J Am Soc Nephrol 13: 745–753, 2002

Renal Insufficiency and Subsequent Death Resulting from Cardiovascular Disease in the United States

PAUL MUNTNER,* JIANG HE,*† LEE HAMM,† CATHERINE LORIA,‡ and PAUL K. WHELTON*†

**Department of Epidemiology, School of Public Health and Tropical Medicine, and †Department of Medicine, School of Medicine, Tulane University, New Orleans, Louisiana, and ‡National Heart, Lung, and Blood Institute, Bethesda, Maryland.*

Abstract. Several epidemiologic studies reported that persons with renal insufficiency might have increased cardiovascular disease-related mortality rates in select populations. The association between renal insufficiency and increased cardiovascular disease-related and all-cause mortality rates during 16 yr of follow-up monitoring was examined among participants who were 30 to 74 yr of age at the baseline examinations in 1976 to 1980, with urinary protein dipstick measurements ($n = 8786$) or serum creatinine levels of ≤3.0 mg/dl ($n = 6354$), from the Second National Health and Nutrition Examination Survey Mortality Study. GFR were estimated by adjusting serum creatinine levels for age, race, and gender, using the Modification of Diet in Renal Disease formula. Cardiovascular disease-related mortality rates were 6.2, 17.9, and 37.2 deaths/1000 person-yr among subjects with urinary protein levels of <30, 30 to 299, and ≥300 mg/dl and were 4.1, 8.6, and 20.5 deaths/1000 person-yr among participants with estimated GFR of ≥90, 70 to 89, and <70 ml/min, respectively. After adjustment for potential confounders, the relative hazards (and 95% confidence intervals) for cardiovascular disease-related death were 1.57 (0.99 to 2.48) and 1.77 (0.97 to 3.21) among subjects with urinary protein levels of 30 to 299 and ≥300 mg/dl, respectively, compared with <30 mg/dl (P trend = 0.02). The corresponding relative hazards for all-cause-related death were 1.64 (1.23 to 2.18) and 2.00 (1.13 to 3.55; P trend < 0.001). Compared with subjects with estimated GFR of ≥90 ml/min, those with estimated GFR of <70 ml/min exhibited higher relative risks of death from cardiovascular disease and all causes [1.68 (1.33 to 2.13) and 1.51 (1.19 to 1.91), respectively]. This study indicates that, in a representative sample of the United States general population, renal insufficiency is independently associated with increased cardiovascular disease-related and all-cause mortality rates.

Within age, race, and gender groups, mortality rates are 10 to 20 times higher among patients with end-stage renal disease, compared with the general population, with >50% of this excess burden being attributable to cardiovascular disease (1). Although dialysis therapy may produce metabolic and hemodynamic abnormalities that contribute to the high cardiovascular disease-related mortality rates noted for patients with end-stage renal disease, both a history of cardiovascular disease and an adverse cardiovascular disease risk profile are common features at the initiation of dialysis therapy (2–4). End-stage renal disease usually develops during a long period, during which renal insufficiency is present (5). Because overt cardiovascular disease and its risk factors are common findings at the initiation of dialysis, it seems reasonable to expect that the incidence of cardiovascular disease in the presence of renal insufficiency before end-stage renal disease would be disproportionately high (6). However, there are scant data from the general population to support or refute this hypothesis.

We used data from the Second National Health and Nutrition Examination Survey (NHANES II) and the NHANES II Mortality Study (a prospective study of a large representative sample of the general population in the United States) to investigate the risk of cardiovascular disease and the overall mortality rates associated with decreased renal function.

Materials and Methods

Study Population

Participants were selected by using a stratified, multistage, probability sampling design, with certain subpopulations being purposely oversampled. As described elsewhere (7), interview and examination data were collected for 14,407 NHANES II participants (age, 17 to 74 yr; response rate, 73%) between 1976 and 1980; of those, all 9250 participants of age 30 to 74 yr were included in the NHANES II Mortality Study. The analyses described here were limited to black subjects and white subjects, because of the small number of participants of other races ($n = 153$). Persons for whom any covariate information was missing were excluded from this study ($n = 28$). Additionally, participants with serum creatinine levels of ≥3.0 mg/dl were excluded because of the high probability that they had end-stage renal disease ($n = 15$). An additional 2989 participants were excluded from the creatinine analyses, primarily because of the loss of serum samples during shipping. Urinary protein measurements were not

Received September 7, 2001. Accepted November 1, 2001.
Correspondence to Dr. Paul Muntner, Department of Epidemiology, Tulane University SPHTM, 1430 Tulane Avenue, SL-18, New Orleans, LA 70112. Phone: 504-988-1047; Fax: 504-988-1568; E-mail: pmuntner@tulane.edu
1046-6673/1303-0745
Journal of the American Society of Nephrology

available for 305 otherwise eligible participants. After these exclusions, 8768 participants were included in the urinary protein analyses and 6534 in the estimated GFR analyses.

Baseline Measurements

Serum creatinine levels were measured by using a Jaffé reaction Smac Technicon device (Western Laboratories, Oakland, CA). Ames reagent strips were used to test for the presence of protein in urine samples.

In addition to demographic information, a history of heart attacks or strokes, recreational physical activity (much, moderate, or little or no activity), the highest grade of education completed, and current smoking status were assessed for each patient, on the basis of self-reported information. Two BP measurements were obtained by a specially trained physician, using a mercury sphygmomanometer. In addition, the body mass index and serum total cholesterol level were measured. Diabetes mellitus was defined as a self-reported history of the disorder or a fasting plasma glucose level of ≥126 mg/dl.

Mortality Assessments

Vital status as of December 31, 1992, was assessed for all NHANES II participants who were 30 to 74 yr of age ($n = 9250$) at the time of the baseline examinations, using the National Death Index and the Social Security Administration Death Master File, as described elsewhere (8). The sensitivity and specificity of outcome assessments using the National Death Index with the same variables but different matching criteria have been estimated to be 87 to 97% and 99% (9–12), respectively, whereas the sensitivity of matching to Social Security Administration data was only 70% (8). In addition to death from all causes, the following cause-specific mortality definitions (death codes from the 9th version of the International Classification of Diseases) were used in our analyses: cardiovascular disease (390 to 459), coronary disease (410 to 414), stroke (430 to 430.9, 436, 437.0, and 437.1), and congestive heart failure (428.0, 428.1, and 428.9).

Statistical Methods

Analyses of death from all causes, cardiovascular disease, heart disease, congestive heart failure, or stroke were conducted separately for estimated GFR and urinary protein levels, as measures of renal function, and used population-sampling weights developed for the NHANES II data set.

For analyses using dipstick urinary protein measurements, the experiences of participants with urinary protein levels of 30 to 299 mg/dl and ≥300 mg/dl were compared with those of their counterparts with urinary protein levels of <30 mg/dl. GFR was estimated by using the abbreviated equation developed at the Cleveland Clinic laboratory for the Modification of Diet in Renal Disease Study, as follows: $\text{GFR} = 186.3 \times (\text{serum creatinine level})^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$ (13). GFR analyses were performed after categorization of participants using distribution cutoffs, *i.e.*, >20th percentile (highest GFR), 5th to 20th percentile, or <5th percentile (lowest GFR). Estimated GFR is calculated for ml/min per 1.73 m^2.

Incidence rates and relative hazards were calculated on the basis of participant age rather than follow-up time (14). Because all-cause mortality rates were disproportionately high after age 85 yr and few participants contributed person-time experience in that age category, all analyses were truncated at that age. Crude cumulative mortality rates were calculated and cumulative mortality curves were plotted according to estimated GFR and urinary protein levels. Because the calculation of cumulative mortality rates is sensitive to small sample sizes, the assessment of cumulative mortality rates was limited to participants who were 50 to 85 yr of age during the follow-up period. Cox proportional-hazards regression analyses were used to determine the adjusted relative risks (and 95% confidence intervals) of death from all causes and the prespecified causes associated with estimated GFR and urinary protein levels, after adjustment for nonmodifiable factors (age, race, and gender) and additional adjustment for baseline systolic BP, cholesterol levels, diabetes mellitus, a history of major cardiovascular disease (myocardial infarction or stroke), body mass index, education, and physical inactivity. Updated measurements for potential confounders are not available for the NHANES II Mortality Study.

The consistency of the associations was assessed by using subgroup analysis and tests for interaction for each of the outcomes. Additionally, all analyses were replicated using elevated serum creatinine levels as the marker of renal function. These analyses were performed after categorization of the participants using the following gender-specific serum creatinine level distribution cutoffs: <80th percentile (lowest creatinine level), 80th to 95th percentile, or >95th percentile (highest creatinine level). All analyses were performed by using Stata version 6.0 (15) and Coxreg (a program developed by the National Cancer Institute for analysis of weighted time-to-event data).

Results

Baseline Characteristics

Of the 8786 participants with urinary protein measurements, 196 and 62 exhibited levels of 30 to 299 and ≥300 mg/dl, respectively (Table 1). The 5 and 20% cutoffs for the estimated GFR distribution were 70 and 90 ml/min, respectively (Table 1). Mean age, systolic and diastolic BP, cholesterol levels, and body mass index all increased with progressively higher urinary protein levels and lower estimated GFR values. The proportion of the sample with diabetes mellitus or a history of cardiovascular disease was also higher with increasing urinary protein levels and decreasing estimated GFR values (P trend < 0.01). However, black subjects exhibited higher urinary protein and estimated GFR levels.

Urinary Protein Measurements

The 8768 NHANES II participants with baseline urinary protein measurements contributed 115,688 person-yr of follow-up data (Table 2). Graded positive associations were noted between higher baseline urinary protein levels and subsequent death as a result of all causes, cardiovascular disease, coronary disease, or congestive heart failure (Figure 1). After adjustment for age, race, and gender and additional adjustment for systolic BP, serum total cholesterol levels, body mass index, diabetes mellitus, a history of cardiovascular disease, physical inactivity, and the level of education, greater baseline urinary protein excretion was associated with increased mortality rates from all causes, cardiovascular disease, and congestive heart failure during the follow-up period (each P trend ≤ 0.03) (Table 2). In contrast, a higher baseline level of urinary protein excretion was significantly associated with increased heart disease-related mortality rates after adjustment for age, race, and gender but the relationship was not statistically significant after full adjustment (P trend = 0.29). A total of 194 stroke-related

Table 1. Characteristics of the study population, according to baseline urinary protein and estimated GFR levels[a]

	Urinary Protein Level				Estimated GFR[b]			
	None/Trace	30 to 299 mg/dl	>300 mg/dl	*P* Trend	<70 ml/min	70 to 89 ml/min	≥90 ml/min	*P* Trend
No. of participants	8528	196	62		4959	1068	327	
Age (yr)	49 ± 0.3	52 ± 1.2	54 ± 2.7	<0.001	48 ± 0.3	55 ± 0.5	63 ± 0.9	<0.001
Systolic BP (mmHg)	129 ± 0.6	140 ± 2.1	152 ± 4.3	<0.001	128 ± 0.6	131 ± 1.2	143 ± 1.8	<0.001
Diastolic BP (mmHg)	80 ± 0.5	88 ± 1.6	88 ± 1.9	<0.001	80 ± 0.5	80 ± 0.9	85 ± 1.0	0.001
Total cholesterol level (mg/dl)	223 ± 1.1	231 ± 4.9	242 ± 12	0.02	221 ± 1.2	230 ± 2.3	239 ± 1.9	<0.001
Body mass index (kg/m^2)	25.9 ± 0.7	26.8 ± 0.4	29.3 ± 1.6	0.002	25.7 ± 0.1	26.1 ± 0.2	27.1 ± 0.3	<0.001
Male gender (%)	46.9 ± 0.5	54.2 ± 4.2	52.8 ± 8.1	0.09	55.1 ± 0.9	50.9 ± 1.6	60.8 ± 2.6	0.99
Black (%)	9.3 ± 1.1	25.2 ± 3.7	30.7 ± 8.8	<0.001	6.0 ± 1.3	5.7 ± 1.5	10.5 ± 1.3	<0.001
Diabetes mellitus (%)	4.9 ± 0.2	14.1 ± 0.3	35.4 ± 6.7	<0.001	4.5 ± 0.3	6.5 ± 0.8	8.5 ± 1.0	0.006
History of cardiovascular disease (%)	6.0 ± 0.2	13.1 ± 3.1	15.8 ± 5.6	<0.001	4.5 ± 0.3	7.9 ± 1.0	12.9 ± 1.2	0.001
Current smoker (%)	35.7 ± 0.7	43.8 ± 3.7	47.6 ± 9.1	<0.001	36.9 ± 0.8	30.9 ± 2.1	20.2 ± 2.8	0.006
Not physically active (%)	38.9 ± 0.8	57.2 ± 5.6	51.0 ± 7.8	<0.001	39.2 ± 1.1	34.7 ± 1.8	46.7 ± 2.8	0.10
Completed high school (%)	63.7 ± 1.1	44.6 ± 3.2	43.4 ± 7.5	<0.001	64.9 ± 1.4	60.5 ± 1.9	54.1 ± 2.6	0.12

[a] Values are mean/percentage ± SEM.
[b] Cutoffs represent the 5th and 20th percentiles of the GFR distributions.

deaths were noted during follow-up monitoring; however, only two and four stroke-related deaths occurred among patients with urinary protein excretion levels of 30 to 299 and ≥300 mg/dl, respectively. Although urinary protein excretion of ≥300 mg/dl was associated with increased age-, race-, and gender-adjusted relative hazard (and 95% confidence interval) for stroke-related death [4.37 (1.11 to 17.1)], the association was decreased and was not statistically significant after full adjustment [1.80 (0.40 to 8.17)].

The presence of urinary protein (≥30 mg/dl) at the baseline examination was statistically significantly associated with an increased risk of death from all causes for each of the subgroups identified in Table 3, except for black subjects and subjects with histories of cardiovascular disease. With the exception of subjects with histories of cardiovascular disease, participants with baseline urinary protein levels of ≥30 mg/dl exhibited a higher risk of subsequent cardiovascular disease-related death; however, the 95% confidence interval included the null value for each of the subgroups except white subjects, female subjects, nonsmokers, and subjects without a history of cardiovascular disease (Table 3). The relative risk of coronary disease-related death was also greater for persons with baseline urinary protein levels of ≥30 mg/dl in all subgroups except subjects with histories of cardiovascular disease; however, the 95% confidence intervals included the null values for all of the subgroups except persons with diabetes mellitus and subjects with no history of cardiovascular disease. The relative risks of death from all causes, cardiovascular disease, or coronary disease associated with baseline urinary protein levels of ≥30 mg/dl were significantly lower among subjects with histories of cardiovascular disease, compared with those without (each *P* interaction < 0.02).

Estimated GFR

The 6453 NHANES II participants with baseline serum creatinine measurements contributed 84,025 person-yr of follow-up data to the estimated GFR analysis. Additionally, 1240 subjects died during the 12- to 16-yr follow-up period (797 died as a result of cardiovascular disease) (Table 4). After adjustment for age, race, and gender, all-cause mortality rates, cardiovascular disease-related mortality rates, and other cause-specific outcome rates were similar for subjects with estimated GFR of ≥90 ml/min and 70 to 89 ml/min but were higher for subjects with estimated GFR of <70 ml/min (Figure 2 and Table 4). Even after additional adjustment for systolic BP, serum total cholesterol levels, body mass index, diabetes mellitus, a history of cardiovascular disease, physical inactivity, and the level of education, patients with estimated GFR of <70 ml/min were at increased risk of all-cause-related, cardiovascular disease-related, and coronary disease-related death, compared with participants with estimated GFR of ≥90 ml/min. The corresponding relative hazards for congestive coronary failure-related death were >1, but the confidence limits included the null values. There were only 26 and 12 stroke-related deaths among patients with estimated GFR of 70 to 89 ml/min and <70 ml/min, respectively, and no statistically significant association with estimated GFR was noted (data not shown). Additionally, results obtained using serum creatinine levels were markedly similar to the associations detected using estimated GFR (data not shown).

Within all subgroups, subjects with estimated GFR of <70 ml/min were at increased risk of death from all causes, cardiovascular disease, or coronary disease, compared with participants with estimated GFR of ≥90 ml/min (Table 5). However, for all-cause-related death, the 95% confidence intervals in-

Table 2. Mortality rates for and relative hazards of death resulting from cardiovascular disease and all causes, according to urinary protein category

	Overall	Urinary Protein Level			*P* Trend
		None/Trace	30 to 299 mg/dl	≥300 mg/dl	
Person-years at risk	115,688	112,925	2248	516	
All causes					
no. of patients	1876	1759	80	37	
no. of deaths/1000 person-yr	10.9	10.4	26.6	50.5	
age-, race-, and gender-adjusted relative hazard		1.0[a]	2.20 (1.75 to 2.77)	3.46 (1.95 to 6.15)	<0.001
multivariate adjusted relative hazard[b]		1.0[a]	1.64 (1.23 to 2.18)	2.00 (1.13 to 3.55)	<0.001
Cardiovascular disease					
no. of patients	1215	1133	54	28	
no. of deaths/1000 person-yr	6.6	6.2	17.9	37.2	
age-, race-, and gender-adjusted relative hazard		1.0[a]	2.38 (1.59 to 3.56)	3.89 (2.30 to 6.58)	<0.001
multivariate adjusted relative hazard[b]		1.0[a]	1.57 (0.99 to 2.48)	1.77 (0.97 to 3.21)	0.02
Coronary disease					
no. of patients	594	554	27	13	
no. of deaths/1000 person-yr	3.1	3.0	8.8	14.5	
age-, race-, and gender-adjusted relative hazard		1.0[a]	2.48 (1.47 to 4.18)	3.17 (1.53 to 6.60)	<0.001
multivariate adjusted relative hazard[b]		1.0[a]	1.47 (0.79 to 2.75)	1.23 (0.55 to 2.71)	0.29
Congestive heart failure					
no. of patients	268	248	16	4	
no. of deaths/1000 person-yr	1.3	1.2	4.9	5.2	
age-, race-, and gender-adjusted relative hazard		1.0[a]	3.72 (2.07 to 6.69)	3.08 (0.96 to 9.95)	0.001
multivariate adjusted relative hazard[b]		1.0[a]	2.28 (1.32 to 3.94)	1.33 (0.43 to 4.06)	0.03

[a] Reference category.
[b] Adjusted for age, race, gender, systolic BP, total cholesterol level, body mass index, diabetes mellitus, history of myocardial infarction or stroke, current cigarette smoking, physical inactivity, and education level.

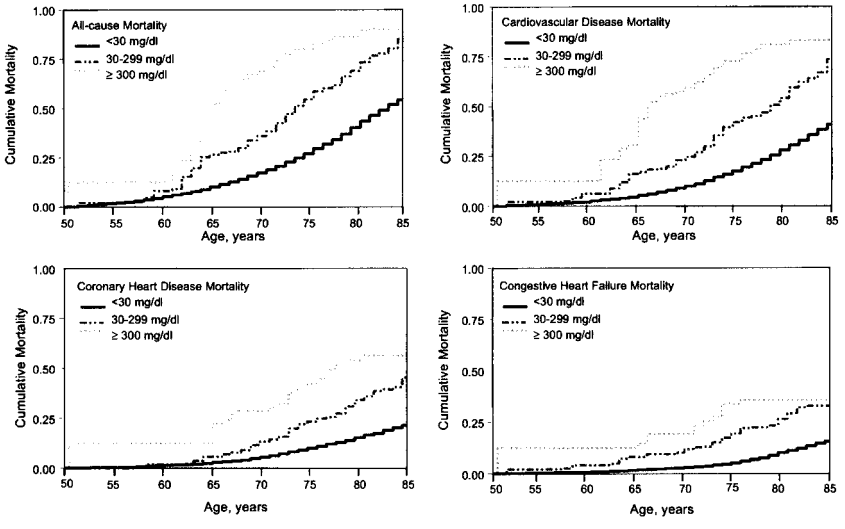

Figure 1. Cumulative mortality curves for 8786 Second National Health and Nutrition Examination Survey (NHANES II) Mortality Study participants, on the basis of urinary protein category (no/trace, 30 to 299 mg/dl, or ≥300 mg/dl), for death resulting from all causes, cardiovascular disease, coronary disease, or congestive heart failure.

cluded the null values for black subjects and subjects with histories of cardiovascular disease. For cardiovascular disease-related death, the confidence interval included the null value for black subjects. For coronary disease-related death, the confidence intervals included the null values for current smokers and subjects with chronic cardiovascular disease. The rel-

Table 3. Adjusted relative hazard of death resulting from all causes, cardiovascular disease, and coronary disease for participants with overt (≥30 mg/dl) *versus* no/trace urinary protein at baseline examinations

	Relative Hazard[a]									
	Race		Gender		Diabetes Mellitus		Current Smoking		History of Cardiovascular Disease	
	Black	White	Female	Male	No	Yes	No	Yes	No	Yes
All causes	1.36 (0.83 to 2.24)	1.85 (1.29 to 2.66)	2.17 (1.43 to 3.30)	1.61 (1.14 to 2.28)	1.61 (1.16 to 2.22)	2.31 (1.46 to 3.65)	1.79 (1.24 to 2.59)	1.65 (1.09 to 2.50)	2.07 (1.62 to 2.65)	1.03 (0.56 to 1.88)
Cardiovascular disease	1.18 (0.64 to 2.16)	1.74 (1.04 to 2.93)	2.23 (1.41 to 3.53)	1.49 (0.89 to 2.48)	1.55 (0.93 to 2.58)	1.95 (0.98 to 3.89)	1.64 (1.02 to 2.66)	1.57 (0.80 to 3.08)	2.15 (1.34 to 3.44)	0.88 (0.46 to 1.66)
Coronary disease	1.86 (0.50 to 6.95)	1.34 (0.75 to 2.38)	1.95 (0.99 to 3.85)	1.40 (0.72 to 2.69)	1.13 (0.51 to 2.51)	2.79 (1.14 to 6.84)	1.45 (0.68 to 3.11)	1.37 (0.66 to 2.85)	1.95 (1.02 to 3.72)	0.90 (0.38 to 2.16)

[a] Adjusted for age, race, gender, systolic BP, total cholesterol level, body mass index, diabetes mellitus, history of myocardial infarction or stroke, current cigarette smoking, physical inactivity, and education level.

ative hazards of coronary disease-related death associated with estimated GFR of <70 ml/min were higher for black subjects, compared with white subjects (P interaction ≤ 0.001). Although differences in the relative hazards of all-cause-, cardiovascular disease-, and coronary disease-related death were observed between subjects with and without diabetes mellitus, tests for interaction did not indicate statistical significance (P interaction = 0.16, 0.20, and 0.07, respectively).

Discussion

The results of this study indicate that the risks of death resulting from cardiovascular disease and all causes were higher for persons with renal insufficiency during 16 yr of follow-up monitoring of the NHANES II study cohort. These associations were consistently identified for white subjects, male subjects, female subjects, nonsmokers, smokers, subjects with diabetes mellitus, subjects without diabetes mellitus, and subjects without a history of cardiovascular disease.

The increased risks of death resulting from cardiovascular disease and from all causes detected in this study were not as high as those noted in studies of patients with end-stage renal disease (6,16) but are worrisome, for several reasons. First, the results suggest that the risks of death resulting from cardiovascular disease and from all causes may increase progressively from the onset of renal dysfunction through end-stage renal disease. Second, although the prevalence of end-stage renal disease in the United States is relatively low (16), the prevalence of renal insufficiency is quite high (17,18). According to recent studies, there are >5 million persons in the United States with renal insufficiency. Therefore, renal insufficiency may result in a greater burden of cardiovascular disease in the population than does end-stage renal disease (6). Finally, compared with the population with end-stage renal disease, the population with renal insufficiency is more difficult to identify and monitor (19). Therefore, targeted prevention of cardiovascular disease in this population is more challenging.

The results of this study indicate that decreases in estimated GFR and proteinuria are predictors of cardiovascular disease that are independent of many potential confounders, including increases in BP and serum cholesterol levels, that might be caused by hemodynamic and biochemical alterations during the early stages of renal insufficiency. Although the mechanisms linking renal insufficiency to excess cardiovascular disease risk require further study, the public health implications of our results seem indisputable. Early detection and treatment of renal insufficiency may reduce the societal burden of cardiovascular disease.

Scant epidemiologic information exists on cardiovascular disease-related morbidity and mortality rates among patients with renal insufficiency (6,20). In the Framingham study, increased serum creatinine levels were associated with a 31% increase in the mortality rate for men but were not associated with the cardiovascular disease incidence or mortality rate among women (21). Additionally, in the Framingham study, elevated serum creatinine levels were not associated with cardiovascular disease incidences among men or women. Our study noted different results, and the reasons for such differ-

Table 4. Mortality rates for and relative hazards of death resulting from cardiovascular disease and all causes, according to serum creatinine level

	Overall	GFR[a]			*P* Trend
		≥90 ml/min	70 to 89 ml/min	<70 ml/min	
Person years at risk	84,025	65,101	14,134	4791	
All causes					
no. of patients	1240	797	269	174	
no. of deaths/1000 person-yr	9.7	8.3	13.7	27.5	
age-, race-, and gender-adjusted relative hazard		1.0[b]	0.91 (0.79 to 1.06)	1.51 (1.21 to 1.87)	0.055
multivariate adjusted relative hazard[c]		1.0[b]	0.96 (0.81 to 1.15)	1.51 (1.19 to 1.91)	0.001
Cardiovascular disease					
no. of patients	797	481	182	134	
no. of deaths/1000 person-yr	5.8	4.6	8.6	20.5	
age-, race-, and gender-adjusted relative hazard		1.0[b]	0.91 (0.75 to 1.11)	1.75 (1.39 to 2.20)	0.003
multivariate adjusted relative hazard[c]		1.0[b]	0.96 (0.79 to 1.17)	1.68 (1.33 to 2.13)	0.001
Coronary disease					
no. of patients	390	222	91	77	
no. of deaths/1000 person-yr	2.7	2.0	4.4	11.4	
age-, race-, and gender-adjusted relative hazard		1.0[b]	1.00 (0.73 to 1.37)	1.86 (1.39 to 2.49)	<0.001
multivariate adjusted relative hazard[c]		1.0[b]	1.01 (0.74 to 1.38)	1.68 (1.23 to 2.30)	<0.001
Congestive heart failure					
no. of patients	160	96	40	24	
no. of deaths/1000 person-yr	1.1	0.9	2.0	3.3	
age-, race-, and gender-adjusted relative hazard		1.0[b]	0.97 (0.59 to 1.58)	1.19 (0.60 to 2.35)	0.69
multivariate adjusted relative hazard[c]		1.0[b]	0.98 (0.59 to 1.60)	1.12 (0.57 to 2.17)	0.82

[a] Cutoffs correspond to the 5th and 20th percentiles of the estimated GFR distribution for the United States population.
[b] Reference category.
[c] Adjusted for age, race, gender, systolic BP, total cholesterol level, body mass index, diabetes mellitus, history of myocardial infarction or stroke, current cigarette smoking, physical inactivity, and education level.

ences must be considered. First, results from the Framingham study may not be generalizable to the United States population. For example, the Framingham cohort was older than our study cohort and included almost entirely Caucasian subjects. However, the differences might have arisen because of different outcome measures in the two studies; the Framingham study was able to investigate all incident events, whereas our study was limited to fatal events. In prospective follow-up monitoring of the Hypertension Detection and Follow-Up Program clinical trial participants, the presence of hypercreatinemia in baseline examinations was associated with higher cardiovascular disease-, coronary disease-, stroke-, renal disease-, and all-cause-related mortality rates (22). Microalbuminuria and proteinuria have also been associated with death resulting from cardiovascular disease or all causes among patients with diabetes mellitus and during prospective follow-up monitoring of clinical trial participants (23,24). For example, higher urinary protein levels were associated with higher cardiovascular disease- and heart disease-related mortality rates among the 12,866 men participating in the Multiple Risk Factor Intervention Trial (23). A recent report by the Heart Outcomes Prevention Evaluation study group noted that all levels of urinary protein excretion were associated with increased risks of cardiovascular events during 4.5 yr of follow-up monitoring of patients enrolled in a clinical trial (25). Because only limited population-based data are available on the relationship between renal insufficiency and cardiovascular disease, the National Kidney Foundation has attached a high priority to research in this area (20).

A limitation of this study is that the outcomes were based on mortality rates rather than disease incidences. A more comprehensive assessment of the risks associated with renal insuffi-

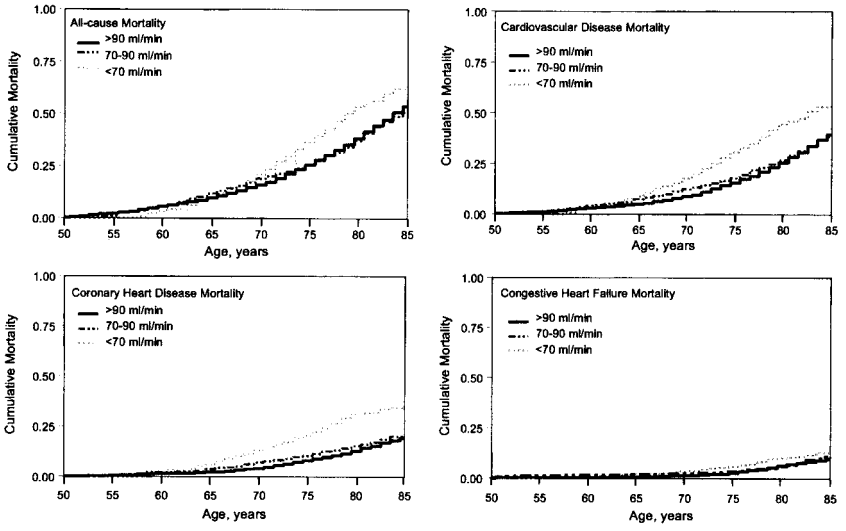

Figure 2. Cumulative mortality curves for 6354 NHANES II Mortality Study participants, with estimated GFR of <70 ml/min, 70 to 89 ml/min, or ≥90 ml/min, for death resulting from all causes, cardiovascular disease, coronary disease, or congestive heart failure.

ciency could have been performed with data on nonfatal cardiovascular disease events. In addition, passive follow-up methods were used to assess mortality rates. It has been suggested that there may have been an undercount of deaths among black subjects in the NHANES II Mortality Study. Such misclassification, if present, would have resulted in underestimation of the association between decreased GFR and proteinuria and cardiovascular disease-related death.

Only 197 and 62 of the 9250 NHANES II participants exhibited baseline urinary protein levels of 30 to 299 and ≥300 mg/dl, respectively. The relatively small number of subjects with baseline urinary protein levels of ≥30 mg/dl may have led to instability in risk estimates for the association between urinary protein excretion and subsequent death, which could account for the borderline associations noted for the subgroups. Only 44 NHANES II participants (including 24 participants for whom serum creatinine measurements were available) died with a mention of renal disease on their death certificates, precluding meaningful analysis of this outcome. Only one dipstick measurement of urinary protein was available for this analysis. Dipstick measurements of urinary protein excretion are not considered as accurate as measurements from 24-h urine collections; however, 24-h urine collections are rarely feasible in large cohort studies. Any misclassification would most likely have been random, resulting in underestimation of the elevated risk associated with the presence of urinary protein excretion. Additionally, GFR estimated from serum creatinine levels may not be as accurate a measure of renal function as actual GFR measurements. More accurate measurements of GFR could be obtained by using [^{125}I]iothalamate, but such a test is not considered feasible for a cohort of >14,000 participants recruited from the general population. However, estimation of renal function on the basis of serum creatinine levels and other characteristics has long been performed, and the equation we used was developed and validated with very large populations. Finally, baseline serum creatinine measurements were unavailable for 28% of the cohort. All-cause mortality rates were 27% higher for subjects with missing serum creatinine levels; however, that finding may be explained by the facts that those participants were older (on average), persons with creatinine levels of ≥3.0 mg/dl were excluded from our analyses, and such subjects exhibit higher mortality rates. Additionally, in sensitivity analyses, the results remained virtually unchanged regardless of which estimated GFR were assigned to persons with missing values (data not shown).

The associations between decreased GFR and death were similar among persons with or without a history of cardiovascular disease at the time of baseline examinations; however, an interaction was present between urinary protein excretion of ≥30 mg/dl and a history of cardiovascular disease for death resulting from all causes, cardiovascular disease, or heart disease. There are several potential explanations for this interaction. It might have resulted from the small number of NHANES II participants with histories of cardiovascular disease ($n = 779$) who were included in this analysis or the small percentage of participants with urinary protein excretion ($n = 49$). In contrast, the relative hazard from all-cause, cardiovascular disease and coronary disease-related mortality rates associated with a urinary protein excretion ≥30 mg/dl may actually be different for persons with and without chronic cardiovascular disease. The risk of death is already high among subjects with histories of cardiovascular disease. More than 50% ($n = 391$) of the NHANES II participants with histories of cardiovascular disease in their baseline interviews died during the follow-up period. The risk of death may not be further increased among persons with urinary protein excretion.

Despite these limitations, our study is one of the largest longest studies of the relationship between renal insufficiency and subsequent cardiovascular disease and is based on prospective follow-up monitoring of a representative sample of the general adult population of the United States. Previous studies

Table 5. Adjusted relative hazard of death resulting from all causes, cardiovascular disease, and coronary disease for participants with estimated GFR of <70 ml/min *versus* ≥90 ml/min

	Relative Hazard[a]									
	Race		Gender		Diabetes Mellitus		Current Smoking		History of Cardiovascular Disease	
	Black	White	Female	Male	No	Yes	No	Yes	No	Yes
All causes	1.68 (0.88 to 3.21)	1.51 (1.19 to 1.91)	1.46 (1.05 to 2.04)	1.54 (1.22 to 1.94)	1.39 (1.08 to 1.79)	2.41 (1.21 to 4.79)	1.38 (1.06 to 1.79)	1.84 (1.15 to 2.95)	1.49 (1.15 to 1.92)	1.54 (0.98 to 2.41)
Cardiovascular disease	1.53 (0.65 to 3.63)	1.68 (1.28 to 2.19)	1.73 (1.19 to 2.52)	1.71 (1.25 to 2.32)	1.52 (1.13 to 2.03)	2.69 (1.30 to 5.56)	1.52 (1.13 to 2.04)	2.16 (1.28 to 3.63)	1.69 (1.24 to 2.32)	1.54 (1.01 to 2.35)
Coronary disease	6.82 (2.37 to 19.7)	1.56 (1.13 to 2.15)	2.11 (1.28 to 3.48)	1.71 (1.14 to 2.56)	1.45 (1.02 to 2.07)	5.10 (2.24 to 11.6)	1.67 (1.19 to 2.32)	1.70 (0.89 to 3.24)	1.67 (1.10 to 2.51)	1.68 (0.90 to 3.14)

[a] Adjusted for age, race, gender, systolic BP, total cholesterol level, body mass index, diabetes mellitus, history of myocardial infarction or stroke, current cigarette smoking, physical inactivity, and education level.

focused on select groups of patients, usually those enrolled in clinical trials. The associations we detected were consistently identified regardless of whether renal insufficiency was assessed by means of baseline measurements of estimated GFR or dipstick assessments of urinary protein excretion. Previous studies focused on one or the other of these two measures but not both. Additionally, data on an extensive number of covariates were available for the NHANES II participants, permitting assessment of the independence of the observed relationship between renal insufficiency and subsequent death.

Although strong associations between end-stage renal disease and cardiovascular disease incidences and mortality rates were previously identified (16), the hemodynamic and metabolic changes caused by renal dysfunction (26) are difficult to account for in the analysis of cardiovascular disease among patients with chronic renal failure (27). Our investigation excluded subjects with advanced renal dysfunction (serum creatinine levels of ≥3.0 mg/dl). Therefore, our results are less likely to have been confounded by changes in BP, total cholesterol levels, or other unmeasured factors resulting from the metabolic effects of advanced renal disease (28).

In conclusion, cardiovascular disease-related and all-cause mortality rates were higher among the United States population with estimated GFR of <70 ml/min. Additionally, a graded relationship was observed between higher urinary protein levels and increased risks of subsequent cardiovascular disease-related or all-cause-related death. These results are especially important because the analysis used a nationally representative cohort to address the National Kidney Foundation research recommendations for determination of the risks of cardiovascular disease and death among subjects with renal insufficiency and early renal disease. This study supports the additional research recommendations made by the National Kidney Foundation, including determination of the prevalence, incidence, and pathogenesis of cardiovascular disease among the population with renal insufficiency (14).

References

1. United States Renal Data System: *USRDS 1997 Annual Data Report*, Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 1998
2. Furth S, Hermann J, Powe N: Cardiovascular risk factors, and comorbidity, and survival outcomes in black and white dialysis patients. *Semin Dial* 11: 102–105, 1998
3. Ma K, Greene E, Raij L: Cardiovascular risk factors in chronic renal failure and hemodialysis populations. *Am J Kidney Dis* 19: 505–513, 1992
4. United States Renal Data System: The USRDS Dialysis Morbidity and Mortality Study: wave 2. *Am J Kidney Dis* 30[suppl 1]: S67–S85, 1997
5. Levey A, Gassman J, Hall P, Walker G: Assessing the progression of renal disease in clinical studies: Effects of duration of follow-up and regression to the mean. *J Am Soc Nephrol* 1: 1087–1093, 1991
6. Foley RN, Parfrey PS, Sarnak MJ: Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 32: S112–S119, 1998

7. McDowell A, Engel A, Massey JT, Maurer K: Plan and operation of the Second National Health and Nutrition Examination Survey, 1976–1980. *Vital Health Stat* 1: 1–144, 1981
8. Loria CM, Sempos CT, Vuong C: Plan and operation of the NHANES II Mortality Study, 1992. *Vital Health Stat* 38: 1–16, 1999
9. Boyle CA, Decoufle P: National sources of vital status information: Extent of coverage and possible selectivity in reporting. *Am J Epidemiol* 131: 160–168, 1990
10. Wentworth DN, Neaton JD, Rasmussen WL: An evaluation of the Social Security Administration master beneficiary record file and the National Death Index in the ascertainment of vital status. *Am J Public Health* 73: 1270–1274, 1983
11. Stampfer MJ, Willett WC, Speizer FE, Dysert DC, Lipnick R, Rosner B, Hennekens CH: Test of the National Death Index. *Am J Epidemiol* 119: 837–839, 1984
12. Williams BC, Demitrack LB, Fries BE: The accuracy of the National Death Index when personal identifiers other than Social Security number are used. *Am J Public Health* 82: 1145–1147, 1992
13. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D: A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. *Ann Intern Med* 130: 877–884, 1999
14. Korn EL, Graubard BI, Midthune D: Time-to-event analysis of longitudinal follow-up of a survey: Choice of the time-scale. *Am J Epidemiol* 145: 72–80, 1997
15. Stata Corp.: Stata Statistical Software, release 6.0, College Station, TX, Stata Corp., 1999
16. United States Renal Data System: *USRDS 1999 Annual Data Report*, Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 1999
17. Jones CA, McQuillan GM, Kusek JW, Eberhardt MS, Herman WH, Coresh J, Salive M, Jones CP, Agodoa LY: Serum creatinine levels in the US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 32: 992–999, 1998
18. Coresh J, Wei GL, McQuillan G, Brancati FL, Levey AS, Jones C, Klag MJ: Prevalence of high blood pressure and elevated serum creatinine level in the United States: Findings from the Third National Health and Nutrition Examination Survey (1988–1994). *Arch Intern Med* 161: 1207–1216, 2001
19. Levey AS: Controlling the epidemic of cardiovascular disease in chronic renal disease: Where do we start? *Am J Kidney Dis* 5: S5–S13, 1998
20. Levey AS: Controlling the epidemic of cardiovascular disease in chronic renal disease: Where do we start? *Am J Kidney Dis* 32: S5–S13, 1998
21. Cullerton BF, Larson MG, Wilson PW, Evans JC, Parfrey PS, Levy D: Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. *Kidney Int* 56: 2214–2219, 1999
22. Shulman N, Ford C, Hall D, Blaufox M, Simon D, Langford H, Schneider K: Prognostic value of serum creatinine and effect of treatment of hypertension on renal function: Results from the Hypertension Detection and Follow-up Program. *Hypertension* 13: I-80–I-93, 1989
23. Grimm RH, Svendsen KH, Kasiske B, Keane WF, Wahi WM: Proteinuria is a risk factor for mortality over 10 years of follow-up. *Kidney Int* 52[suppl]: S10–S14, 1997
24. Valmadrid CT, Klein R, Moss SE, Klein BK: The risk of cardiovascular disease mortality associated with microalbuminuria and gross proteinuria in persons with older-onset diabetes mellitus. *Arch Intern Med* 160: 1093–1100, 2000
25. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, Halle JP, Young J, Rashkow A, Joyce C, Nawaz S, Yusuf S: Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 286: 421–426, 2001
26. Coresh J, Longenecker J, Miller E, Young H, Klag M: Epide miology of cardiovascular risk factors in chronic renal disease. *J Am Soc Nephrol* 9[suppl]: S24–S30, 1999
27. Perneger TV, Brancati FL, Whelton PK, Klag MJ: Studying the causes of kidney disease in humans: A review of methodologic obstacles and possible solutions. *Am J Kidney Dis* 25: 722–731, 1995
28. Perneger TV, Whelton PK, Klag MJ: History of hypertension in patients treated for end-stage renal disease. *J Hypertens* 15: 451–456, 1997