Supplemental Materials

Complete Methods

Study Population

The NHANES are cross-sectional, multistage, stratified, clustered probability samples of the US civilian non-institutionalized population conducted by the National Center for Health Statistics (NCHS). The NHANES included in the current analysis were conducted from 1988-1994 in 2 phases (1988-1991 [n=9,488] and 1991-1994[n=9,337]) and from 1999- 2006 in 4 phases (1999-2000 [n=4880], 2001-2002 [n=5411], 2003-2004[n=5041], 2005-2006[n=4979]). Data from all phases were combined herein following NCHS recommendations.[30] The overall sample size of the pooled NHANES III/NHANES 1999-2006 was 39,136. We excluded 6,202 individuals for missing serum creatinine or ACR data, 1,283 women who were pregnant at the time of their study exam, 61 with eGFR < 15 ml/min/1.73 m^2, and 1,062 individuals missing data on any of the six complications" The study population was limited to participants who completed a medical evaluation in the NHANES mobile examination center and were aged 20 years or older. Those who were pregnant or were missing measurements of urinary albumin or creatinine excretion, serum creatinine, phosphorous, hemoglobin, bicarbonate, serum albumin or blood pressure were excluded from the current analyses. Participants with eGFR < 15 mL/min/1.73m^2 (CKD stage 5) were also excluded because the small number of individuals available in this group. After these exclusions, data for 30,528 participants were available for the analysis of anemia, acidosis, hyperphosphatemia, hypoalbuminemia, and hypertension. Intact parathyroid hormone (iPTH) was measured only in NHANES 2003-2004 and NHANES 2005-2006. The overall sample size of the NHANES 2003-2006 with PTH available was 10,020. We excluded 1,255 individuals for missing serum creatinine or ACR data, 506 women who were pregnant at

the time of their study exam, 13 with eGFR < 15 ml/min/1.73 m^2, and 4 individuals missing data on PTH. As such, data were available for 8,242 participants for the analysis of iPTH.

Information on age, sex, and race/ethnicity (categorized as non-Hispanic white, non-Hispanic black, Mexican American, or all other) was based on self-report collected during the interview portion of the survey. Participants who reported having smoked 100 or more cigarettes during their lifetime were classified as current smokers if they reported currently smoking in NHANES III or smoking "some days" or "most days" in NHANES 1999-2006. Height and weight were measured and body mass index was calculated. Diabetes mellitus was defined as a self-report of a previous diagnosis, not during pregnancy, with concurrent use of insulin or oral hypoglycemic medication or a glucose ≥ 126 mg/dL among participants who fasted 9 or more hours prior to their study visit or ≥ 200 mg/dL among non-fasting participants.

Measures of Kidney Function

Serum creatinine was assayed using the Synchron AS/Astra Analyzer (Beckman Coulter, Fullerton, California) in NHANES III and a LX20 analyzer (Beckman Coulter, Fullerton, California) in NHANES 1999- 2006. To appropriately estimate GFR, all serum creatinine measurements were recalibrated to standardized creatinine measurements obtained at the Cleveland Clinic Research Laboratory.[31] eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[2]. eGFR categories included: ≥120, 90-119, 60-89, 45-59, 30-44, and 15-29 ml/min per 1.73 m^2 as defined by the National Kidney Foundation's Kidney Disease Outcome Quality Initiative (KDOQI) with Stage 3 classified into Stage 3a and Stage 3b as has been recommended recently.[28]

A random spot urine sample was obtained from participants examined at the mobile examination center using a clean-catch technique and sterile containers. Frozen non-hematuric 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) in NHANES III and a CX3 analyzer (Beckman Coulter, Fullerton, California) in NHANES 1999- 2006. Urinary albumin-to creatinine ratio (ACR) was computed and is reported in milligrams per gram (mg/g; 1 mg/g = 0.131 mg/mmol). Albuminuria categories included normal, high-normal, high and very high defined as ACR < 10, 10-29,30 to 299, and 300 mg/g or higher, respectively.

Assessment of CKD complications

Complications which reflect different biological mechanisms were included. Hemoglobin was measured by Coulter Splus Jrin NHANES III and Beckman Coulter MAXM in the later surveys. Anemia was defined by the World Health Organization as hemoglobin levels less than 12 g/dL for women and less than 13.5 g/dL for men. Bicarbonate, phosphate, and serum albumin were assayed using Hitachi 737 in NHANES III, Hitachi 704 in NHANES1999-200 and Beckman-Synchron LX20 in the NHANES 2001-2006. Acidosis was defined as serum bicarbonate less than 22 mEq/L. Hyperphosphatemia was defined as serum phosphate ≥ 4.5 mg/dl. Hypoalbuminemia was defined as serum albumin less than 3.5 g/dL. Serum iPTH was measured at the University of Washington, in Seattle, WA on an Elecsys 1010 autoanalyzer (Roche Diagnostics, Mannheim, Germany), using a electrochemiluminescent process. This second

generation method employs a biotinylated monoclonal PTH-specific antibody and monoclonal PTH-specific antibody labeled with a ruthenium complex to form a sandwich complex. Hyperparathyroidism was defined as iPTH levels ≥ 70 pg/mL. To standardize the laboratory values across all surveys, the age, sex, and race/ethnicity adjusted difference in the mean level for hemoglobin, bicarbonate, phosphate, serum albumin and iPTH for participants 20-39 year olds without diabetes and hypertension, and eGFR > 60 ml/min/1.73m^2 and ACR < 10 for each survey was calculated. Differences from the value for NHANES 2005 – 2006 was then added/subtracted for values for the other NHANES phases. Blood pressure was measured six times in NHANES III and three times in NHANES 1999-2006. Using the average of all available blood pressure measurements, hypertension was defined as a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or self-reported use of antihypertensive medication.

Statistical Analyses

Demographic and clinical characteristics were summarized as means or proportions by level of albuminuria and eGFR, separately. The unadjusted prevalence ratios for each CKD complication associated with ACR and eGFR, modeled separately as continuous variables, were calculated using restricted quadratic splines with knots at ACR levels of 10, 30, 100 and 300 mg/g and eGFR levels of 30, 60, 90 and 120 ml/min/1.73m^2. Due to its skewed distribution and anticipated log-linear association with outcomes[9], ACR was log-transformed for the spline analyses. Prevalence ratios are recommended for use in cross-sectional studies with common outcomes[32], and therefore using ACR < 10 mg/g as the reference group, using log-linear generalized estimating equations, prevalence ratios were adjusted initially for age and subsequently for age, sex, race/ethnicity and eGFR (or ACR for the associations of eGFR with

complications), and survey. A final model included additional adjustment for cigarette smoking, body mass index, diabetes mellitus, and hypertension, except in the final model with hypertension as the outcome which included cigarette smoking, body mass index, and diabetes mellitus,. The prevalence ratios for these complications associated with eGFR categories, with levels of 90 to 119 ml/min/1.73 m^2 as the referent, were also calculated. The age, race/ethnicity, and sex adjusted prevalence of anemia, acidosis, hyperphosphatemia, hypoalbuminemia, and hypertension were calculated by the cross-categorization of ACR and eGFR. Prevalence rates were adjusted to age 60 years and to a gender-race distribution similar to the US population (50% women, 75% non-Hispanic white, 10% non-Hispanic black, 10% Hispanic, and 5% other race-ethnicity). The joint effect of ACR and eGFR levels with complications was tested by comparing the log likelihood for multivariable adjusted models with and without interaction terms for eGFR*ACR categories. The number of participants with iPTH levels was not sufficient to achieve reliable estimates for the cross-categorization analysis. Therefore, this analysis is not presented for iPTH.

Analyses were performed incorporating the sampling weights to obtain unbiased estimates using SUDAAN version 10 (Research Triangle Institute, Research Triangle Park, NC). Sampling weights were combined across all survey phases from NHANES 1988-2006. The standard errors for all estimates were obtained using the Taylor series (linearization) method accounting for the complex, multi-stage recruitment of NHANES participants.

Supplemental Table 1: Characteristics of study participants by level of estimated glomerular filtration rate.

	Estimated GFR, ml/min/1.73m^2						
	≥ 120 (n=4680)	90 – 119 (n=13915)	60 – 89 (n=9407)	45 - 59 (n=1733)	30- 44 (n=636)	<30 (n=157)	p-trend
% of population	12.4%	51.5%	30.6%	3.9%	1.3%	0.3%	
Age in years, mean (SD)	27.7 (0.2)	40.5 (0.2)	56.4 (0.4)	71.4 (0.5)	74.5 (0.7)	74.8 (1.2)	<0.001
Men, %	43.6	51.1	49.9	41.0	39.3	44.2	0.621
Race							
Non-Hispanic White, %	49.4	73.9	84.5	84.7	85.1	75.4	Ref
Non-Hispanic Blacks, %	24.7	9.0	6.7	7.7	9.4	11.8	<0.001
Hispanic, %	17.5	10.0	4.8	3.7	2.8	3.5	<0.001
Other, %	8.4	7.1	4.0	4.0	2.7	9.3	<0.001
Current smoker, %	32.7	29.3	16.1	10.0	5.6	12.0	<0.001
Body mass index, kg/m^2	26.3 (0.1)	27.2 (0.1)	28.0 (0.1)	28.2 (0.2)	28.3 (0.3)	28.3 (0.7)	<0.001
Diabetes mellitus, %	3.1	4.9	8.3	16.9	24.0	36.0	<0.001
C-reactive protein, mg/L							
< 3.0, %	71.9	69.6	64.4	55.4	45.6	47.3	Ref
3.0 – 9.9, %	19.4	22.9	26.9	30.9	34.3	34.9	<0.001
≥ 10.0, %	8.7	7.5	8.7	13.8	20.1	17.8	<0.001
ACR, mg/g, median (25–75%)	6.0 (3.9, 10.1)	5.5 (3.7, 9.6)	6.1 (3.8, 12.1)	10.3 (5.4, 29.7)	21.3 (8.0, 96.7)	58.7 (15.6, 663)	<0.001
Hemoglobin, g/dL mean (SD)	14.1 (0.1)	14.5 (0.1)	14.5 (0.1)	14.0 (0.1)	13.4 (0.1)	12.4 (0.2)	0.003
Bicarbonate, mEq/L mean (SD)	26.3 (0.2)	26.1 (0.1)	26.2 (0.1)	26.1 (0.1)	25.7 (0.2)	24.2 (0.4)	0.030
Phosphorus, mg/dL mean (SD)	3.61 (0.02)	3.56 (0.01)	3.58 (0.01)	3.61 (0.02)	3.62 (0.03)	3.95 (0.08)	0.174
Albumin, mg/dL mean (SD)	4.28 (0.02)	4.29 (0.01)	4.25 (0.01)	4.14 (0.01)	4.04 (0.02)	3.99 (0.04)	<0.001
iPTH, pg/mL median (25th – 75th percentile)	35.2 (26.8, 48.4)	36.8 (28.0, 47.7)	40.7 (31.3, 53.2)	48.8 (36.6, 65.9)	64.6 (41.9, 96.2)	90.2 (62.4, 148)	<0.001
Systolic blood pressure, mmHg mean (SD)	114.4 (0.3)	119.7 (0.2)	128.6 (0.4)	140.0 (0.8)	142.9 (1.1)	145.5 (2.5)	<0.001
Diastolic blood pressure, mmHg mean (SD)	69.5 (0.2)	73.6 (0.2)	74.2 (0.2)	71.2 (0.4)	68.7 (0.9)	68.0 (1.9)	<0.001

Abbreviations: SD – standard deviation; eGFR – Estimated glomerular filtration rate; ACR – Albumin to creatinine ratio

Supplemental Table 2: Number of participants included in the current analysis by category of estimated glomerular filtration rate and albumin-to-creatinine ratio.

eGFR category	ACR category				
	Overall	**<10**	**10-29**	**30-299**	**≥300**
All analyses except iPTH					
Overall		20416	6115	3044	953
≥ 120	4680	3469	824	295	92
90 – 119	13915	10152	2493	1037	233
60−89	9407	5836	2134	1130	307
45−59	1733	734	486	356	148
30−44	636	198	148	181	109
<30	157	18	30	45	64
p-trend					
iPTH analyses					
	Overall	**<10**	**10-29**	**30-299**	**≥300**
Overall		5462	1757	862	161
≥ 120	942	673	196	68	5
90 – 119	3633	2614	711	266	42
60−89	2825	1819	632	337	37
45−59	564	273	153	113	25
30−44	212	75	49	59	29
<30	66	8	16	19	23