CKD and Cardiovascular Disease in Screened High-Risk Volunteer and General Populations: The Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES) 1999-2004

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Background: Chronic kidney disease (CKD) is recognized as an independent cardiovascular disease risk state. The relationship between CKD and cardiovascular disease in volunteer and general populations has not been explored.

Methods: The National Kidney Foundation Kidney Early Evaluation Program (KEEP) is a community-based health-screening program to raise kidney disease awareness and detect CKD for early disease intervention in individuals 18 years or older with diabetes, hypertension, or family history of kidney disease, diabetes, or hypertension. KEEP volunteers completed surveys and underwent blood pressure and laboratory testing. Estimated glomerular filtration rate (eGFR) was computed, and urine albumin-creatinine ratio (ACR) was measured. In KEEP, CKD was defined as eGFR less than 60 mL/min/1.73 m^2 or ACR of 30 mg/g or greater. Cardiovascular disease was defined as self-reported myocardial infarction or stroke. Data were compared with National Health and Nutrition Examination Survey (NHANES) 1999-2004 data for prevalence of cardiovascular disease risk factors and cardiovascular outcomes.

Results: Of 69,244 KEEP participants, mean age was 53.4 $\pm$ 15.7 years, 68.3% were women, 33.0% were African American, and 27.6% had diabetes. Of 17,061 NHANES participants, mean age was 45.1 $\pm$ 0.27 years, 52% were women, 11.2% were African American, and 6.7% had diabetes. In KEEP, 26.8% had CKD, and in NHANES, 15.3%. ACR was the dominant positive screening test for younger age groups, and eGFR, for older age groups, for both populations. Prevalences of myocardial infarction or stroke were 16.5% in KEEP and 15.1% in NHANES ($P < 0.001$) and 7.8% in KEEP and 3.7% in NHANES ($P < 0.001$) for individuals with and without CKD, respectively. In adjusted analysis of both KEEP and NHANES data, CKD was associated with a significantly increased risk of prevalent myocardial infarction or stroke (odds ratio, 1.34; 95% confidence interval, 1.25 to 1.43; odds ratio, 1.37; 95% confidence interval, 1.10 to 1.70, respectively). In KEEP, short-term mortality was greater in individuals with CKD (1.52 versus 0.33 events/1,000 patient-years).

Conclusions: CKD is independently associated with myocardial infarction or stroke in participants in a voluntary screening program and a randomly selected survey population. Heightened concerns regarding risks in volunteers yielded greater cardiovascular disease prevalence in KEEP, which was associated with increased short-term mortality.

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INDEX WORDS: Age; atherosclerosis; cardiovascular disease; chronic kidney disease; microalbuminuria; mortality; myocardial infarction; stroke.

Chronic kidney disease (CKD) is becoming a global public health problem because of the pandemics of obesity, hypertension, and type 2 diabetes mellitus.[1,2] CKD is defined by markers of kidney damage, most commonly urine albumin-creatinine ratio (ACR) of 30 mg/g or greater or decreased estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2 (<1.0 mL/s/1.73 m^2) in the absence of markers of kidney damage. Both albuminuria and decreased eGFR were linked to fatal and nonfatal cardiovascular disease (CVD).[3,4] In these studies, the cause of death is more likely CVD than CKD.[5-10] CKD therefore is widely recognized as an independent CVD risk state and a subject of considerable interest among cardiologists and nephrologists.[11]

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There is support for the notion that CKD independently contributes to accelerated atherosclerotic disease in the coronary, cerebral, and peripheral circulation, making management of this condition more difficult.[12-15] In addition, the development of both heart failure and cardiac arrhythmias is influenced by level of kidney function and degree of structural heart disease that developed during the course of CKD.[15-17] Our aim is to evaluate the relationships between measures of CKD and self-reported CVD in a large volunteer screening population at risk of CKD and in a randomly selected general community population not at particular risk of CKD or any chronic disease.

METHODS

Subjects

The National Kidney Foundation Kidney Early Evaluation Program (KEEP) is a free ongoing community-based screening program designed to identify individuals at increased risk of kidney disease and encourage them to seek follow-up care.[18] From August 1, 2000, through December 31, 2006, participants were recruited from 47 National Kidney Foundation affiliates representing 49 states and the District of Columbia and 1,608 screening events. Eligible participants were men or women 18 years or older with diabetes or hypertension or with a family history of diabetes, hypertension, or kidney disease. After excluding repeated screening visits, this yielded a sample of 69,244 participants from the KEEP data set through December 31, 2006.

The National Health and Nutrition Examination Survey (NHANES) 1999-2004 is a series of nationally representative cross-sectional surveys conducted by the National Center for Health Statistics and designed to monitor the health and nutritional status of the noninstitutionalized civilian population in the United States. For comparison purposes with KEEP data, all samples analyzed using data collected in NHANES 1999-2004 were restricted to individuals 18 years or older (n = 17,061). For all analyses related to smoking status, self-reported CVD, and family history of comorbidity, the NHANES study population is limited to participants 20 years or older (n = 15,332). KEEP and the NHANES database are fully described elsewhere in this supplement.[19]

Measures

Screening data were collected for participant demographic characteristics and medical history, including self-reported personal and family history of CVD. One-time seated cuff blood pressure measurements were obtained, and blood and urine specimens were collected and tested to determine blood glucose, creatinine, and urine albumin levels. Screening methods used in KEEP were described previously.[18]

Definitions and Outcomes

To ensure unbiased comparison of participants in the KEEP and NHANES 1999-2004 populations, special attention was applied in standardizing disease definitions and measurements of outcomes. KEEP participants were classified as hypertensive for reported use of medications for hypertension, self-reported history of high blood pressure, or systolic blood pressure of 130 mm Hg or greater or diastolic blood pressure of 80 mm Hg or greater for those with a history of diabetes or CKD, otherwise systolic blood pressure of 140 mm Hg or greater or diastolic blood pressure of 90 mm Hg or greater. In NHANES, the definition of hypertension does not consider medication use. KEEP participants were classified as having diabetes for reported diabetes or retinopathy, use of medication for diabetes or insulin, or blood glucose level greater than 125 mg/dL (>6.9 mmol/L) if fasting or greater than 200 mg/dL (>11.1 mmol/L) if nonfasting. In NHANES, diabetes is self-reported comorbidity.

eGFR was calculated using the isotope dilution mass spectrometry–traceable 4-variable Modification of Diet in Renal Disease Study equation reexpressed for standardized creatinine values ($175 \times [\text{serum creatinine}^{-1.154}] \times [\text{age}^{-0.203}]$); calculated values were multiplied by 0.742 for women and 1.21 for African Americans.[4] Calculated eGFR values were categorized as less than 30, 30 to 59, 60 to 89, and 90 mL/min/1.73 m^2 or greater (<0.50, 0.50 to 0.98, 1.00 to 1.48, and ≥1.50 mL/s/1.73 m^2) based on the Kidney Disease Outcomes Quality Initiative (KDOQI) classification of kidney function; eGFR values less than 60 mL/min/1.73 m^2 (<1.0 mL/s/1.73 m^2) were considered abnormal and indicative of moderately decreased kidney function.[4] In KEEP, albuminuria was determined by using spot urine ACR; 30 mg/g or greater was considered microalbuminuria. CKD was defined as eGFR less than 60 mL/min/1.73 m^2 (<1.0 mL/s/1.73 m^2) or ACR of 30 mg/g or greater. Participants were categorized as anemic by using the 2006 KDOQI definition of hemoglobin level less than 13.5 g/dL (<135 g/L) for men and less than 12 g/dL (<120 g/L) for women. CVD was recorded as the composite self-reported myocardial infarction or stroke in both KEEP and NHANES databases.

All-cause mortality was determined by using a previously validated multilevel tracking system by the Chronic Disease Research Group at Minneapolis Medical Research Foundation, Hennepin County Medical Center. These methods are analogous to methods used by the US Renal Data System Coordinating Center by the same coinvestigators. This system is capable of using name and social security number data and incident end-stage renal disease patient records with cross-checks against the US Medicare database and Social Security Administration Death Files. To calculate death rate, we defined follow-up time from the screening date until December 31, 2006, or death date.

Analysis

Univariate statistics are reported as mean ± SD or count with proportion, as appropriate. Stratified analyses were carried out across the presence or absence of CKD. We adopted a simpler method for *P* values in comparing KEEP and NHANES samples. We merged the 2 data sets and

calculated χ^2 P for categorical variables and t-test P for continuous variables (body mass index and mean eGFR). NHANES surveys were nationally representative cross-sectional health examination surveys using a complex, stratified, multistage probability cluster sampling design. However, we did not use weight for the NHANES sample to calculate these P values. Therefore, the interpretation between differences in the 2 samples based on P values listed in Tables 1 to 3 may not be generalized to the population. Cochran-Armitage test for proportions was used to determine P for trend across these groups. Multiple logistic regression was used to determine independent relationships between the composite CVD variable and predictor variables, including the presence of CKD, demographic characteristics (age, sex, race, education, smoking status, health insurance coverage, and family history of diabetes, hypertension, or kidney disease), and anemia. P less than 0.05 is considered statistically significant.

RESULTS

Compared with NHANES participants, KEEP participants were older, more likely to be African American, less likely to be smokers, and, according to entry criteria, had a greater prevalence of CKD risk factors (Table 1). According to KEEP entry criteria, greater than 90% of participants had a family history of diabetes, hypertension, or kidney disease.

KEEP participants had greater rates of CKD detected by means of either ACR or eGFR measurements than NHANES participants (Table 2). Figure 1 shows proportions of participants identified as having CKD based on ACR of 30 mg/g or greater, eGFR less than 60 mL/min/1.73 m^2 ($<$1.0 mL/s/1.73 m^2), or both for KEEP and NHANES. ACR was more likely to be the positive screening test for younger age groups, and eGFR was more likely to be decreased and define CKD for older age groups. For most age groups, the degree of overlap between ACR and eGFR was relatively small compared with fractions of ACR-positive alone or eGFR-decreased alone.

Table 3 lists prevalences of self-reported myocardial infarction and stroke at the time of screening, and Fig 2 shows individual and composite prevalences of myocardial infarction, stroke, and death by CKD groups. Considering the varying follow-up times, we also calculated death rates. Results from multivariate analysis for the outcome of prevalent myocardial infarction or stroke are listed in Table 4 for the KEEP and NHANES databases. All odds ratios for independent variables associated with CVD were concordant (greater or less than unity) for the KEEP and NHANES populations. Age, smoking, diabetes, and CKD were the most prominently associated variables with CVD in both populations.

Table 1. Demographic Characteristics of the Population: KEEP and NHANES 1999-2004

	KEEP* (n = 69,244)	NHANES (n = 17,061)	P†
Sex			<0.001
Men	21,938 (31.7)	8,091 (48.0)	
Women	47,245 (68.3)	8,970 (52.0)	
Race/ethnicity			<0.001
Non-Hispanic white	29,755 (43.2)	8,302 (71.4)	
Non-Hispanic African American	22,722 (33.0)	3,458 (11.2)	
Other race	7,725 (11.2)	5,301 (17.5)	
Hispanic	8,623 (12.5)	4,776 (13.2)	
≥High school education	57,514 (84.4)	11,115 (78.4)	<0.001
Current smoker‡	8,061 (12.4)	3,301 (24.9)	<0.001
Health insurance coverage	54,112 (81.5)	13,283 (82.1)	<0.001
Family history of diabetes, hypertension, or kidney disease§	63,028 (91.0)	9,008 (63.1)	<0.001

Note: Values expressed as number (percent).

Abbreviations: KEEP, Kidney Early Evaluation Program; NHANES, National Health and Nutrition Examination Survey.

*In KEEP, missing values are excluded in calculating percentage.

†χ^2 test for KEEP and NHANES sample comparison. Results may not be generalized to the population.

‡For all analyses related to smoking status, cardiovascular disease, or family history of diabetes and hypertension in NHANES, the study population is 20 years and older.

§NHANES 1999-2004 data do not include information for family history of kidney disease.

DISCUSSION

We found that in participants with CKD at the screening event, urine ACR was the dominant positive test for the younger age groups, and eGFR was the test most likely to define CKD for the older age groups in both KEEP and NHANES. This finding suggests that both tests should be firmly positioned as complementary screening tests for CKD in the general population. Rates of myocardial infarction or stroke were greater in KEEP, in which the enriched screening population likely was motivated to recognize and attempt to improve CKD and potential CVD risk factors. Despite this recognition, mortality rates during the short term were high for KEEP partici-

Table 2. Health Screening Results: KEEP and NHANES 1999-2004

	KEEP	NHANES	*P**
Body mass index (kg/m^2)†	30.2 ± 6.8	28.0 ± 0.10	<0.001
Diabetes‡	19,122 (27.6)	1,545 (6.7)	<0.001
Hypertension	47,309 (68.3)	6,518 (37.9)	<0.001
eGFR (mL/min/1.73 m^2)			
Mean†	81.0 ± 23.5	88.3 ± 0.45	<0.001
<30	601 (0.9)	121 (0.5)	
30-59	10,454 (16.0)	1,317 (7.4)	
<60	11,055 (16.9)	1,438 (7.9)	<0.001
60-89	33,314 (51.1)	6,056 (49.7)	
≥90	20,878 (32.0)	7,311 (42.4)	
Urinary ACR ≥ 30 mg/g§	7,073 (11.8)	1,892 (9.6)	0.07
Chronic kidney disease§			
eGFR< 60 mL/min/1.73 m^2 or ACR ≥ 30 mg/g	15,661 (26.8)	2,734 (15.3)	<0.001
Chronic kidney disease stage§			<0.001
1; eGFR ≥ 90 mL/min/1.73 m^2, ACR ≥ 30 mg/g	1,761 (3.0)	614 (3.2)	
2; eGFR 60-89 mL/min/1.73 m^2, ACR ≥ 30 mg/g	2,845 (4.9)	682 (4.0)	
3; eGFR 30-59 mL/min/1.73 m^2	10,454 (17.9)	1,317 (7.5)	
4-5; eGFR < 30 mL/min/1.73 m^2	601 (1.0)	121 (0.5)	

Note: Values expressed as number (percent) unless noted otherwise. To convert eGFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.01667.

Abbreviations: KEEP, Kidney Early Evaluation Program; NHANES, National Health and Nutrition Examination Survey; ACR, urinary albumin-creatinine ratio; eGFR, estimated glomerular filtration rate.

*χ^2 test (*t*-test for body mass index and mean eGFR) for KEEP sample and NHANES sample comparison. Results may not be generalized to the population.

†Mean ± SD, KEEP; mean ± SE, NHANES.

‡Self-reported in NHANES.

§Excludes cases with missing data.

pants who had CKD, highlighting the importance of CKD screening and the relative urgency to mitigate risks of death by decreasing risk factors.

This study has several important implications. Of them, confounding by volunteerism and concerns about CKD cannot explain the consistency between associations of CKD risk markers and CVD prevalence in both the KEEP and NHANES populations.[13,20] In general, KEEP is consistent with observations by Go et al,[7] who found a similar steep gradient between eGFR and subsequent mortality. In both KEEP and NHANES, the relationship between CKD and CVD was independent of other conventional Framingham CVD risk factors, such as diabetes and smoking.

Potential explanations for how the CKD state can cause, accelerate, worsen, and complicate

Table 3. Prevalence of Myocardial Infarction and Stroke by Chronic Kidney Disease Status: KEEP and NHANES 1999-2004

	KEEP	NHANES	*P**
No chronic kidney disease	n = 40,013	n = 10,486	
Prevalent myocardial infarction	1,817 (4.5)	307 (2.5)	<0.001
Prevalent stroke	1,499 (3.8)	201 (1.5)	<0.001
Prevalent myocardial infarction or stroke	2,845 (7.1)	465 (3.7)	<0.001
Chronic kidney disease	n = 14,592	n = 2,634	
Prevalent myocardial infarction	1,499 (10.3)	294 (9.2)	0.2
Prevalent stroke	1,122 (7.7)	240 (7.5)	0.01
Prevalent myocardial infarction or stroke	2,262 (15.5)	480 (15.1)	<0.001

Note: Values expressed as number (percent).

Abbreviations: KEEP, Kidney Early Evaluation Program; NHANES, National Health and Nutrition Examination Survey.

*χ^2 test for KEEP and NHANES sample comparison. Results may not be generalized to the population.

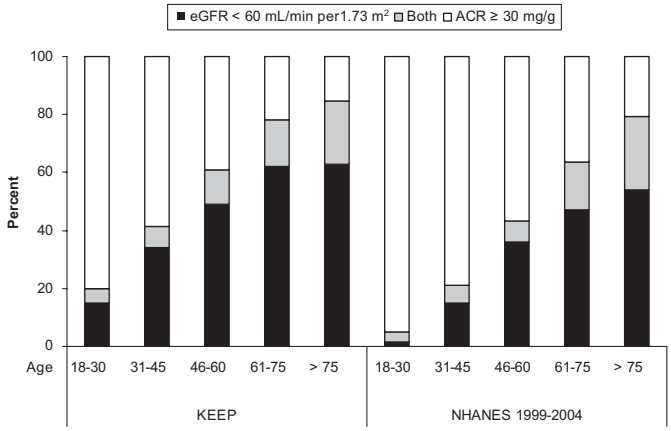

Figure 1. Relative proportions of albumin-creatinine ratio (ACR) of 30 mg/g or greater, estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2, and both as positive screening tests for chronic kidney disease in the Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES) 1999-2004. $P < 0.001$ for eGFR and ACR trend. To convert eGFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.01667.

CVD have been of considerable recent interest. The 4 basic explanations are: (1) uncontrolled confounding, or the impact of comorbid conditions that accompany CKD; (2) therapeutic nihilism, or patients with CKD receiving lesser degrees of beneficial therapies; (3) treatment with a less favorable benefit-risk ratio for patients with CKD; and (4) unique vascular pathobiological characteristics in the CKD state.[13,14,21]

We can speculate that urine ACR is a marker of early glomerular change that precedes a decrease in eGFR and thus is an important screening test for younger adults. In patients with both type 1 and type 2 diabetes, urine albumin excretion rate correlated histologically with increased glomerular basement membrane width and mesangial fractional volume, with increasing severity from normoalbuminuria to microalbuminuria to proteinuria, but considerable overlap among groups.[22,23] Whether these changes occur in patients with microalbuminuria without diabetes is unknown.

The presence of either urine ACR of 30 mg/g or greater or eGFR less than 60 mL/min/1.73 m^2 ($<$1.0 mL/s/1.73 m^2) identifies a patient with a complex set of biological processes. A decrease in renal clearance of a variety of nitrogenous products could be injurious to the vascular system in many ways.[12] This could be caused in part by activation of a variety of neurohormonal, inflammatory, and oxidative pathways that work to accelerate atherosclerosis, causing vascular injury throughout the body.[21] For example, calcification of coronary atherosclerosis is well known to accelerate when eGFR decreases to less than 60 mL/min/1.73 m^2 ($<$1.0 mL/s/1.73 m^2) as part of the CKD mineral and bone disorder syndrome.[12] Neurohormonal activation is clearly implicated in myocardial injury and the development of heart failure as one form of CVD in patients with CKD.[24] If ACR is viewed as a surrogate of glomerular vascular injury, a decrease in eGFR can be thought of as a surrogate for a decrease in global renal organ function.[17]

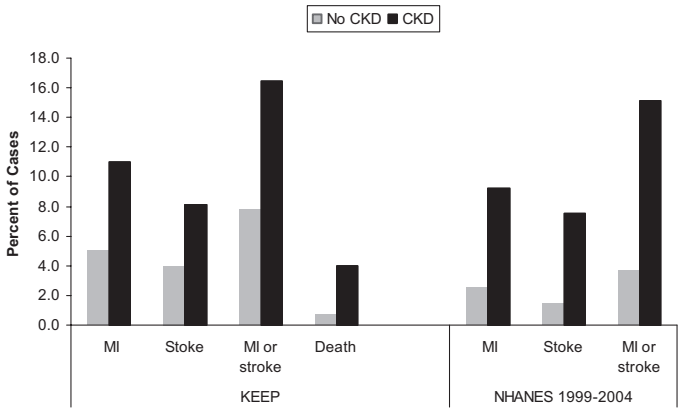

Figure 2. Rates of self-reported myocardial infarction (MI) and stroke stratified by chronic kidney disease (CKD) status for the Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES) 1999-2004. Death rates were 0.33 and 1.52/1,000 patient-years for non-CKD and CKD, respectively. NHANES 1999-2004 study population is 20 years and older. $P < 0.001$ for all pairwise comparisons.

Table 4. Independent Predictors of Cardiovascular Disease (myocardial infarction or stroke): KEEP and NHANES 1999-2004

	Odds Ratio (95% confidence interval)			
	KEEP n = 49,192	*P*	NHANES 1999-2004* n = 11,574	*P*
Age (/1-y increase)	1.04 (1.04-1.05)	<0.001	1.06 (1.05-1.07)	<0.001
White (reference)	1.00	—	1.00	—
African American	0.94 (0.87-1.01)	0.07	0.88 (0.65-1.19)	0.4
Other race	0.85 (0.78-0.94)	<0.001	0.64 (0.45-0.91)	0.01
Current smoker	1.69 (1.54-1.86)	<0.001	2.20 (1.65-2.93)	<0.001
Having insurance	0.93 (0.84-1.01)	0.1	0.99 (0.68-1.44)	0.9
≥High school education	0.79 (0.73-0.86)	<0.001	0.70 (0.55-0.88)	0.003
Family history†	1.07 (0.97-1.17)	0.2	1.23 (0.98-1.54)	0.07
Body mass index	1.01 (1.00-1.05)	<0.001	1.02 (1.01-1.04)	0.01
Diabetes	1.76 (1.65-1.88)	<0.001	1.92 (1.43-2.56)	<0.001
Hypertension	1.75 (1.59-1.93)	<0.001	1.64 (1.22-2.21)	0.002
Anemia	1.27 (1.17-1.37)	<0.001	1.22 (0.90-1.63)	0.2
Chronic kidney disease‡	1.34 (1.25-1.43)	<0.001	1.37 (1.10-1.70)	0.005

Abbreviations: KEEP, Kidney Early Evaluation Program; NHANES, National Health and Nutrition Examination Survey.

*NHANES 1999-2004 study population aged 20 years and older. Race in model is non-Hispanic white, non-Hispanic African American, and other. Diabetes is self-reported.

†Family history of diabetes, hypertension, or kidney disease. NHANES 1999-2004 data do not include family history of kidney disease. For a detailed definition of family history of comorbidity, see Methods.

‡Estimated glomerular filtration rate less than 60 mL/min/1.73 m^2 (<1.0 mL/s/1.73 m^2) or urinary albumin-creatinine ratio of 30 mg/g or greater.

With this decrease in renal function is a relative deficiency in renally produced protective substances, including erythropoietin, calcitriol, and perhaps a variety of other proteins.[17] We recently showed in the overall KEEP cohort that anemia is part of a CKD risk triad, along with microalbuminuria and decreased eGFR, for CVD outcomes.[25]

Our program has the limitations common to population studies. KEEP subjects were volunteers who likely were motivated by their recognized risk of CKD. However, because the screening process does not recruit individuals by using the terms "heart" or "cardiovascular disease," we believe that participants enrolled based on concern about CKD, and CVD represents a measured variable disclosed by the individual. NHANES subjects are randomly selected by a standardized process and thus could not have been activated regarding perceived CKD risk. We acknowledge that self-reported CVD has inherent variance related to both overreporting and underreporting. Because measurements were obtained once, random misclassification bias according to groupings by measure worked to bias hypothesis testing to the null. The eGFR variable may have underestimated actual GFR and misclassified participants with greater levels with those with eGFR less than 60 mL/min/1.73 m^2 (<1.0 mL/s/1.73 m^2) and thus diluted the biological impact of CKD on CVD. Lipid values were not measured in KEEP and could be a source of uncontrolled confounding. We did not have electrocardiographic, echocardiographic, or clinical records to confirm self-reported events. However, surveys were completed by participants assisted by health care professionals trained in eliciting the most accurate and complete medical information possible in both KEEP and NHANES. Last, we had only short-term follow-up to date and very few deaths in KEEP. As follow-up continues, we expect additional deaths to shed more light on the CKD and CVD relationships.

CKD is independently associated with myocardial infarction, stroke, and death in both people at risk of CKD and the general population. These data suggest that CKD-related biological changes that promote CVD cannot be explained simply by screening bias in the KEEP population because similar associations were observed in the randomly selected NHANES population. Screen-

ing for CKD by using both ACR and eGFR tests should be considered for detection of this disease in the general population. Intensive modification of both CKD and CVD risk factors is warranted given the greater morbidity and mortality outcomes in patients with CKD.[26]

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