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Temporal Trends in Prevalence of CKD: The Glass Is Half Full and Not Half Empty

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In this issue of *AJKD*, Grams et al¹ report new information regarding the secular trend in chronic kidney disease (CKD) prevalence in the US population by comparing the prevalence of reduced cystatin C estimated glomerular filtration rate (eGFR) in 2 survey periods spanning more than a decade: NHANES III (Third National Health and Nutrition Examination Survey; 1988–1994) and NHANES 1999–2002.¹ Compared with prior studies (Table 1), this article's novel contributions include the use of cystatin C as filtration marker after alignment of calibration in the 2 survey periods and use of the latest cystatin C GFR estimating equations. Grams et al¹ found that the prevalence of eGFR <60 mL/min/1.73 m² in the United States increased significantly between those periods, from 5.5% to 8.7%, when cystatin C level was used to estimate GFR (eGFR_{cys}) and from 4.4% to 7.1% when cystatin C and creatinine levels were used together to estimate GFR (eGFR_{cr-cys}; both *P* < 0.001).

Where does this article stand in the context of the prior literature? The first study to examine changes in the prevalence CKD in the United States over time systemically was by Hsu et al,² who analyzed data from NHANES II (1976–1980) and III (1998–1994). Hsu et al² relied on the fact that for whites in both surveys who were aged 20–39 years and did not have diabetes or hypertension, median serum creatinine levels were 1.1 mg/dL in men and 0.9 mg/dL in women, which led them to conclude that there were no creatinine calibration differences. The authors found that in black and white adults aged 20–74 years, there was an increase in prevalence of stages 3–4 CKD from 2.0% to 2.5%. Stages 1 and 2 CKD could not be studied because proteinuria was not quantified in a consistent manner (NHANES II had only dipstick urinalysis).

Subsequently, Coresh et al³ (in an article not cited by Grams et al¹) reported that there was no statistically significant difference in the unadjusted prevalence of CKD from NHANES III (1998–1994) and the next NHANES survey in 1999–2000. All stages of CKD were analyzed. For stages 3–4 CKD alone, there was even a trend toward a lower prevalence in later years (Table 1).

Two years later, Coresh et al⁴ updated their analysis using NHANES 1999–2004 data and a different serum creatinine calibration methodology to conclude that there had been an

increase in CKD prevalence in the US population since NHANES III (1988–1994). The primary analysis of the second report by Coresh et al⁴ showed that the overall prevalence of stage 1–4 CKD increased from 10.0% to 13.1% from 1988 to 2004. These results garnered much attention from the medical and lay press. However, the authors very appropriately detailed an additional conservative trend analysis. The conservative trend analysis addressed the fact that after calibration, mean serum creatinine level in those aged 20–39 years who did not have diabetes or hypertension was higher in NHANES 1999–2004 than NHANES III (1988–1994) by 0.04 mg/dL, and this was matched by a shifting of the entire US population eGFR distribution to a lower range. In the conservative trend analysis, 0.04 mg/dL was added to all 1988–1994 measurement data to make the mean serum creatinine value of the young healthy group identical across surveys. With this adjustment, the conservative trend analysis showed a much less substantial increase in disease prevalence for stages 3–4 CKD than the primary analysis (1.4% rather than 3.5% per annum increased; Table 1).⁴

Then in 2009, Foley et al⁵ published a study examining CKD prevalence trends that relied on cystatin C as an alternative filtration marker. Cystatin C was measured in a subset of NHANES III (1988–1994) and NHANES 1999–2002 participants. Foley et al⁵ reported that this approach, which should avoid serum creatinine calibration issues, found no change in prevalence of CKD overall or for stages 3–4 (Table 1).

The present report by Grams et al¹ leverages the same cystatin C measurements. The authors note that because cystatin C measurements were conducted in 2 batches corresponding to the 2 survey periods, there was assay drift that may have biased results in the article by Foley et al.⁵ This study by Grams et al¹ thus makes a contribution to the literature. However, it is unlikely to be the final word on this subject for at least 4 reasons.

First, post hoc regression analysis will not perfectly resolve the calibration problem. It would have been ideal if the cystatin C substudy in NHANES had been designed so that serum samples from the 2 surveys were assayed within the same batch.

Second, rather disappointingly, the authors did not analyze data for albuminuria to derive estimates of temporal changes in stages 1 and 2 CKD using cystatin C level, as the same research group had done previously.^{3,4,6} Thus, a more complete picture of temporal trend in CKD prevalence is not provided. One should not automatically assume that different GFR estimation methods would not impact trends in stages 1 and 2 CKD. The overlap between those identified as having CKD by cystatin C level versus albuminuria versus creatinine level is incompletely defined. It also is unclear how this varies by subsets of the population, some of whom have become more populous over time (eg, the elderly).

Third, that there was no difference in mean standardized cystatin C levels between NHANES III (1988–1994) and NHANES 1999–2002 in those who were young and healthy is strong evidence that there was residual calibration bias in the primary analysis of the 2007 report by Coresh et al.⁴ In other words, there was no wholesale shift in the entire US population's GFR distribution to a lower range between the 2 NHANES surveys. Hence, results of the conservative trend analysis may present a more accurate picture.⁴ By that conservative trend analysis, unadjusted disease prevalence increased at a rate of ~1.4% per

year, much less than the increase in prevalence of approximately 4.9%–5.0% per year reported by Grams et al¹ (Table 1).

Fourth, these data are a decade old or older by now. The US Centers for Disease Control and Prevention CKD Surveillance System has been analyzing more recent NHANES survey data.⁷ Interestingly, no change in CKD disease prevalence has been noted during the past 10 years (in analyses taking into account drifts in creatinine assays over time). Specifically, the prevalence of stages 3–4 CKD was 8.1% in 2001–2002, 7.7% in 2003–2004, 8.1% in 2005–2006, 8.0% in 2007–2008, and 7.8% in 2009–2010.⁷ The prevalence of earlier stage CKD also has not increased in the last decade.⁷ These observations are remarkable considering that the analyses are unadjusted and therefore the aging of the population is not factored in.

That not all studies have uniformly shown an increase in CKD prevalence over time may come as a surprise to some readers. It is easy to assume that as a result of CKD risk factors such as older age and diabetes mellitus becoming more common, CKD must have become more prevalent (Table 1 shows crude prevalence rates). However, this is not necessarily true because medical treatment also has advanced considerably in the past several decades. For example, when the landmark United Kingdom Prospective Diabetes Study (UKPDS) trial was conducted in the 1980s, it was thought acceptable to allow patients with type 2 diabetes in the control arm to have blood pressures as high as 200/105 mm Hg (this was lowered to 180/105 mm Hg in 1992).⁸ The first large randomized controlled trial to demonstrate the reno-protective effect of renin-angiotensin system blockade was not published until 1993.⁹ Large strides have been made in glycemic control, which has been shown to be effective in reducing the risk of incident CKD.¹⁰ A Finnish study found that those with a diagnosis of type 1 diabetes in 1980 through 1999 have less than half the risk of developing end-stage renal disease (ESRD) compared with those given the diagnosis in 1965 through 1969.¹¹ A fact that is not widely appreciated is that the US Renal Data System consistently has reported that the incidence of ESRD in the United States has reached a plateau in many groups during the past decade, in sharp contrast to the rapid increase seen the 1980s and 1990s.^{12,13} For example, in Americans aged 60–64 years, the incidence of ESRD was 913 per million in 2001, but 853 per million in 2010 (this despite the fact that dialysis therapy is being initiated earlier and earlier in the course of advanced CKD, a practice pattern change that would automatically drive up the number of patients with “ESRD” without a true change in underlying disease prevalence¹³).

Thus, readers of this report by Grams et al¹ should realize that the news is not all gloomy. There is other evidence that our collective efforts at preventing and treating CKD have achieved some lowering of the burden of disease at a societal level.

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Table 1

Summary of Studies of Temporal Trends in CKD Prevalence in US Population Derived From NHANES

Study	CKD Definition	Prevalence 1976–1980	Prevalence 1988–1994	Prevalence 1999–2004	Change in Prevalence (per y)	GFR Estimating Equation	Filtration Marker Calibration and Alignment
Hsu et al. ² <i>Annals</i> (2004)	eGFR _{cr} <60 mL/min/1.73 m ²	2.0% ^a	2.5% ^a	—	+1.7% ^b	4-variable MDRD Study Equation ¹⁴	For both periods, Cleveland Clinic calibrated Cr ^c = Cr – 0.23
Corresh et al. ³ <i>JASN</i> (2005)	CKD 1–4 (eGFR _{cr} and ACR)	—	8.8%	9.4% ^d	+0.8%	4-variable MDRD Study Equation ¹⁴	1988–1994: Cleveland Clinic calibrated Cr ^c = Cr – 0.23; 1999–2000: Cleveland Clinic calibrated Cr = Cr + 0.13
Corresh et al. ⁴ <i>JAMA</i> (2007)	CKD stages 1–4 (eGFR _{cr} and ACR)	—	4.4%	3.8% ^d	–1.7%	4-variable MDRD Study Equation ¹⁴	
	eGFR _{cr} <60 mL/min/1.73 m ²	—	10.0%	13.1%	+2.6% ^b	IDMS-traceable MDRD Study Equation ¹⁵	
	eGFR _{cr} <60 mL/min/1.73 m ² (primary analysis)	—	5.6%	8.1%	+3.5% ^b	IDMS-traceable MDRD Study Equation ¹⁵	1998–1994: standardized Cr = –0.184 + 0.960 × Cr; 1999–2000: standardized Cr = 0.147 + 1.013 × Cr; after 2000: did not require calibration; conservative trend analysis added 0.04 mg/dL to 1988–1994 creatinine values
Foley et al. ⁵ <i>CJASN</i> (2009)	eGFR _{cr} <60 mL/min/1.73 m ² (conservative trend analysis)	—	NR	NR	+1.4% ^b	IDMS-traceable MDRD Study Equation ¹⁵	
	CKD 1–5 (eGFR _{cys} and ACR)	—	15.1%	14.9% ^e	–0.1%	CKD-EPI CysC 2008 ¹⁶	No calibration performed for CysC
	eGFR _{cys} <60 mL/min/1.73 m ²	—	6.4%	6.9% ^e	+0.8%	CKD-EPI CysC 2008 ¹⁶	
Grams et al. ¹ <i>AJKD</i> (2013)	eGFR _{cys} <60 mL/min/1.73 m ²	—	5.5%	8.7% ^e	+4.9% ^b	CKD-EPI CysC 2012 ¹⁷	1988–1994: standardized CysC = 1.12 × [0.022 + 0.80 × CysC]; 1999–2002: standardized CysC = 1.12 × [CysC – 0.12]
	eGFR _{cr-cys} <60 mL/min/1.73 m ²	—	4.4%	7.1% ^e	+5.0% ^b	CKD-EPI Cr-CysC 2012 ¹⁷	

Abbreviations: ACR, albumin-creatinine ratio; AJKD, American Journal of Kidney Diseases; Annals, Annals of Internal Medicine; CKD, chronic kidney disease; CJASN, Clinical Journal of the American Society of Nephrology; CKD-EPI, CKD Epidemiology Collaboration; Cr, creatinine (in mg/dL); CysC, cystatin C (in mg/L); eGFR_{cr}, creatinine based estimated GFR; eGFR_{cr-cys}, creatinine and cystatin C based estimated GFR; eGFR_{cys}, cystatin C based estimated GFR; GFR, glomerular filtration rate; IDMS, isotope-dilution mass spectrometry; JAMA, Journal of the American Medical Association; JASN, Journal of the American Society of Nephrology; MDRD, Modification of Diet in Renal Disease; NHANES, National Health and Nutrition Examination Surveys; NR, not reported.

^aFor blacks and whites aged 20–74 years only.

^bStatistically significant change in the original study.

^cThe MDRD Study used the Cleveland Clinic laboratory for determining Cr concentration; thus, Cleveland Clinic–calibrated Cr is suitable for use in the 4-variable MDRD Study equation.

^dPrevalence in 1999–2000.

^ePrevalence from 1999–2002.

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