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Original Contribution

Glomerular Filtration Rate, Albuminuria, and Risk of Cardiovascular and All-Cause Mortality in the US Population

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Decreased glomerular filtration rate (GFR) and albuminuria are used in combination to define chronic kidney disease, but their separate and combined effects on cardiovascular and all-cause mortality have not been studied in the general population. The linked mortality file of the Third National Health and Nutrition Examination Survey includes data from 13 years of follow-up (1988–2000) for 14,586 US adults. The authors estimated GFR from standardized serum creatinine levels. Albuminuria was defined by the urinary albumin:creatinine ratio. Incidence rate ratios (IRRs) were adjusted for major cardiovascular disease risk factors and C-reactive protein. Lower estimated GFR was associated with higher risks of cardiovascular and all-cause mortality overall and within every albuminuria category. Likewise, increasing albuminuria was associated with higher risk of estimated GFR overall and within every category. When estimated GFR and albuminuria were examined simultaneously, a 10-ml/minute/1.73 m^2 lower estimated GFR (among persons with estimated GFR $<$60 ml/minute/1.73 m^2) was associated with an IRR of 1.29 (95% confidence interval: 1.06, 1.55) for cardiovascular mortality and a doubling of albuminuria was associated with an IRR of 1.06 (95% confidence interval: 1.04, 1.08) for cardiovascular mortality. The authors conclude that moderately decreased estimated GFR and albuminuria independently predict cardiovascular and all-cause mortality in the general population. These data support recent recommendations defining chronic kidney disease and stratifying subsequent risks based on both decreased GFR and albuminuria.

albuminuria; glomerular filtration rate; kidney diseases; mortality

Abbreviations: ACR, albumin:creatinine ratio; CI, confidence interval; GFR, glomerular filtration rate; ICD-10, *International Classification of Diseases*, Tenth Revision; MDRD, Modification of Diet in Renal Disease; NHANES III, Third National Health and Nutrition Examination Survey.

Chronic kidney disease affects an estimated 19 million adults in the United States (1, 2). While progression to kidney failure is the most recognized consequence of kidney disease, persons with chronic kidney disease are much more likely to die of cardiovascular disease than to experience kidney failure (3). Recent statements from the National Kidney Foundation and the American Heart Association have proposed using chronic kidney disease in cardiovascular risk stratification and treatment guidelines (1, 3). Defining and staging kidney disease relies on combining information

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on kidney damage, usually detected by albuminuria, and decreased renal filtration, usually based on glomerular filtration rate (GFR) (1). However, most prospective studies of cardiovascular disease and mortality have examined either albuminuria or GFR but not both.

Lower GFR predicts cardiovascular events and mortality in patients with existing cardiovascular disease (4–6), patients at high risk of cardiovascular disease (7), and the general population (3, 8, 9). Most of these studies have relied on the abbreviated Modification of Diet in Renal Disease (MDRD) Study equation to estimate GFR from serum creatinine level, age, sex, and race. In a prospective study of older adults (10), elevated cystatin C, another marker of decreased kidney filtration, predicted cardiovascular and mortality risk more strongly than did creatinine-based estimates of GFR. However, creatinine remains the most widely used marker of decreased kidney function. None of these large prospective studies of decreased kidney function included quantitative data on albuminuria.

Leakage of protein in the urine is a sensitive indicator of early kidney damage, especially in persons with diabetes (11). Albumin is the recommended marker for detection of proteinuria in adults (1). Both prevalence and severity of albuminuria are higher at lower GFRs and among persons with diabetes (12, 13). Albuminuria is one of the strongest predictors of GFR decline, and it is associated with a higher risk of cardiovascular disease and mortality in both diabetic and nondiabetic persons (14). Even levels of urinary albumin below the cutoff for microalbuminura have been associated with a higher risk of cardiovascular and noncardiovascular mortality (15, 16). However, the risk associated with varying levels of albuminuria by level of kidney function has not been quantified in large cohort studies.

We analyzed up to 13 years of mortality follow-up data (1988–2000) on participants in the Third National Health and Nutrition Examination Survey (NHANES III) in order to assess the combined impact of decreased estimated GFR and albuminuria, measured simultaneously, on the risk of cardiovascular and all-cause mortality. Here we present absolute risk estimates, as well as adjusted relative risks, from this representative sample of US adults.

MATERIALS AND METHODS

Study sample

In this study, we used data on 15,762 participants aged 20 years or older in the NHANES III. Baseline data collection was conducted during 1988–1994 by the National Center for Health Statistics (Centers for Disease Control and Prevention). Mortality follow-up was conducted through linkage to National Death Index records. The NHANES III used a complex, multistage cluster sampling design and provided cross-sectional, nationally representative data on the health and nutritional status of the civilian, noninstitutionalized US population (17, 18). Non-Hispanic Blacks, Mexican Americans, and the elderly were deliberately oversampled, allowing calculation of more precise estimates of the distribution of variables in these groups. The National Death Index records provided data on dates of death and underlying and multiple causes of death.

Measurements

In NHANES III, standardized questionnaires were administered in the home, followed by a physical examination and serum collection at a mobile examination center, as described previously (17). Race/ethnicity was self-reported and was categorized as non-Hispanic White, non-Hispanic Black, Mexican-American, or other. A participant was considered to have diabetes mellitus if he or she reported ever having been told by a doctor that he or she had diabetes or ''sugar diabetes'' at a time other than during pregnancy, or if he or she was taking insulin or a ''diabetes pill'' at the time of questionnaire administration. Use of antihypertensive medication and prior cardiovascular disease were defined by self-report. Prior cardiovascular disease was considered positive if the participant reported ever having been told that he or she had had a heart attack, heart failure, or stroke or had undergone a surgical or percutaneous procedure for any of these conditions. Intensity of physical activity was based on self-reported participation in a variety of activities during the past month; participants were categorized as inactive, moderately active, or active based on ratings of frequency and vigor for each activity (19).

A spot urine sample was obtained in the morning, following an overnight fast, using a clean-catch technique and sterile containers, and was frozen for later analysis (13, 17). Urinary albumin level was measured by solid-phase fluorescence immunoassay, and urinary creatinine level was measured by the modified kinetic method of Jaffe using a Beckman Coulter Synchron AS/Astra Analyzer (Beckman Coulter, Inc., Fullerton, California). Serum creatinine level was measured by the modified kinetic method of Jaffe using a Roche Hitachi 737 analyzer (Roche Diagnostics Corporation, Indianapolis, Indiana). GFR was estimated on the basis of serum creatinine level, with the most recent expression of the MDRD prediction equation for standardized serum creatinine (20). Specifically, estimated GFR $= 175 \times$ (standardized serum creatinine in mg/dl)$^{-1.154} \times$ age$^{-0.203}$ ($\times$ 0.742 if female) ($\times$ 1.21 if Black). The serum creatinine values reported in NHANES III were adjusted to the creatinine assay used in the development of the MDRD equation (21). Estimated GFR is reported in ml/minute per 1.73 m^2 of body surface area. C-reactive protein level was measured by latex-enhanced nephelometry (Behring Diagnostics, Inc., Somerville, New Jersey).

Linkage and causes of death

Linkage of NHANES III and National Death Index records through December 31, 2000, was performed by probabilistic matching, and data were made available in June 2005 (22). The method used up to 12 identifying data items. A selected sample of death certificates was reviewed manually to validate the process. The underlying cause of death was coded according to the *International Classification of Diseases, Ninth Revision, Clinical Modification* (23) for deaths occurring between 1988 and 1998 and according to

the *International Classification of Diseases*, Tenth Revision (ICD-10) (24) for deaths occurring between 1999 and 2000. Underlying causes of death were grouped by the National Center for Health Statistics for each coding system, and all deaths from 1988–1998 that were coded under *International Classification of Diseases, Ninth Revision, Clinical Modification* guidelines were recoded into comparable groups based on the ICD-10 underlying cause of death (25). For this analysis, cardiovascular disease mortality included deaths coded as due to hypertensive disease (ICD-10 codes I10–I13), ischemic heart disease (ICD-10 codes I20–I25), arrhythmia (ICD-10 codes I44–I49), heart failure (I50), cerebrovascular disease (ICD-10 codes I60–I69), or atherosclerosis or other diseases of the arteries (ICD-10 codes I70–I78). Mortality status was known for all but 11 participants, and 2,498 deaths were identified.

Statistical analyses

All analyses were performed using the sampling weights provided by the National Center for Health Statistics. These weights account for the differential probability of selection and nonresponse and allow estimation of prevalence in the civilian, noninstitutionalized US population. Analyses were performed using Stata software (26). These Stata commands implement algorithms similar to those of SUDAAN software (27).

Estimated GFR was analyzed both as a continuous measure and divided into three categories (15–59, 60–89, and $\geq$90 ml/minute/1.73 m^2) based on clinical practice guidelines (1). Patients with an estimated GFR below 15 ml/minute/1.73 m^2 ($n = 25$) were excluded from all analyses. Persons with a physiologically implausibly high estimated GFR were assigned a maximum value of 200 ml/minute/1.73 m^2. Microalbuminuria was defined as a urinary albumin:creatinine ratio (ACR) of 30–299 mg/g and macroalbuminuria as an ACR of $\geq$300 mg/g. In other models, ACR was log-transformed. Systolic and diastolic blood pressure were collapsed into a joint categorical variable (normal: systolic pressure <120 mmHg and diastolic pressure <80 mmHg; prehypertension: systolic pressure 120–139 mmHg or diastolic pressure 80–89 mmHg; stage 1 hypertension: systolic pressure 140–159 mmHg or diastolic pressure 90–99 mmHg; stage 2 hypertension: systolic pressure $\geq$160 mmHg or diastolic pressure $\geq$100 mmHg) (28). C-reactive protein level was categorized as either undetectable by the assay (<0.22 mg/dl), minimal (0.22–0.99 mg/dl), or elevated ($\geq$1.0 mg/dl). Triglyceride levels were log-transformed because of a skewed distribution. Persons who were missing data on any variable or had fasted for fewer than 8 hours were excluded ($n = 1{,}140$). Analyses included the 14,586 participants remaining after further exclusion of those with an unknown mortality status ($n = 11$) and those with an estimated GFR below 15 ml/minute/1.73 m^2 ($n = 25$).

Linear or logistic regression, as appropriate, was used to evaluate relations between variables and estimated GFR while accounting for the sampling probability. Incidence rates were adjusted to those of a 60-year-old non-Hispanic White male. Associations of estimated GFR and ACR categories with mortality were examined using multivariable Poisson regression models, which yielded results similar to those of Cox proportional hazards regression. Tests for trend were conducted for the entire study population and within ACR and estimated GFR categories separately. Analyses were repeated after stratification by diabetes status, sex, and race/ethnicity. Some analyses were repeated after the addition of serum insulin or, in diabetic persons, glycated hemoglobin and duration of diabetes to the models. To examine the shape of the association between estimated GFR and mortality, we used a linear spline model with three initial knots (60, 75, and 90 ml/minute/1.73 m^2) within each ACR category. To avoid overfitting, knots that did not add significantly ($p < 0.15$) to the fit of the model were removed from analyses. Absolute rates are shown here to allow estimation of both relative and attributable risks. The predicted risk was calculated for a 60-year-old non-Hispanic White male. Results are presented separately for cardiovascular and all-cause mortality.

RESULTS

Lower estimated GFR was associated with higher age, non-Hispanic White race/ethnicity, diabetes mellitus, prevalent coronary heart disease, higher blood pressure, use of antihypertensive medication, former smoking status, higher body mass index (weight (kg)/height $(m)^2$), less physical activity, higher low density lipoprotein cholesterol, lower high density lipoprotein cholesterol, higher triglycerides, and higher C-reactive protein (table 1). Compared with non-Hispanic Whites, serum creatinine levels were higher in non-Hispanic Blacks and lower in Mexican Americans for both men and women (table 2). Non-Hispanic Whites had lower mean estimated GFRs than did persons of other races/ethnicities and were more likely to have decreased estimated GFR.

Estimated GFR and urinary ACR were significantly, though weakly, correlated (Spearman correlation coefficient = -0.12; $p < 0.001$). Among persons with an estimated GFR of 15–59 ml/minute/1.73 m^2, 23.2 percent had microalbuminuria and 8.6 percent had macroalbuminuria, as compared with 6.0 percent and 0.6 percent, respectively, of persons with an estimated GFR of $\geq$90 ml/minute/1.73 m^2 (table 3).

Between 1988 and 2000, a total of 2,054 (14.1 percent) participants died during a median follow-up period of 8.7 years. A total of 887 (6.1 percent) died of cardiovascular disease. Persons with lower estimated GFR or albuminuria were much more likely than those with higher estimated GFR and those without albuminuria to have died from cardiovascular disease or all causes (figure 1). The age-, race-, and sex-adjusted incidence (per 100 person-years) of cardiovascular mortality increased from 0.5 (95 percent confidence interval (CI): 0.3, 0.6) per 100 person-years among persons with normal kidney function and no albuminuria to 4.1 (95 percent CI: 2.6, 4.6) among persons in the lowest estimated GFR category with macroalbuminuria. Similarly, the incidence of all-cause mortality increased from 1.8 (95 percent CI: 0.8, 2.1) per 100 person-years to 8.8 (95 percent CI: 3.9, 10.3) per 100 person-years.

TABLE 1. Characteristics of participants by estimated glomerular filtration rate, Third National Health and Nutrition Examination Survey, 1988–2000

	Total	Estimated mean glomerular filtration rate (ml/minute/1.73 m^2)			*p* value
		≥90	60–89	15–59	
No. of participants	14,586	9,693	4,052	841	
Mean age (years)	44.2	38.5	52.8	70.4	<0.001
Female sex (%)	52.1	51.4	52.5	60.7	<0.001
Race/ethnicity (%)					<0.001
Non-Hispanic White	76.0	70.6	86.1	85.5	
Non-Hispanic Black	11.1	13.6	6.2	8.3	
Mexican-American	5.2	6.8	2.3	1.3	
Other	7.7	9.0	5.4	4.9	
Diabetes mellitus (%)	4.8	3.4	6.2	15.8	<0.001
Prevalent coronary heart disease (%)	7.6	4.1	10.9	38.4	<0.001
Hypertension category (%)					<0.001
Optimal	47.1	54.4	36.1	13.3	
Prehypertension	34.9	33.6	37.9	32.0	
Stage 1 hypertension	13.4	9.6	18.9	33.3	
Stage 2 hypertension	4.6	2.4	7.1	21.4	
Use of antihypertensive medication (%)	12.7	6.8	17.9	52.3	<0.001
Smoking status (%)					<0.001
Never smoker	45.7	45.3	46.5	44.6	
Former smoker	25.8	21.3	33.3	41.6	
Current smoker	28.5	33.4	20.2	13.9	
Body mass index*	26.5	26.2	27.1	27.6	<0.001
Physical activity (%)					<0.001
Inactive	25.1	25.7	22.6	34.4	
Moderately active	53.6	51.4	57.6	58.1	
Active	21.3	22.9	19.8	7.5	
Low density lipoprotein cholesterol level (mg/dl)	123.5	118.4	131.6	144.1	0.003
High density lipoprotein cholesterol level (mg/dl)	50.8	51.0	50.5	48.9	0.005
Triglyceride level (mg/dl)	145.9	139.1	153.9	194.6	<0.001
C-reactive protein level (%)					0.002
<0.22 mg/dl	71.5	73.7	69.6	51.6	
0.22–0.99 mg/dl	21.1	19.6	22.8	31.7	
≥1.00 mg/dl	7.4	6.7	7.6	16.7	

* Weight (kg)/height $(m)^2$.

These associations remained after further adjustment for diabetes mellitus, prevalent coronary heart disease, blood pressure, use of antihypertensive medication, smoking status, body mass index, physical activity level, low density lipoprotein and high density lipoprotein cholesterol, log triglycerides, and C-reactive protein (table 4). In this fully adjusted model, persons with low estimated GFR and macroalbuminuria were four and three times more likely to die from cardiovascular disease or any cause, respectively, than persons with normal kidney function and no albuminuria. Lower estimated GFR was associated with higher risk of cardiovascular (all p's < 0.04) and all-cause (all p's < 0.05) mortality overall and within every category of ACR. Similar results were observed from models using the inverse of serum creatinine level rather than estimated GFR. Likewise, ACR was associated with higher risk of cardiovascular (all p's < 0.003) and all-cause (all p's < 0.001) mortality overall and within every category of estimated GFR. Results from models including serum insulin were similar. No significant interactions were found between estimated GFR and

TABLE 2. Mean serum creatinine level and estimated glomerular filtration rate, by race/ethnicity, Third National Health and Nutrition Examination Survey, 1988–2000

	Race/ethnicity			
	Non-Hispanic White	Non-Hispanic Black	Mexican-American	Other
Men				
Mean serum creatinine level (mg/dl)	0.95	1.04**	0.87**	0.93
Estimated mean glomerular filtration rate (%)	96.8	108.4**	111.3*	101.4**
≥90 ml/minute/1.73 m^2	62.0	79.2	85.2	74.1
60–89 ml/minute/1.73 m^2	34.5	18.0	14.0	22.6
15–59 ml/minute/1.73 m^2	3.5	2.8	0.9	3.3
Women				
Mean serum creatinine level (mg/dl)	0.74	0.78**	0.64**	0.67**
Estimated mean glomerular filtration rate (%)	96.3**	113.2**	118.3**	110.2**
≥90 ml/minute/1.73 m^2	58.9	80.0	85.9	77.3
60–89 ml/minute/1.73 m^2	35.6	16.7	12.9	20.9
15–59 ml/minute/1.73 m^2	5.4	3.2	1.2	1.8

* $p < 0.05$; ** $p < 0.001$ (vs. Non-Hispanic Whites).

ACR categories for either cardiovascular or all-cause mortality (p's for interaction were 0.47 and 0.64, respectively).

The relation between mortality associated with lower estimated GFR, analyzed as a continuous variable, and higher ACR category is shown graphically in figure 2. For both outcomes, the predicted incidence rate was highest among persons with macroalbuminuria for any estimated GFR, and it increased with lower estimated GFR for all ACR groups. In linear models adjusting for log ACR, a 10-ml/minute/1.73 m^2 lower estimated GFR was associated with a 9.3 percent (95 percent CI: 4.3, 14.6) higher risk of cardiovascular mortality and a 3.0 percent (95 percent CI: 0.0, 6.7) higher risk of all-cause mortality. The relative risks per 10-ml/minute/1.73 m^2 lower estimated GFR were stronger below 60 ml/minute/1.73 m^2: a 29 percent (95 percent CI: 6.4, 55.2) higher risk of cardiovascular mortality and a 22 percent (95 percent CI: 6.1, 39.5) higher risk of all-cause

TABLE 3. Prevalences (%) of microalbuminuria and macroalbuminuria, by estimated glomerular filtration rate, Third National Health and Nutrition Examination Survey, 1988–2000

	Total (n = 14,586)	Estimated mean glomerular filtration rate (ml/minute/1.73 m^2)		
		≥90 (n = 9,693; 66.5%)	60–89 (n = 4,052; 27.8%)	15–59 (n = 841; 5.8%)
Microalbuminuria (ACR* 30–299 mg/g)	7.4	6.0	8.3	23.2
Macroalbuminuria (ACR ≥300 mg/g)	1.1	0.6	1.2	8.6

* ACR, albumin:creatinine ratio.

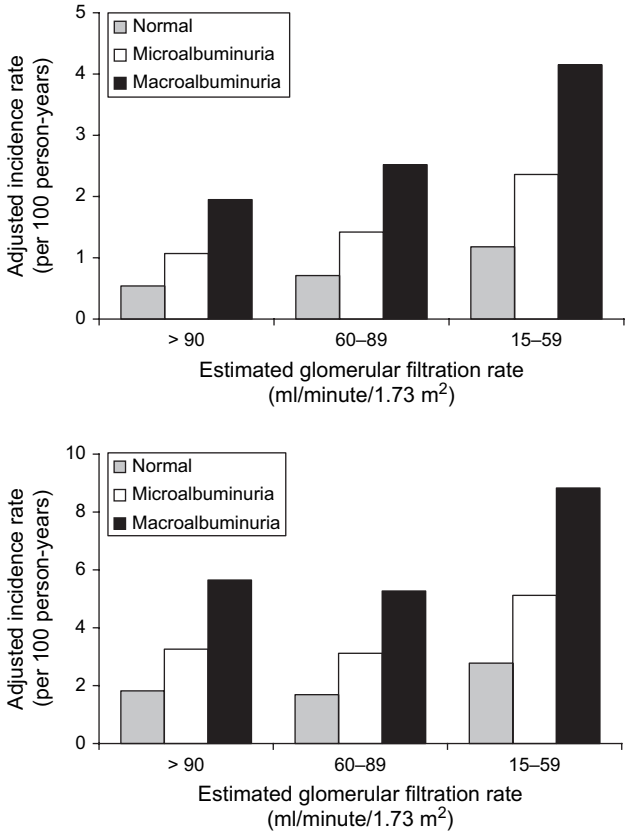

FIGURE 1. Adjusted incidence rate of cardiovascular (top) and all-cause (bottom) mortality, by category of estimated glomerular filtration rate and albuminuria, Third National Health and Nutrition Examination Survey, 1988–2000. Models were adjusted to the incidence rates of a 60-year-old non-Hispanic White male.

TABLE 4. Adjusted* relative risk of cardiovascular and all-cause mortality, by estimated glomerular filtration rate and albuminuria, Third National Health and Nutrition Examination Survey, 1988–2000

	Estimated mean glomerular filtration rate (ml/minute/1.73 m^2)						*p*-trend	Total	
	≥90		60–89		15–59				
	RR†	95% CI†	RR	95% CI	RR	95% CI		RR	95% CI
Cardiovascular disease mortality									
Normal (ACR† <30 mg/g)	1.0	Referent	1.48	1.13, 1.93	2.36	1.67, 3.34	<0.001	1.0	Referent
Microalbuminuria (ACR 30–299 mg/g)	2.18	1.45, 3.29	2.19	1.55, 3.10	3.01	2.04, 4.42	0.04	1.62	1.32, 1.99
Macroalbuminuria (ACR ≥300 mg/g)	2.42	0.99, 5.93	4.38	2.32, 8.28	4.35	2.39, 7.90	0.02	2.62	1.77, 3.89
p-trend		0.001		0.002		0.003			<0.001
Total	1.0	Referent	1.37	1.07, 1.75	2.12	1.65, 2.73	<0.001		
All-cause mortality									
Normal (ACR <30 mg/g)	1.0	Referent	1.07	0.90, 1.28	1.78	1.45, 2.20	<0.001	1.0	Referent
Microalbuminuria (ACR 30–299 mg/g)	1.56	1.18, 2.06	1.55	1.21, 1.99	2.51	1.99, 3.17	0.008	1.52	1.35, 1.72
Macroalbuminuria (ACR ≥300 mg/g)	2.91	1.59, 5.34	2.89	1.77, 4.40	3.01	2.06, 4.41	0.05	2.44	1.91, 3.12
p-trend		<0.001		<0.001		0.001			<0.001
Total	1.0	Referent	1.05	0.89, 1.25	1.77	1.47, 2.13	<0.001		

* Adjusted for age, sex, race/ethnicity, previous cardiovascular disease, blood pressure category, use of antihypertensive medication, diabetes mellitus, smoking status, body mass index, physical activity level, low density lipoprotein and high density lipoprotein cholesterol, log triglyceride level, and C-reactive protein category.

† RR, relative risk; CI, confidence interval; ACR, albumin:creatinine ratio.

mortality. In models adjusting for estimated GFR, a doubling of ACR was associated with a 6.3 percent (95 percent CI: 3.9, 8.8) higher risk of cardiovascular mortality and a 6.3 percent (95 percent CI: 4.7, 8.0) higher risk of all-cause mortality. These relative risks were similar above and below 60 ml/minute/1.73 m^2.

Results were similar among persons with and without diabetes. Among persons without diabetes, those in the lowest category of estimated GFR and the highest category of ACR had a relative risk of 5.10 (95 percent CI: 2.41, 10.79) for cardiovascular mortality and a relative risk of 3.27 (95 percent CI: 1.99, 5.38) for all-cause mortality, as compared with those with normal ACR and estimated GFR. Among persons with diabetes, these relative risks were 2.72 (95 percent CI: 1.14, 6.50) and 2.48 (95 percent CI: 1.27, 4.86), respectively, but absolute risks were higher than those in nondiabetic persons. Results among diabetic persons were largely unchanged by including duration of diabetes and glycated hemoglobin level in the models. Results were similar in models stratified by race/ethnicity or sex.

DISCUSSION

In this study of a representative sample of US adults, both lower estimated GFR and higher urinary ACR independently predicted cardiovascular and all-cause mortality. The presence of both abnormalities was associated with an even greater risk. Higher urinary albumin excretion was associated with a higher risk within each category of estimated GFR, and, similarly, lower estimated GFR was associated with a higher risk among persons with and without albuminuria. These elevated risks remained strong even after adjustment for numerous potential confounders and intermediate factors, including diabetes, lipid levels, prior cardiovascular disease, and C-reactive protein level. Similar results were seen among persons with and without diabetes. This study also provided estimates of absolute mortality risk by level of albuminuria and estimated GFR for a representative sample of the US population.

In the present study, an estimated GFR less than 60 ml/1.73 m^2 was associated with an approximately twofold higher risk of cardiovascular mortality in comparison with normal estimated GFR (>90 ml/1.73 m^2) at all levels of albuminuria. An increased risk of cardiovascular events and mortality with decreased estimated GFR has been observed previously among patients with existing cardiovascular disease (4, 5) and patients at high risk of cardiovascular disease (7). Recent large epidemiologic studies have also clearly demonstrated an elevated risk associated with decreased estimated GFR in the general population (9, 29). In a study of over 1 million persons, estimated GFR ranges of 30–44 ml/minute/1.73 m^2 and 45–59 ml/minute/1.73 m^2 were associated with 1.2 and 1.8 times' higher risks of mortality, respectively, in comparison with an estimated GFR of ≥60 ml/minute/1.73 m^2, after adjustment (9). An analysis of data pooled from four large community-based studies found a 1.4 times' higher risk of mortality among participants with an estimated GFR less than 60 ml/1.73 m^2 (30). These studies, however, could not control for some potentially important factors, such as level of inflammation, and none considered the effect of albuminuria. One recent study, using data from over 96,000 adults undergoing an annual health check-up in Japan, found that those with an estimated GFR less than 60 ml/minute/1.73 m^2 had a 1.7- to 1.8-fold higher risk of cardiovascular mortality and a 1.3- to 1.4-fold higher risk of all-cause

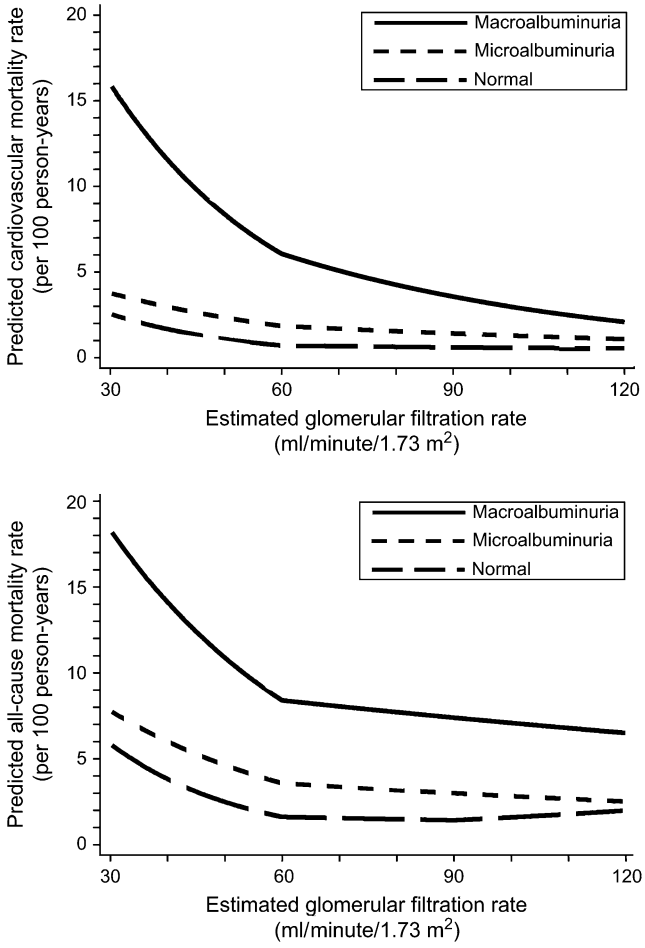

FIGURE 2. Predicted incidence rate of cardiovascular (top) and all-cause (bottom) mortality associated with estimated glomerular filtration rate, by category of albuminuria, Third National Health and Nutrition Examination Survey, 1988–2000. Rates were adjusted to the mortality rate of a 60-year-old non-Hispanic White male and were calculated using smoothed linear splines with knots at 60, 75, and 90 ml/minute/1.73 m^2. Knots that did not significantly improve the fit of the model ($p > 0.15$) were removed.

mortality after adjustment for dipstick-positive proteinuria (31). Persons with both proteinuria and reduced estimated GFR had a 2.2- to 4.0-fold higher risk of CVD mortality and a 2.4- to 2.9-fold higher risk of all-cause mortality.

In the same Japanese study, dipstick-positive proteinuria also was associated with higher risks of cardiovascular and all-cause mortality (31). In the community-based PREVEND [Prevention of Renal and Vascular End-Stage Disease] Study, a study of over 40,000 participants conducted in the Netherlands, urinary albumin concentrations as low as 10–20 mg/liter were associated with a higher risk of cardiovascular and noncardiovascular mortality than were urinary albumin concentrations less than 10 mg/liter (15). In the Third Copenhagen City Heart Study, urinary albumin excretion in the upper quartile (>4.8 μg/minute, approximately equivalent to 7.2 mg/g) was associated with a twofold higher risk of coronary heart disease and death than urinary albumin excretion in the lowest quartile (<2.1 μg/minute) after adjustment for other risk factors, including creatinine clearance (32).

The reasons for the increased risk of cardiovascular disease in persons with decreased GFR and/or albuminuria are not fully understood. Persons with chronic kidney disease have a higher prevalence of several cardiovascular disease risk factors, including dyslipidemia, hypertension, left ventricular hypertrophy, and inflammatory markers (3, 8). Among NHANES III participants with an estimated GFR of <60 ml/minute/1.73 m^2, as compared with those with an estimated GFR of ≥90 ml/minute/1.73 m^2, diabetes was four times higher, stage 1 or 2 hypertension was four times higher, and a history of cardiovascular disease was nearly 10 times higher. Twice as many had elevated C-reactive protein levels. Thus, both albuminuria and decreased estimated GFR indicate a high-risk state. The observed associations with all-cause and cardiovascular mortality in this study, however, remained after adjustment for all measured risk factors. Thus, other mechanisms appear necessary to explain the observed associations. Albuminuria indicates greater vascular permeability throughout the vascular tree and is accompanied by abnormalities in the endothelial-related components of the coagulation or fibrinolytic systems (33). Decreased GFR also results in lower clearance and higher plasma levels of a wide range of factors not measured in the present study, including homocysteine and asymmetric dimethylarginine. These factors, as well as increased inflammation and oxidative stress, may explain the higher risk of cardiovascular and all-cause mortality in chronic kidney disease (3). Interestingly, we observed no synergistic interaction between albuminuria and decreased estimated GFR in their relation with mortality, though the presence of albuminuria strongly predicts a progressive decline in estimated GFR (14). Similar effects of albuminuria across levels of estimated GFR would be expected if albuminuria also confers an increased risk of an early decline in estimated GFR among persons with initially normal function (estimated GFR ≥90 ml/minute/1.73 m^2). There were few participants in this study with both normal estimated GFR and albuminuria.

Higher risks of cardiovascular and all-cause mortality with decreased estimated GFR and albuminuria were observed in all racial/ethnic groups and in both men and women. Consistent with previous studies, African Americans in this study had higher sex-specific mean serum creatinine levels than Whites, but the MDRD equation used to estimate GFR results in higher sex-specific estimated GFR levels in African Americans than in Whites (20). Creatinine is a by-product of muscle metabolism and therefore is affected significantly by differences in muscle mass. Muscle mass is, on average, higher in African Americans than in Whites, higher in men than in women, and higher in younger adults than in older adults. The MDRD equation was developed to account for average differences in muscle mass by age, race, and sex, but it cannot account for individual differences (20). The validity of the MDRD equation was recently demonstrated across 10 studies and several subgroups, including African Americans, though its precision is lower among persons with preserved renal filtration. The MDRD equation also agrees very well with equations developed in African-American study populations (34).

This study was limited by the use of a single, untimed urine collection for assessment of albuminuria. However, urinary ACR measured in a spot urine sample closely correlates with timed urinary albumin excretion (35). Urinary albumin excretion also varies from day to day. A subsample of 1,241 NHANES III participants was reexamined a median of 2 weeks after the initial examination. The Spearman correlation coefficient for these two measurements was 0.61 ($p < 0.001$). Of those participants with microalbuminuria at the first visit, 63.2 percent had micro- or macroalbuminuria at the second visit. All sampled participants with macroalbuminuria at the first visit had micro- or macroalbuminuria at the second visit (12). Because of this variability in albumin excretion, the increased risks observed in our study probably underestimate the true risks associated with persistent microalbuminuria. The estimation of GFR from serum creatinine also has several limitations, including variation in creatinine production based on muscle mass and other factors (36). Laboratory variation also can have a significant impact on estimated GFR levels (21). To minimize these effects, we used an estimating equation which decreases bias, and we calibrated the serum creatinine measurements to the laboratory that generated the measurements from which the equation was developed (37). Even with these adjustments, estimated GFR is less accurate at higher levels of kidney function (i.e., lower serum creatinine levels), which may weaken any observed associations in the near-normal range (21, 38). The use of other estimating equations (e.g., Cockroft-Gault) was not explored. Estimates of GFR based on serum creatinine have a lower sensitivity for detecting decreased filtration in persons with decreased muscle mass. Even with the likely underestimation of filtration at moderately decreased levels of GFR and overestimation in persons with less muscle mass, this study indicates that lower estimated GFR is an independent risk factor after adjustment for albuminuria and other cardiovascular risk factors.

In summary, we found that both moderately decreased estimated GFR and albuminuria are independent risk factors for cardiovascular and all-cause mortality in the general population. These data support recent recommendations (1, 3) proposing the use of chronic kidney disease, as defined by estimated GFR or albuminuria, in risk stratification and treatment guidelines.

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