), and body mass index (28.1 versus 26.6 kg/m<sup>2</sup>).

Mean cystatin C levels (0.9 versus 0.9 mg/L), eGFR<sub>cystatin C</sub> (94.6 versus 93.1 versus ml/min/1.73 m<sup>2</sup>), and urinary ACR (5.9 versus 5.8 mg/g) were similar in the two study eras (Table 2). In contrast, standardized serum creatinine (0.9 versus 0.8 mg/dl) was higher and eGFR<sub>creatinine</sub> was lower (87.6 versus 93.2 ml/min/1.73 m<sup>2</sup>) in 1999–2002. Figure 2 illustrates eGFR<sub>cystatin C</sub> and eGFR<sub>creatinine</sub> values by study era in subgroups defined by age, sex, and race. The qualitative pattern described above, with similar eGFR<sub>cystatin C</sub> in both time frames and lower eGFR<sub>creatinine</sub> in 1999–2002, was maintained in the subgroups.

As defined by eGFR<sub>cystatin C</sub> and ACR, distributions of CKD stages were similar in 1988–1994 and 1999–2002. As defined by eGFR<sub>creatinine</sub> and ACR, stage 3a (6.2% versus 4.1%), stage 3b (1.8% versus 1.2%), and eGFR <30 ml/min/1.73 m<sup>2</sup> (0.5% versus 0.3%) were all more prevalent in the 1999–2002 population (Table 2). The prevalence of CKD was higher on the basis of cystatin C-based estimates in both earlier (11.1% versus 10.5%) and later (12.4% versus 10.9%) time periods. Creatinine values were 0.06 mg/dl higher in 1999–2002 among participants aged 20 to 39 yr without diabetes or hypertension. When 0.06 mg/dl was subtracted from all 1999–2002 creatinine values, the proportion of participants with CKD stage 2 fell between study

Table 1. Comparison of NHANES 1988–1994 and 1999–2002 participants

	Participants with Cystatin C Levels			All Participants		
	1988–1994 (n = 6877)	1999–2002 (n = 4563)	P	1988–1994 (n = 17,030)	1999–2002 (n = 9471)	P
Age, yrs	44.6 (0.8)	46.0 (0.4)	0.12	44.7 (0.5)	46.1 (0.3)	0.03
Age category, yrs (%)						<0.001
20–39	46.2 (2.1)	39.9 (1.3)		46.2 (1.0)	39.9 (1.0)	
40–59	31.2 (1.2)	37.7 (1.4)		31.2 (0.6)	37.7 (0.8)	
60–69	11.4 (0.9)	10.5 (0.6)		11.3 (0.5)	10.5 (0.5)	
≥ 70	11.3 (1.0)	12.0 (0.5)		11.3 (0.6)	12.0 (0.5)	
Women (%)	52.4 (1.5)	52.2 (1.1)	0.94	52.4 (0.4)	52.2 (0.4)	0.82
Race/ethnicity (%)			<0.001			<0.001
White	76.6 (2.0)	71.7 (2.1)		76.3 (1.3)	71.5 (1.8)	
African American	10.9 (1.0)	10.9 (1.3)		10.9 (0.7)	10.9 (1.2)	
Hispanic	5.1 (0.6)	13.0 (2.2)		5.1 (0.4)	13.9 (2.0)	
Other	7.4 (1.2)	4.4 (0.6)		7.7 (0.8)	3.7 (0.5)	
Diabetes (%)	5.0 (0.5)	6.7 (0.4)	<0.01	5.5 (0.3)	6.7 (0.3)	<0.01
Hypertension (%)	23.8 (0.9)	26.3 (1.2)	0.10	23.9 (0.6)	25.7 (0.8)	0.11
Smoker (%)	28.7 (1.3)	20.5 (1.2)	<0.001	28.4 (0.8)	20.5 (0.8)	<0.001
Body mass index, kg/m <sup>2</sup>	26.6 (0.2)	28.1 (0.2)	<0.001	26.5 (0.1)	28.0 (0.1)	<0.001
Body mass index category, kg/m <sup>2</sup> (%)						<0.001
< 25	43.6 (1.5)	36.1 (1.5)		45.1 (0.9)	35.2 (0.8)	
25–29	33.9 (1.2)	33.9 (1.3)		32.7 (0.6)	34.7 (0.8)	
≥ 30	22.5 (1.2)	30.0 (1.4)		22.2 (0.7)	30.2 (0.9)	

The analysis was adjusted for the sampling weights used in the study design. The chi-square test (for categorical variables) and analysis of variance (for continuous variable) were used to compare the characteristics of 1988–1994 and 1999–2002 participants. Standard errors are shown in parentheses.

periods (4.9% versus 3.1%) and the proportion with stages 4/5 rose (0.3% versus 0.5%).

1999–2002, using 1988–1994 as reference group. With staging based on eGFR<sub>cystatin C</sub> and ACR, statistically significant changes were observed only for stage 2 (adjusted prevalence

Table 3 shows adjusted prevalence ratios of CKD stages in

Table 2. Comparison of cystatin C, creatinine, eGFR, and CKD stage, NHANES 1988–1994 and 1999–2004 (n = 11,440)

Variables	1988–1994	1999–2004	P <sup>a</sup>
Cystatin C, mg/L	0.9 (< 0.1)	0.9 (< 0.1)	0.65
eGFR <sub>cystatin C</sub> , ml/min/1.73 m <sup>2</sup>	93.1 (0.8)	94.6 (0.9)	0.17
eGFR <sub>cystatin C</sub> (%)			
≥ 90	56.2 (1.7)	58.7 (1.8)	0.28
60–89	37.4 (1.4)	34.3 (1.5)	0.14
45–59	4.3 (0.4)	4.8 (0.5)	0.48
30–44	1.7 (0.2)	1.5 (0.2)	0.67
< 30	0.4 (0.1)	0.6 (0.1)	0.12
CKD stage, eGFR <sub>cystatin C</sub> , ACR (%)			
normal	84.9 (1.1)	85.1 (0.9)	0.87
stage 1	3.9 (0.5)	4.0 (0.5)	0.88
stage 2	4.7 (0.4)	3.9 (0.4)	0.11
stage 3a	4.3 (0.4)	4.8 (0.5)	0.43
stage 3b	1.7 (0.2)	1.6 (0.2)	0.72
stage 4/5	0.4 (0.1)	0.6 (0.1)	0.11
Standard creatinine in 1988–1994 and 1999–2004			
Creatinine, mg/dl	0.8 (< 0.1)	0.9 (< 0.1)	< 0.001
eGFR <sub>creatinine</sub> , ml/min/1.73 m <sup>2</sup>	93.2 (0.7)	87.6 (0.7)	< 0.001
eGFR <sub>creatinine</sub> (%)			
≥ 90	53.2 (1.9)	41.9 (1.7)	< 0.001
60–89	41.1 (1.8)	49.7 (1.5)	< 0.001
45–59	4.1 (0.3)	6.1 (0.4)	< 0.01
30–44	1.2 (0.1)	1.8 (0.2)	0.01
< 30	0.3 (< 0.1)	0.5 (0.1)	< 0.01
CKD stage, eGFR <sub>creatinine</sub> , ACR (%)			
normal	85.2 (1.0)	83.6 (0.8)	0.18
stage 1	4.3 (0.6)	3.9 (0.5)	0.67
stage 2	4.9 (0.4)	3.9 (0.4)	0.10
stage 3a	4.1 (0.3)	6.2 (0.4)	< 0.01
stage 3b	1.2 (0.1)	1.8 (0.2)	0.01
Standard creatinine in 1988–1994, minus 0.06 in 1999–2004 <sup>b</sup>			
Creatinine, mg/dl	0.8 (< 0.1)	0.8 (< 0.1)	0.80
eGFR <sub>creatinine</sub> , ml/min/1.73 m <sup>2</sup>	93.2 (0.7)	95.9 (0.8)	0.02
eGFR <sub>creatinine</sub> (%)			
≥ 90	53.2 (1.9)	55.1 (1.5)	0.48
60–89	41.1 (1.8)	38.9 (1.4)	0.37
45–59	4.1 (0.3)	3.9 (0.3)	0.69
30–44	1.2 (0.1)	1.5 (0.2)	0.19
< 30	0.3 (< 0.1)	0.5 (0.1)	0.02
CKD stage, eGFR <sub>creatinine</sub> , ACR (%)			
normal	85.2 (1.0)	85.8 (0.8)	0.63
stage 1	4.3 (0.6)	5.1 (0.6)	0.29
stage 2	4.9 (0.4)	3.1 (0.4)	< 0.01
stage 3a	4.1 (0.3)	4.0 (0.3)	0.77
stage 3b	1.2 (0.1)	1.5 (0.2)	0.16
ACR, mg/g	5.8 (3.6–11.2)	5.9 (3.9–11.0)	0.19

Table 2. (Continued)

Variables	1988–1994	1999–2004	P <sup>a</sup>
ACR (%)			
< 30	89.0 (0.9)	89.7 (0.7)	0.45
30–299	8.1 (0.8)	8.6 (0.7)	0.65
≥ 300	3.0 (0.4)	1.7 (0.2)	0.01

ACR, urinary albumin-creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate. CKD stages: stage 1, eGFR ≥ 90 ml/min/1.73 m<sup>2</sup>, ACR ≥ 30; stage 2, eGFR 60–89 ml/min/1.73 m<sup>2</sup>, ACR ≥ 30; stage 3a, eGFR 45–59 ml/min/1.73 m<sup>2</sup>; stage 3b, eGFR 30–44 ml/min/1.73 m<sup>2</sup>; stage 4 eGFR 15–30; stage 5 eGFR < 15 ml/min/1.73 m<sup>2</sup>.

<sup>a</sup>Comparing 1988–1994 and 1999–2004. The analysis was adjusted for the sampling weights used in the study design. The chi-square test (for categorical variables) and analysis of variance (for continuous variables) were used to compare the characteristics of 1988–1994 and 1999–2002 participants. Standard errors are shown in parentheses except for ACR, where median and interquartile range are shown. For kidney function outcomes, participants in each kidney function category were compared with all other participants. For example, for eGFR<sub>cystatin C</sub>, 45–59 ml/min/1.73 m<sup>2</sup>, participants with this characteristic were compared with participants with eGFR<sub>cystatin C</sub> ≥ 60 or <45 ml/min/1.73 m<sup>2</sup>.

<sup>b</sup>When reference populations (ages 20 to 39 yr without diabetes or hypertension) were compared, serum creatinine values were 0.06 mg higher in the 1999–2002 than the 1988–1994 population.

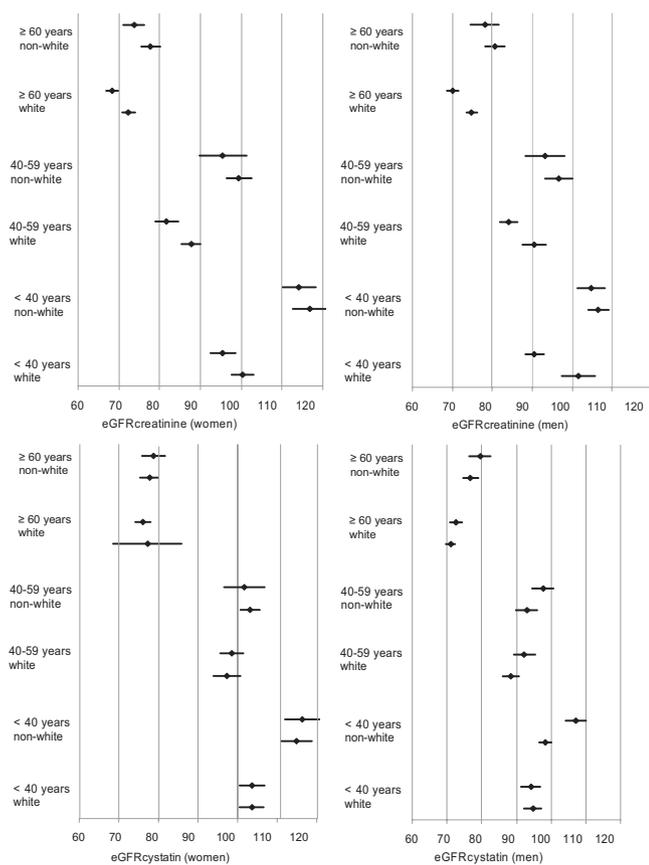


Figure 2. Mean eGFR<sub>cystatin</sub> and eGFR<sub>creatinine</sub> levels within subgroups defined by sex, age, and race. The lower and upper members of each two-member cluster represent 1988–1994 and 1999–2002, respectively. Error bars represent 95% confidence intervals. eGFR, estimated GFR.

ratio, 0.70). With creatinine-based methods, stage 2 was less prevalent (ratio, 0.73) and stages 3a (ratio, 1.50), 3b (ratio, 1.26) and 4/5 (ratio, 1.90) were more prevalent. When 0.06 mg/dl was subtracted from serum creatinine values in 1999–2002,

stage 2 declined (ratio, 0.57) and stages 4/5 became more prevalent (ratio, 1.77).

### Discussion

We found substantial declines in eGFR values on the basis of standardized serum creatinine levels. In contrast, serum cystatin C levels (the primary outcome for this study) and ACRs showed no such trends.

Ideally, to compare a given biologic analyte in different eras, the following might be desirable: measurement in all participants and a single, accurate assay throughout. In this study, while all study participants had serum creatinine measurements, three analyzers were used for the original measurements. Standardization to a single reference standard in 2006 included approximately 1% of NHANES 1988–1994 participants and was restricted to those aged 60 yr or older (18). For cystatin C, a systematic sampling design was used; more than 40% of participants were sampled using a single assay. Although issues related to differential sample drift for stored creatinine and cystatin C are theoretically possible, this seems an unlikely explanation for the findings we observed for cystatin C and creatinine-based GFR estimates. It is tempting to speculate that differences in sampling strategies or residual differences in serum creatinine calibration between study eras may be responsible. This being said, it is also possible that findings based on serum creatinine may be correct. In this regard, the findings for eGFR < 30 ml/min/1.73 m<sup>2</sup> were notable: creatinine-based methods showed 88% and 76% rises in adjusted prevalence ratios, whereas cystatin C-based methods showed no such trend. In addition, differential evolution of nonrenal and renal cystatin C determinants could explain static cystatin C values in the face of a real fall in GFR values.

Some of the population findings based on serum creatinine in this study are similar to those reported by Coresh *et al.* (11), who found that prevalence of creatinine-based estimated GFR levels < 60 ml/min/1.73 m<sup>2</sup> rose by a factor of 1.4, from 5.63% to 8.04%, over an interval of approximately a decade (NHANES 1999–2004 versus NHANES 1988–1994). Of note, the higher

Table 3. Cystatin C, creatinine, eGFR, and CKD Stage, 1999–2002 vs. 1988–1994, multivariate analysis<sup>a</sup>

Variables	Adjusted Prevalence Ratios for 1999–2002 (vs. 1988–1994)	P
eGFR <sub>cystatin C</sub> (ml/min/1.73 m <sup>2</sup> )	Ratio (95% CI)	
≥ 90	1.31 (1.02–1.67)	0.03
60–89	0.81 (0.67–1.00)	0.05
45–59	0.95 (0.74–1.22)	0.69
30–44	0.77 (0.53–1.13)	0.18
< 30	1.10 (0.70–1.74)	0.66
CKD stage, eGFR <sub>cystatin C</sub> , ACR		
normal	1.16 (0.94–1.41)	0.16
stage 1	1.09 (0.73–1.64)	0.66
stage 2	0.70 (0.53–0.93)	0.02
stage 3a	0.96 (0.75–1.23)	0.76
stage 3b	0.78 (0.54–1.14)	0.20
stage 4/5	1.12 (0.71–1.76)	0.62
Standard creatinine in 1988–1994 and 1999–2004		
eGFR <sub>creatinine</sub> (ml/min/1.73 m <sup>2</sup> )		
≥ 90	0.59 (0.45–0.76)	<0.001
60–89	1.44 (1.18–1.76)	<0.001
45–59	1.49 (1.20–1.84)	<0.001
30–44	1.24 (0.99–1.56)	0.06
< 30	1.88 (1.22–2.90)	<0.01
CKD stage, eGFR <sub>creatinine</sub> , ACR		
normal	0.95 (0.81–1.13)	0.57
stage 1	0.93 (0.64–1.34)	0.69
stage 2	0.73 (0.54–0.99)	0.04
stage 3a	1.50 (1.21–1.87)	<0.001
stage 3b	1.26 (1.00–1.58)	0.05
stage 4/5	1.90 (1.23–2.94)	<0.01
Standard creatinine in 1988–1994, minus 0.06 in 1999–2004 <sup>b</sup>		
eGFR <sub>creatinine</sub> (ml/min/1.73 m <sup>2</sup> )		
≥ 90	1.21 (0.95–1.55)	0.12
60–89	0.87 (0.70–1.07)	0.18
45–59	0.86 (0.69–1.08)	0.19
30–44	1.03 (0.81–1.30)	0.82
< 30	1.76 (1.11–2.77)	0.02
CKD stage, eGFR <sub>creatinine</sub> , ACR		
Normal	1.16 (0.97–1.38)	0.10
stage 1	1.22 (0.86–1.73)	0.27
stage 2	0.57 (0.42–0.79)	<0.001
stage 3a	0.87 (0.70–1.09)	0.23
stage 3b	1.04 (0.82–1.31)	0.74
stage 4/5	1.77 (1.12–2.81)	0.02
ACR, mg/g		
< 30	1.17 (0.95–1.44)	0.14
30–299	1.04 (0.80–1.35)	0.77
≥ 300	0.45 (0.31–0.67)	<0.001

ACR, urinary albumin-creatinine ratio; CKD, chronic kidney disease; CI, confidence interval; eGFR, estimated glomerular filtration rate. CKD stages: stage 1, eGFR ≥ 90 ml/min/1.73 m<sup>2</sup>, ACR ≥ 30; stage 2, eGFR 60–89 ml/min/1.73 m<sup>2</sup>, ACR ≥ 30; stage 3a, eGFR 45–59 ml/min/1.73 m<sup>2</sup>; stage 3b, eGFR 30–44 ml/min/1.73 m<sup>2</sup>; stage 4 eGFR 15–30 ml/min/1.73 m<sup>2</sup>; stage 5 eGFR < 15 ml/min/1.73 m<sup>2</sup>.

<sup>a</sup>The analysis was adjusted for the sampling weights used in the study design. Logistic regression was used to calculate prevalence ratios. For kidney function outcomes, participants in each kidney function category were compared with all other participants. For example, for eGFR<sub>cystatin C</sub> 45–59 ml/min/1.73 m<sup>2</sup>, participants with this characteristic were compared with participants with eGFR<sub>cystatin C</sub> ≥ 60 or < 45 ml/min/1.73 m<sup>2</sup>. Adjustment was made for age, sex, race, body mass index, and self-reported diabetes, hypertension, and smoking.

<sup>b</sup>When reference populations (aged 20 to 39 yr without diabetes or hypertension) were compared, serum creatinine values were 0.06 mg higher in the 1999–2002 than the 1988–1994 population.

prevalence of GFR values  $< 60$  ml/min/1.73 m<sup>2</sup> among later participants was inadequately explained by changes in age distribution or by changes in burdens of diabetes, obesity, or hypertension. Other noticeable features of the more recent report were mean serum creatinine values 0.04 mg/dl higher in 1999–2004 study participants aged 20 to 39 yr without hypertension or diabetes (11). These findings differed from those of a previous report based on nonstandardized serum creatinine values in NHANES 1988–1994 and 1999–2000, which showed stable CKD prevalence estimates (24).

The limitations of this study deserve attention. Gold standard measurements of kidney function, such as insulin or radioisotope clearance, were not performed. The study was cross-sectional; hence, identification of participants with progressive loss of kidney function was not feasible. When conditions are defined by numerical variables that vary intrinsically within individuals, such as GFR or urinary protein excretion, cross-sectional studies can provide reasonable estimates of disease prevalence; all things being equal, it would be expected that individuals showing atypically high values of a given variable would be balanced by individuals with atypically low levels at the time of measurement. In contrast, cross-sectional designs are unsuitable for identifying individual cases, as demonstrating persistently abnormal values requires repeated measurements. In addition, the presence of diabetes and hypertension was based on self-report; possibly, differential ascertainment of these parameters may have occurred in 1988–1994 and 1999–2004.

Despite its limitations, we believe this study provides useful information. The population prevalence of CKD is clearly challenging in scope, and finding an increasing disease burden without apparent explanation could be seen as a major public health concern, as it implies an ongoing epidemic without logical targets for intervention. The disparity between temporal trends when kidney function is addressed with different measurements suggests that estimating trends in disease burden remains an open question.

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## Disclosures

None.

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