Prevalence of CKD and Comorbid Illness in Elderly Patients in the United States: Results From the Kidney Early Evaluation Program (KEEP)

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Background: Elderly individuals with chronic kidney disease (CKD) have high rates of comorbid conditions, including cardiovascular disease and its risk factors, and CKD-related complications. In individuals aged ≥ 65 years, we sought to describe the prevalence of CKD determined from laboratory test results in the Kidney Early Evaluation Program (KEEP; n = 27,017) and National Health and Nutrition Examination Survey (NHANES) 1999-2006 (n = 5,538) and the prevalence of diagnosed CKD determined from billing codes in the Medicare 5% sample (n = 1,236,946). In all 3 data sources, we also explored comorbid conditions and CKD-related complications.

Methods: CKD was identified as decreased estimated glomerular filtration rate (<60 mL/min/1.73 m^2) or increased albumin-creatinine ratio in KEEP and NHANES; CKD was identified using *International Classification of Diseases, Ninth Revision, Clinical Modification* codes in Medicare. Investigated comorbid conditions included diabetes, hypertension, high cholesterol level, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, and cancer, and CKD-related complications included anemia, hypocalcemia, hyperphosphatemia, and hyperparathyroidism.

Results: The prevalence of CKD was ~44% in both KEEP and NHANES participants, and the prevalence of diagnosed CKD was 7% in Medicare beneficiaries. In all 3 data sets, the prevalence of CKD or diagnosed CKD was higher in participants aged ≥ 80 years and those with comorbid conditions. For KEEP and NHANES participants, the prevalence of most comorbid conditions and CKD complications increased with decreasing estimated glomerular filtration rate. For participants with CKD stages 3-5, a total of 29.2% (95% CI, 27.8-30.6) in KEEP and 19.9% (95% CI, 17.0-23.1) in NHANES had anemia, 0.7% (95% CI, 0.4-0.9) and 0.6% (95% CI, 0.3-1.3) had hypocalcemia, 5.4% (95% CI, 4.7-6.1) and 6.4% (95% CI, 5.1-8.0) had hyperphosphatemia, and 52.0% (95% CI, 50.4-53.6) and 30.0% (95% CI, 25.9-34.3) had hyperparathyroidism, respectively.

Conclusions: CKD is common in the elderly population and is associated with high frequencies of concomitant comorbid conditions and biochemical abnormalities. Because CKD is not commonly diagnosed, greater emphasis on physician education may be beneficial.

Am J Kidney Dis 55(S2):S23-S33. © *2010 by the National Kidney Foundation, Inc.*

INDEX WORDS: Aged; chronic kidney disease; comorbidity.

The proportion of the US population aged ≥ 65 years is growing rapidly and is expected to approach ~20%, or 71 million people, by 2030.[1] Age-associated increases in chronic disease and disability represent a significant financial burden on the health care system. People aged > 75 years represent the fastest growing group of incident dialysis patients.[2] Recent data

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0272-6386/10/5503-0104$36.00/0
doi:10.1053/j.ajkd.2009.09.035

from the National Health and Nutrition Examination Survey (NHANES) suggest that chronic kidney disease (CKD) prevalence is highest in the elderly; the prevalence is 38% in participants aged > 65 years compared with 13% in the overall US population.[3] In addition, data from population-based prospective cohort studies, such as the Community Health Study (CHS), or from clinical populations, such as Kaiser Permanente, support that risk of cardiovascular disease morbidity and mortality associated with decreased kidney function is dramatically increased in the elderly.[4-11] The presence of CKD affects diagnosis and treatment decisions for these other conditions, and clinical care for patients with CKD requires a careful approach and ongoing monitoring.

Elderly patients with CKD are more likely than younger patients to have high rates of comorbid conditions, including cardiovascular disease risk factors, and CKD-related abnormalities that complicate the management of these comorbid conditions.[12] However, data are lacking regarding the prevalence of these conditions in the elderly, contributing to the lack of understanding regarding the impact of CKD in this population. Thus, we sought to describe the prevalence of CKD and diagnosed CKD, comorbid conditions, and CKD-related complications in people aged ≥ 65 years using 3 cohorts: the Kidney Early Evaluation Program (KEEP), NHANES 1999-2006, and the Medicare 5% sample. Comparisons among these 3 populations can inform us of the strengths and limitations of each data set.

METHODS

Kidney Early Evaluation Program

KEEP is a free community-based health screening program that targets populations aged ≥ 18 years at high risk of kidney disease, defined as history of diabetes or hypertension or first-order relative with diabetes, hypertension, or kidney disease, as described in detail previously.[13] Since August 2000, the program has screened > 128,000 participants from 49 states and the District of Colombia. In this study, we included 107,309 eligible KEEP participants from August 2000 through December 31, 2008, from 47 National Kidney Foundation affiliates and 2,336 screening programs in 49 states and the District of Columbia. We excluded participants with missing creatinine or albuminuria data and participants aged < 65 years, leaving a study population of 27,017 (Fig 1).

NHANES (1999-2006)

NHANES consists of cross-sectional, multistage, stratified, clustered probability samples of the civilian noninstitutionalized US population. The surveys are conducted by the National Center for Health Statistics, and data are appropriate for estimating the prevalence of chronic conditions in the United States. Survey participants were interviewed in their homes and/or received standardized medical examinations in mobile examination centers. In 1999, NHANES became a continuous annual survey to allow annual estimates, with release of public-use data files every 2 years. The study population was restricted to NHANES 1999-2006 participants aged ≥ 65 years (n = 5,538).

Medicare 5% Sample

The Chronic Disease Research Group has created Standard Analysis Files from the Centers for Medicare & Medicaid Services billing data and denominator files, as described previously.[14] Standard Analysis Files are compiled from the Medicare 5% files, which comprise all claims for a random sample of 5% of the Medicare population. Data include 2

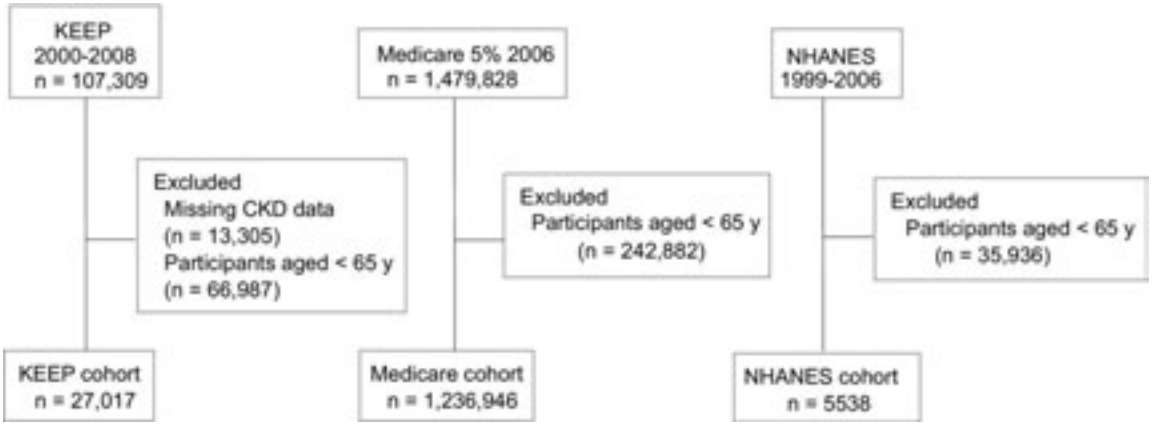

Figure 1. Creation of the analytical data sets. Abbreviations: CKD, chronic kidney disease; KEEP, Kidney Early Evaluation Program; NHANES, National Health and Nutrition Examination Survey.

types of claims data (Part A institutional claims and Part B physician/supplier claims) and demographic and enrollment information from the annual denominator data. The study population was restricted to 2006 Medicare beneficiaries aged ≥ 65 years (n = 1,236,946; Fig 1).

Definition of CKD

In KEEP and NHANES, CKD was defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 or albuminuria. GFR was estimated using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation.[15] Serum creatinine values for KEEP and NHANES were calibrated to standardized serum creatinine levels at the Cleveland Clinic Research Laboratory.[16,17] Albuminuria was defined as albumin-creatinine ratio ≥ 30 mg/g from a single measurement. In the Medicare 5% sample, laboratory tests were not available and CKD was defined as ≥ 1 inpatient claim or ≥ 2 outpatient or physician or supplier claims during the year with appropriate *International Classification of Diseases, Ninth Edition, Clinical Modification* codes (*ICD-9-CM*), shown in Item S1 (provided as online supplementary material available with this article at www.ajkd.org). To differentiate between CKD determined using laboratory tests and using billing codes, we use the term "CKD" for KEEP and NHANES participants and "diagnosed CKD" for Medicare beneficiaries.

Definitions of Comorbid Conditions

In the KEEP cohort, comorbid conditions were defined as follows. Diabetes was defined as history of diabetes (self-report or retinopathy), use of medications to treat diabetes, or, in the absence of these factors, fasting blood glucose level ≥ 126 mg/dL or nonfasting blood glucose level ≥ 200 mg/dL as measured in KEEP laboratory tests. Hypertension was defined as history of hypertension (self-report) or use of medications to treat hypertension, or by blood pressure measurements obtained during the KEEP screening of systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 80 mm Hg for participants with a history of diabetes or CKD or otherwise systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg.[18] All other comorbid conditions were self-reported.

Hemoglobin was measured for all participants, and anemia was defined as hemoglobin level < 13.5 g/dL for men and < 12 g/dL for women.[19] However, because anemia in people with eGFR ≥ 60 mL/min/1.73 m^2 is unlikely to be caused by CKD, we report anemia for only participants with eGFR < 60 mL/min/1.73 m^2. Other biochemical tests, including parathyroid hormone, calcium, and phosphorus, were performed only for participants with eGFR < 60 mL/min/1.73 m^2. High cholesterol level was defined as total cholesterol level > 200 mg/dL; hypocalcemia, as calcium level < 8.4 mg/dL; hyperphosphatemia, as serum phosphate level > 4.6 mg/dL for CKD stages 3 and 4 and > 5.5 mg/dL for stage 5; and hyperparathyroidism, as parathyroid hormone level > 70 pg/mL for CKD stage 3, 110 pg/mL for stage 4, or 300 pg/mL for stage 5.

In NHANES, self-reported comorbid conditions included diabetes, heart attack, coronary heart disease, angina/angina pectoris, congestive heart failure, stroke, and cancer. Blood pressure, cholesterol, phosphate, calcium, and parathyroid hormone were measured for all participants. However, for comparison with KEEP data, they are reported for only participants with eGFR < 60 mL/min/1.73 m^2 and are described using the same definitions as in KEEP. Definitions for abnormal biochemical parameters were the same as in KEEP.

In Medicare data, diabetes, hypertension, atherosclerotic heart disease, congestive heart failure, cerebrovascular accident/transient ischemic attack, peripheral vascular disease, and cancer were defined as ≥ 1 inpatient claim or ≥ 2 outpatient or physician or supplier claims with the appropriate *ICD-9-CM* codes during the year;[20] relevant codes are listed in Item S1. The Medicare sample analysis is based on diagnostic codes, and analyses of biochemical data were not possible.

Statistical Analysis

The overall prevalence of CKD in the KEEP and NHANES populations and risk factors for CKD were determined. Most analyses were descriptive, and χ^2 tests were used to compare CKD prevalence by risk factors and comorbid condition prevalence by CKD status. To assess the prevalence of CKD complications in participants with CKD, we also calculated 95% confidence intervals for prevalence. Analyses were performed incorporating NHANES sampling weights to obtain unbiased estimates from the complex NHANES sampling design using SUDAAN (Research Triangle Institute, www.rti.org). $P < 0.05$ is considered statistically significant. However, we did not statistically test differences in prevalence across study cohorts (KEEP, NHANES 1999-2006, and Medicare) because: (1) the data sets are different (KEEP is volunteer data, NHANES is random-survey data, and Medicare is claims data) and (2) definitions of comorbid conditions are different for different data sets.

RESULTS

Of the 3 cohorts, the KEEP population was younger with higher proportions of women, African Americans, and diabetes and hypertension, and lower prevalences of high cholesterol levels, coronary artery disease, and peripheral vascular disease (Table 1). Distributions of age, sex, and race were similar in the NHANES and Medicare populations.

In both the KEEP and NHANES populations, ~44% of participants aged ≥ 65 years were determined to have CKD, with similar proportions in subgroups defined by age, sex, and race (Table 2). Figure 2 shows a similar decrease in eGFR level by age in these populations. Of KEEP participants with CKD, 77% had stage 3 and 5% had stage 4 or 5. In NHANES, the comparative percentages were 69.3% and 4.8%, respectively. In contrast, only 7% of Medicare beneficiaries had claims with a CKD diagnosis

Table 1. Cohort Characteristics

	KEEP	NHANES 1999-2006	Medicare 5% 2006
No. of participants	27,017	5,538	1,236,946
Age (y)			
65-74 (%)	61.9	55.0	50.8
75-79 (%)	20.9	20.4	20.7
≥80 (%)	17.1	24.6	28.5
Women (%)	66.7	57.5	58.7
Race (%)			
White	62.9	83.2	88.2
African American	24.5	8.1	7.3
Other	12.7	8.7	4.5
Diabetes	11,017 (40.8)	1,029 (16.6)	26,2256 (21.2)
Hypertension	24,069 (89.1)	3,649 (79.2)	70,3876 (56.9)
High cholesterol[a]	7,381 (40.8)	2,361 (53.3)	—
Coronary artery disease[b]	4,476 (17.4)	1,151 (21)	25,2130 (20.4)
Congestive heart failure	905 (6.6)	511 (8.8)	12,0847 (9.8)
Cerebrovascular disease[c]	2,335 (9.3)	560 (9.1)	10,3581 (8.4)
Peripheral vascular disease[d]	183 (1.1)	164 (5.8)	13,8031 (11.2)
Cancer	4,910 (19.3)	1,162 (23.2)	12,4571 (10.1)

Note: Values expressed as number (percentage) unless indicated otherwise.

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

[a]Excludes 8,904 KEEP participants with missing cholesterol values; cholesterol values were unavailable in Medicare claims. High cholesterol level was defined as total cholesterol level > 200 mg/dL (>5.2 mmol/L) in KEEP and NHANES 1999-2006.

[b]Coronary artery disease included history of heart attack, coronary artery bypass graft, and angioplasty in KEEP; history of heart attack, coronary heart disease, and angina in NHANES, and atherosclerotic heart disease in Medicare.

[c]Cerebrovascular disease is defined as stroke in KEEP and NHANES and cerebrovascular accident or transient ischemic attack in Medicare.

[d]Peripheral vascular disease includes limb amputation in KEEP. In NHANES 1999-2004, peripheral vascular disease is defined as ankle-brachial index < 0.9; the higher of 2 measurements was used in this study.[21]

code in 2006. In all 3 data sets, the prevalence of CKD or diagnosed CKD was higher for participants aged ≥ 80 years and participants with diabetes, hypertension, coronary artery disease, congestive heart failure, peripheral vascular disease, or cancer than for younger participants and participants without these conditions.

Table 3 lists prevalences of comorbid conditions in participants with and without CKD. In all 3 data sets, most participants with CKD had multiple concomitant conditions, and people with CKD were more likely than people without CKD to have diabetes, hypertension, high cholesterol levels, coronary artery disease, cerebrovascular disease, and cancer. In NHANES and Medicare, people with CKD also were more likely to have peripheral vascular disease. Prevalences of diabetes and cancer were lower in NHANES participants with CKD relative to the KEEP and 5% Medicare samples. Diabetes, coronary heart disease, heart failure, and cerebrovascular and peripheral vascular disease were more prevalent in the Medicare CKD population. These findings are consistent with diabetes as a criterion for KEEP screening and Medicare as a referred population.

Figure 3 shows prevalences of comorbid conditions by eGFR level in the KEEP (Fig 3A) and NHANES (Fig 3B) populations. In KEEP, coronary artery disease, congestive heart failure, cardiovascular disease, and cancer increase with decreasing eGFR. The pattern is similar in

Table 2. CKD Prevalence

Characteristics	KEEP[a]		NHANES 1999-2006[a]		Medicare 5% 2006[b]	
	%	*P*	%	*P*	%	*P*
All	43.6		44.2		6.5	
Age (y)		<0.001		<0.001		<0.001
65-74	37.4		32.7		4.6	
75-79	48.5		47.7		7.2	
≥80	59.7		68.6		9.4	
Sex		<0.001		0.02		<0.001
Men	41.0		41.8		7.7	
Women	44.9		46		5.7	
Race		<0.001		0.08		<0.001
White	46.0		44.8		6.2	
African American	37.5		43.4		10.1	
Other	43.3		38.8		6.7	
Diabetes		<0.001		<0.001		<0.001
No	40.4		41.4		4.4	
Yes	48.2		58.3		14.2	
Hypertension		<0.001		<0.001		<0.001
No	21.9		16.9		1.5	
Yes	46.2		50.0		10.3	
High cholesterol[c]		<0.001		0.01		
No	42.5		47.1		—	
Yes	39.2		41.7		—	
Coronary artery disease[d]		<0.001		<0.001		<0.001
No	41.7		41.0		4.3	
Yes	52.7		55.7		15.3	
Congestive heart failure		<0.001		<0.001		<0.001
No	39.9		41.5		4.5	
Yes	55.0		71.8		25.3	
Cerebrovascular disease[e]		<0.001		<0.001		<0.001
No	42.6		42.3		5.7	
Yes	52.3		63.3		16.0	
Peripheral vascular disease[f]		0.09		<0.001		<0.001
No	40.7		38.1		5.0	
Yes	47.0		57.9		18.9	
Cancer		<0.001		0.03		<0.001
No	43.1		42.9		5.9	
Yes	45.7		48.1		12.4	

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

[a]Percentage of participants with CKD as determined using laboratory tests.

[b]Percentage of participants with diagnosed CKD, as determined using diagnosis codes.

[c]Excludes 8,904 KEEP participants with missing cholesterol values; cholesterol values unavailable in Medicare claims. High cholesterol level was defined as total cholesterol level > 200 mg/dL (>5.2 mmol/L) in KEEP and NHANES 1999-2006.

[d]Coronary artery disease included history of heart attack, coronary artery bypass graft, and angioplasty in KEEP; history of heart attack, coronary heart disease, and angina in NHANES, and atherosclerotic heart disease in Medicare.

[e]Cerebrovascular disease is defined as stroke in KEEP and NHANES and as cerebrovascular accident or transient ischemic attack in Medicare.

[f]Peripheral vascular disease includes limb amputation in KEEP. In NHANES 1999-2004, peripheral vascular disease is defined as ankle-brachial index < 0.9; the higher of 2 measurements was used in this study.[21]

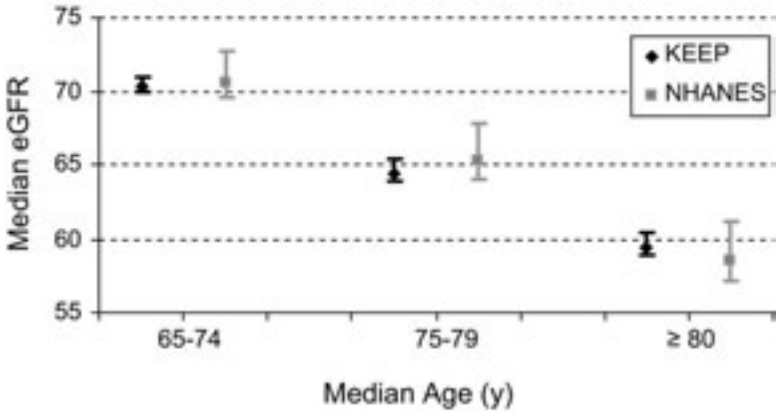

Figure 2. Changes in mean estimated glomerular filtration rate (eGFR) by age in the Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES). Bars represent 95% confidence intervals.

NHANES. In both data sets, the prevalence of high cholesterol level decreased with decreasing eGFR.

In KEEP and NHANES participants with available laboratory data and GFR < 60 mL/min/1.73 m^2, a substantial proportion of participants had anemia or abnormally increased phosphate or parathyroid hormone levels (Table 4). The prevalence of high cholesterol levels was higher in NHANES participants, and prevalences of ane-

Table 3. Prevalence of Comorbid Conditions in Patients With and Without CKD

	KEEP			NHANES 1999-2006			Medicare 2006		
Comorbid Conditions[a]	CKD	No CKD	*P*	CKD	No CKD	*P*	CKD	No CKD	*P*
Diabetes	45.1	37.4	<0.001	21.4	12.1	<0.001	46.2	19.5	<0.001
Hypertension	94.5	84.9	<0.001	91.6	69.0	<0.001	89.8	54.6	<0.001
High cholesterol	38.8	42.1	<0.001	50.5	56.0	0.01	NA	NA	NA
Coronary artery disease	21.0	14.6	<0.001	26.7	16.8	<0.001	48.0	18.5	<0.001
Congestive heart failure	7.5	4.2	<0.001	13.5	4.2	<0.001	37.9	7.8	<0.001
Peripheral vascular disease	1.3	1.0	0.09	8.5	4.0	0.002	32.3	9.7	<0.001
Cerebrovascular disease	11.1	7.8	<0.001	12.4	5.7	<0.001	20.6	7.5	<0.001
Cancer	20.3	18.6	<0.001	13.2	4.0	0.03	19.2	9.4	<0.001
Frequency[b] (no. of conditions)									
0	1.6	5.4	<0.001	2.1[c]	6.2	<0.001	2.3	32.6	<0.001
1	25.2	30.0	<0.001	16.8	31.8	<0.001	14.6	30.8	<0.001
2	40.1	39.3	0.2	40.1	38.0	0.4	24.3	21.0	<0.001
3	22.6	18.3	<0.001	26.1	17.0	<0.001	24.0	9.9	<0.001
>3	10.5	7.0	<0.001	15.0	7.1	<0.001	34.8	5.6	<0.001

Abbreviations: CKD, chronic kidney disease; KEEP, Kidney Early Evaluation Program; NA, not available; NHANES, National Health and Nutrition Examination Survey.

[a]In KEEP, diabetes is defined as self-reported or fasting glucose level ≥ 126 mg/dL or nonfasting glucose level ≥ 200 mg/dL (7.1 or 11.1 mmol/L); hypertension is defined as self-reported or blood pressure ≥ 130/80 mm Hg for patients with diabetes or CKD and ≥ 140/90 otherwise; other conditions are defined as in Table 1. In NHANES, comorbid conditions are defined as in Table 1.

[b]Because of data limitations, frequency results are for NHANES 1999-2004 only.

[c]Estimate is not reliable.

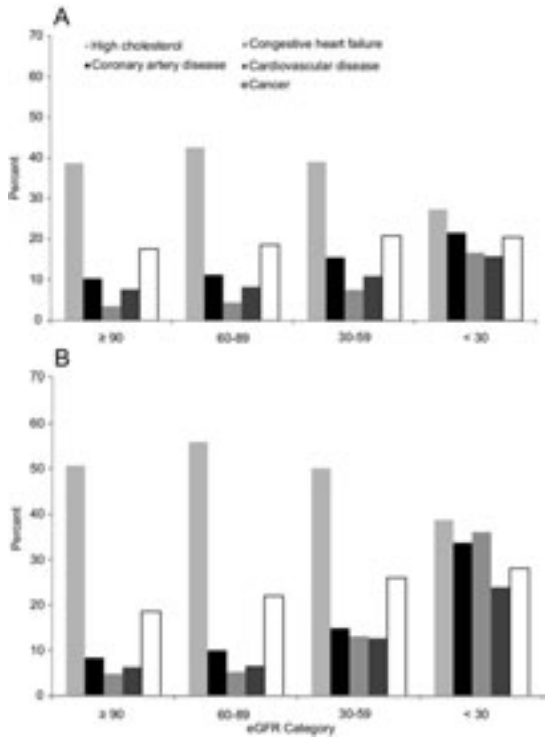

Figure 3. Comorbid conditions by level of estimated glomerular filtration rate (eGFR) in (A) Kidney Early Evaluation Program and (B) National Health and Nutrition Examination Survey.

mia and hyperparathyroidism were higher in KEEP participants. Figure 4 shows calcium, phosphate, and parathyroid hormone levels by eGFR level for participants with eGFR $<$ 60 mL/min/1.73 m^2 in KEEP and NHANES. In both populations, serum calcium levels were lower and serum phosphorus and parathyroid hormone levels were higher for participants with eGFR $<$ 30 mL/min/1.73 m^2 than for participants with higher eGFRs.

DISCUSSION

Chronic kidney failure disproportionately burdens the elderly. The median age of new dialysis patients now is 65 years, and the fastest growing age group is $>$ 75 years. Thus, kidney disease in elderly patients is an important focus for public health and clinical care.[22] Because earlier CKD stages precede and are far more common than kidney failure, understanding the characteristics of CKD in elderly patients at these earlier stages is essential to patient care and can help identify resources required to organize this care. Understanding the characteristics of the data sets from which we drew our conclusions can inform us of potential biases in our results.

The high prevalence of CKD in patients aged $\geq$ 65 years noted in our analyses of KEEP and NHANES data is consistent with prior reports in the United States[3,23] and other countries.[24,25] Despite consistent prevalence reports, there has been considerable discussion about whether CKD

Table 4. Prevalence of Chronic Kidney Disease Complications in KEEP and NHANES 1999-2006 Participants With eGFR $<$ 60 mL/min/1.73 m^2 and Laboratory Data

	KEEP (n = 3,818)	NHANES 1999-2006 (n = 1,461[a])
Anemia[b]	29.2 (27.8-30.6)	19.9 (17.0-23.1)
Hypocalcemia (%)	0.7 (0.4-0.9)	0.6 (0.3-1.3)[c]
Stage 3 CKD	0.5 (0.2-0.7)	0.4 (0.2-0.9)[c]
Stage 4/5 CKD	3.5 (1.1-5.9)	3.2 (0.6-14.7)[c]
Hyperphosphatemia (%)	5.4 (4.7-6.1)	6.4 (5.1-8.0)
Stage 3 CKD	4.7 (4.0-5.3)	5.5 (4.2-7.2)
Stage 4/5 CKD	16.5 (11.7-21.3)	18.6 (11.5-28.8)
Hyperparathyroidism (%)	52.0 (50.4-53.6)	30.0 (25.9-34.3)
Stage 3 CKD	51.9 (50.2-53.5)	28.9 (25.4-32.7)
Stage 4/5 CKD	53.5 (47.0-59.9)	42.2 (22.0-65.4)
High cholesterol (%)	36.8 (35.2-38.3)	49.3 (45.7-52.9)
Stage 3 CKD	37.5 (35.9-39.1)	50.1 (46.6-53.6)
Stage 4/5 CKD	25.2 (19.6-30.8)	38.7 (27.0-51.8)

Note: Values expressed as percentage (95% confidence interval).

Abbreviations and Definitions: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; hypocalcemia, calcium $<$ 8.4 mg/dL ($<$2.1 mmol/L); hyperphosphatemia, phosphate $>$ 4.6 mg/dL for stage 3 and 4, $>$5.5 mg/dL for stage 5 (1.5 and 1.8 mmol/L); hyperparathyroidism, parathyroid hormone $>$ 70 pg/mL for stage 3, $>$110 pg/mL for stage 4, $>$300 pg/mL for stage 5 (values are equivalent in ng/L); high cholesterol, total cholesterol $>$ 200 mg/dL (5.2 mmol/L); NHANES, National Health and Nutrition Examination Survey; KEEP, Kidney Early Evaluation Program.

[a]Sample size for eGFR $<$ 60 mL/min/1.73 m^2 in NHANES 1999-2006. NHANES 2003-2006 was used for parathyroid hormone; sample size (eGFR $<$ 60 mL/min/1.73 m^2), 766.

[b]Anemia defined as hemoglobin level $<$ 13.5 g/dL for men and $<$ 12.0 g/dL for women (135 and 120 g/L). Excludes missing values in KEEP.

[c]Estimate is not reliable.

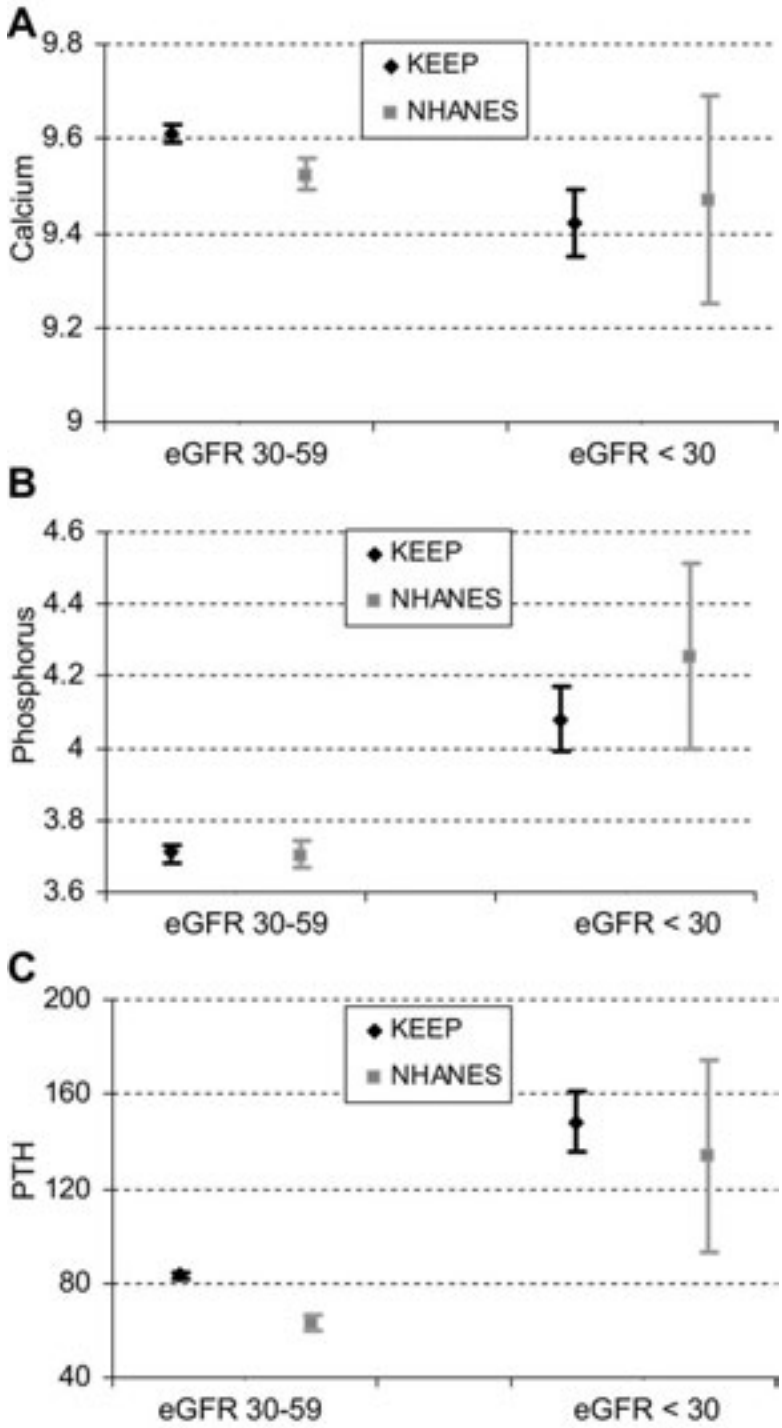

Figure 4. Changes in (A) calcium, (B) phosphorus, and (C) parathyroid hormone (PTH) levels by level of estimated glomerular filtration rate (eGFR). Conversion factors for units: serum calcium in mg/dL to mmol/L, ×0.2495; serum phosphate in mg/dL to mmol/L, ×0.3229; no conversion necessary for parathyroid hormone in pg/mL and ng/L. Bars represent 95% confidence intervals. Abbreviations: KEEP, Kidney Early Evaluation Program; NHANES, National Health and Nutrition Examination Survey.

in the absence of a known cause of kidney disease should be considered kidney disease.[26-29] In our analyses, prevalences of concomitant illnesses and biochemical abnormalities were high for patients with CKD; this in itself supports CKD detection, even if it is only a marker of other diseases, because these patients require more intensive care and monitoring. Furthermore, many of the illnesses are risk factors for CKD, and the biochemical abnormalities are complications of decreased kidney function; therefore, their presence also provides some evidence that decreased GFR represents actual kidney disease rather than an age-related decrease.

The high prevalence of cardiovascular risk factors in patients with CKD, as well as cardiac and other vascular diseases, suggests that the underlying cause of CKD in elderly patients may be a form of diffuse atherosclerotic vascular disease. This hypothesis is consistent with prior autopsy, pathophysiologic, and epidemiologic studies and suggests that the current perspective, that kidney disease cause in the elderly is related primarily to diabetes, hypertension, or both, may be too simplistic.[30,31] The strong association between CKD and cardiovascular disease events and mortality has been shown in multiple populations, possibly suggesting that CKD represents a complex cardiovascular risk state that is not caused simply by the presence of shared cardiovascular disease risk factors.[5-11] More mid- and late-life studies are needed to more fully explore this hypothesis.

We found a lower prevalence of diagnosed CKD in Medicare beneficiaries than in the KEEP and NHANES participants. In the Medicare cohort, CKD was defined on the basis of claims data, whereas in the KEEP and NHANES cohorts, CKD was defined using laboratory tests. This provides evidence for the low sensitivity of diagnosis codes to identify CKD and likely reflects low awareness of CKD among physicians or coding practices,[25,32,33] possibly caused in part by continued use of serum creatinine measures instead of eGFR.[34,35] Thus, Medicare or other administrative data should not be used to determine CKD prevalence per se. Nevertheless, the Medicare data showed associations of CKD with concomitant illnesses consistent with those observed in the KEEP and NHANES data, suggesting that Medicare data can be used to study CKD burden in people identified by claims as having CKD. The higher prevalence of vascular disease in the Medicare population compared with KEEP and NHANES may represent that patients identified as having CKD from Medicare data are seeking medical care; they are not members of a screening sample or the general population. Therefore, Medicare data in particular may be useful to quantify the burden of CKD on the health care system.

Some abnormal biochemical findings were more common in KEEP than NHANES participants, consistent with KEEP being a targeted at-risk population. Interestingly, despite the higher prevalence of abnormal biochemical findings in KEEP, CKD prevalence was similar and the decrease in eGFR observed with older age was consistent in both data sets, suggesting the generalizability of KEEP to the elderly population in the United States. However, KEEP participants with CKD were more likely to have diabetes and cancer, and NHANES participants with CKD were more likely to have high cholesterol levels, coronary artery disease, heart failure, and peripheral vascular disease.

All together, these data reinforce and show the high burden of chronic conditions in elderly patients with CKD-related complications. CKD affects diagnosis and treatment decisions for these other conditions.[36] Clinical care for patients with CKD requires a careful approach and ongoing monitoring. Elderly patients are susceptible to acute kidney injury and side effects from medications and diagnostic and therapeutic procedures,[37-40] which are a major source of morbidity and cost in hospitalized elderly patients.[40] Early detection of CKD and appropriate management will help prevent these adverse outcomes.

The strengths of this study include the use of 3 different cohorts, each with its own characteristics, showing persistence of CKD prevalence in 2 data sets, with multiple comorbid conditions and CKD-related complications across all 3 populations. In addition, the comprehensive description of concomitant illnesses and biochemical abnormalities provides a comprehensive view of the burden of CKD in these populations.

The study has several limitations. First, because biochemical data are unavailable in Medicare claims, we were unable to extend analyses of biochemical variables to the Medicare popula-

tion. Second, different disease definitions sometimes were used in the different data sets; however, when possible, we defined the diseases similarly, and definitions in KEEP were designed to be consistent with those used in NHANES. Different assays were used in NHANES and KEEP, a difference most relevant to parathyroid hormone. Third, CKD diagnosis in KEEP and NHANES is made on a single sample; therefore, we cannot confirm the chronicity of the disease. Fourth, the MDRD Study equation is not accurate at higher levels of GFR and overestimates GFR in people with reduced muscle mass, such as the frail elderly.[41] Finally, KEEP is a self-selected population; however, the demonstrated results, consistent with NHANES, support its generalizability.

In conclusion, CKD is common in the elderly population and is associated with a high frequency of concomitant chronic illnesses and biochemical abnormalities. Elderly patients with CKD require careful attention and monitoring. They are at high risk of cardiovascular disease and require intensive risk management. They also are at high risk of side effects from medications and procedures related to these conditions, many of which increase risk of acute kidney injury and CKD progression. However, it is likely that CKD is not commonly diagnosed in clinical practice; greater emphasis should be placed on physician education about CKD.

ACKNOWLEDGEMENTS

The authors thank Shane Nygaard, BA, and Nan Booth, MSW, MPH, of the Chronic Disease Group for manuscript preparation and manuscript editing, respectively.

Support: This study was supported by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases (K23-DK081017; Kidney Function and Aging). KEEP is a program of the National Kidney Foundation Inc and is supported by Amgen, Abbott, Novartis, Siemens, Genentech, Genzyme, Nephroceuticals, Pfizer, LifeScan, and Suplena.

Financial Disclosure: Dr Stevens receives grant support from Gilead Inc. The other authors report that they have no relevant financial interests.

SUPPLEMENTARY MATERIAL

Item S1: *ICD-9-CM* diagnosis codes for CKD and comorbid conditions

Note: The supplementary material accompanying this article (doi:10.1053/j.ajkd.2009.09.035) is available at www.ajkd.org.

REFERENCES

1. Centers for Disease Control and Prevention. Trends in aging—United States and worldwide. *MMWR Morb Mortal Wkly Rep.* 2003;52:101-104, 106.

2. US Renal Data System. USRDS 2005 Annual Data Report. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2005.

3. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *JAMA.* 2007;298:2038-2047.

4. Shlipak MG, Katz R, Cushman M, et al. Cystatin-C and inflammatory markers in the ambulatory elderly. *Am J Med.* 2005;118:1416.e25-1416.e31.

5. Sarnak MJ, Katz R, Stehman-Breen CO, et al. Cystatin C concentration as a risk factor for heart failure in older adults. *Ann Intern Med.* 2005;142:497-505.

6. Manjunath G, Tighiouart H, Coresh J, et al. Level of kidney function as a risk factor for cardiovascular outcomes in the elderly. *Kidney Int.* 2003;63:1121-1129.

7. Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med.* 2004;164:659-663.

8. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med.* 2004;351:1296-1305.

9. Shlipak MG, Sarnak MJ, Katz R, et al. Cystatin C and the risk of death and cardiovascular events among elderly persons. *N Engl J Med.* 2005;352:2049-2060.

10. Shlipak MG, Katz R, Fried LF, et al. Cystatin-C and mortality in elderly persons with heart failure. *J Am Coll Cardiol.* 2005;45:268-271.

11. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation.* 2003;108:2154-2169.

12. Stevens LA, Levey AS. Chronic kidney disease in the elderly—how to assess risk. *N Engl J Med.* 2005;352:2122-2124.

13. Jurkovitz CT, Qiu Y, Wang C, Gilbertson DT, Brown WW. The Kidney Early Evaluation Program (KEEP): program design and demographic characteristics of the population. *Am J Kidney Dis.* 2008;51(suppl 2):S3-12.

14. Research Data Assistance Center. Medicare data file descriptions. 2009. Available at http://www.resdac.umn.edu/Medicare/file_descriptions.asp#inpatient. Accessed September 18, 2009.

15. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate. *Ann Intern Med.* 2006;145:247-254.

16. Stevens LA, Stoycheff N. Standardization of serum creatinine and estimated glomerular filtration rate in the National Kidney Foundation Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis.* 2008;51(suppl 2):S77-82.

17. Selvin E, Manzi J, Stevens LA, et al. Calibration of serum creatinine in the National Health and Nutrition Examination Surveys (NHANES) 1988-1994, 1999-2004. *Am J Kidney Dis.* 2007;50:918-926.

18. Chobanian AV, Bakris GL, Black HR, et al. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension.* 2003;42:1206-1252.

19. National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease. 2006. Available at: http://www.kidney.org/professionals/kdoqi/guidelines_anemia/guide2.htm#cpr11. Accessed September 18, 2009.

20. US Renal Data System. USRDS 2007 Annual Data Report, vol II. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2007.

21. Lane JS, Vittinghoff E, Lane KT, Hiramoto JS, Messina LM. Risk factors for premature peripheral vascular disease: results for the National Health and Nutritional Survey, 1999-2002. *J Vasc Surg.* 2006;44:319-324.

22. Stevens LA, Coresh J, Levey AS. CKD in the elderly—old questions and new challenges: World Kidney Day 2008. *Am J Kidney Dis.* 2008;51:353-357.

23. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150:604-612.

24. Zhang L, Zhang P, Wang F, et al. Prevalence and factors associated with CKD: a population study from Beijing. *Am J Kidney Dis.* 2008;51:373-384.

25. US Renal Data System. USRDS 2008 Annual Data Report, vol 1. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2008.

26. Glassock RJ. Estimated glomerular filtration rate: time for a performance review? *Kidney Int.* 2009;75:1001-1003.

27. Glassock RJ, Winearls C. An epidemic of chronic kidney disease: fact or fiction? *Nephrol Dial Transplant.* 2008;23:1117-1121.

28. Glassock RJ, Winearls C. Screening for CKD with eGFR: doubts and dangers. *Clin J Am Soc Nephrol.* 2008;3:1563-1568.

29. Melamed ML, Bauer C, Hostetter TH. eGFR: is it ready for early identification of CKD? *Clin J Am Soc Nephrol.* 2008;3:1569-1572.

30. Kasiske BL. Relationship between vascular disease and age-associated changes in the human kidney. *Kidney Int.* 1987;31:1153-1159.

31. Anderson S, Brenner BM. Effects of aging on the renal glomerulus. *Am J Med.* 1986;80:435-442.

32. Stevens LA, Fares G, Fleming J, et al. Low rates of testing and diagnostic codes usage in a commercial clinical laboratory: evidence for lack of physician awareness of chronic kidney disease. *J Am Soc Nephrol.* 2005;16:2439-2448.

33. Lentine KL, Schnitzler MA, Abbott KC, Bramesfeld K, Buchanan PM, Brennan DC. Sensitivity of billing claims for cardiovascular disease events among kidney transplant recipients. *Clin J Am Soc Nephrol.* 2009;4:1213-1221.

34. Duru OK, Vargas RB, Kermah D, Nissenson AR, Norris KC. High prevalence of stage 3 chronic kidney disease in older adults despite normal serum creatinine. *J Gen Intern Med.* 2009;24:86-92.

35. Jain AK, McLeod I, Huo C, et al. When laboratories report estimated glomerular filtration rates in addition to serum creatinines, nephrology consults increase. *Kidney Int.* 2009;76:318-323.

36. Dukkipati R, Adler S, Mehrotra R. Cardiovascular implications of chronic kidney disease in older adults. *Drugs Aging.* 2008;25:241-253.

37. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci.* 2004;59:255-263.

38. Grobner T, Prischl FC. Gadolinium and nephrogenic systemic fibrosis. *Kidney Int.* 2007;72:260-264.

39. Hurst FP, Bohen EM, Osgard EM, et al. Association of oral sodium phosphate purgative use with acute kidney injury. *J Am Soc Nephrol.* 2007;18:3192-3198.

40. Steinman MA, Landefeld CS, Rosenthal GE, Berthenthal D, Sen S, Kaboli PJ. Polypharmacy and prescribing quality in older people. *J Am Geriatr Soc.* 2006;54:1516-1523.

41. Stevens LA, Coresh J, Feldman HI, et al. Evaluation of the Modification of Diet in Renal Disease Study Equation in a large diverse population. *J Am Soc Nephrol.* 2007;18:2749-2757.