Age-Specific Association of Reduced Estimated Glomerular Filtration Rate and Albuminuria with All-Cause Mortality

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Summary

Background and objectives It has been suggested that reduced estimated GFR (eGFR) among older adults does not necessarily reflect a pathologic phenomenon.

Design, setting, participants, & measurements We examined the association between eGFR and albumin-to-creatinine ratio (ACR) and all-cause mortality stratified by age (45 to 59.9, 60 to 69.9, 70 to 79.9, and ≥80 years) among 24,350 U.S. adults in the population-based REasons for Geographic and Racial Differences in Stroke (REGARDS) study. A spot urine sample was used to calculate ACR, and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate eGFR. All-cause mortality was assessed over a median follow-up of 4.5 years.

Results Among participants ≥80 years of age (n = 1669), the age, race, gender, and geographic region of residence adjusted hazard ratios (95% confidence intervals) for mortality associated with eGFR levels of 45 to 59.9 and <45 ml/min per 1.73 m^2, *versus* ≥60 ml/min per 1.73 m^2, were 1.6 (1.3 – 2.1) and 2.2 (1.7 – 2.9), respectively. Also, among participants ≥80 years of age, the hazard ratios for mortality associated with ACR levels of 10 to 29.9, 30 to 299.9, and ≥300 mg/g, *versus* <10 mg/g, were 1.7 (1.3 – 2.1), 2.5 (1.9 – 3.3), and 5.1 (3.6 – 7.4), respectively. These associations were present after further multivariable adjustment and within the younger age groupings studied.

Conclusions These data suggest that reduced eGFR and albuminuria confer an increased risk for mortality in all age groups, including adults ≥80 years of age.

Clin J Am Soc Nephrol 6: 2200–2207, 2011. doi: 10.2215/CJN.02030311

Introduction

The prevalence of chronic kidney disease (CKD) is markedly higher at older ages (1–3). However, controversy exists as to whether CKD is a risk factor for adverse outcomes among older adults (4,5). Two large studies found that moderate reductions in eGFR were not associated with increased mortality among older adults (*i.e.*, ≥ 60 years of age in one study and ≥65 years in the other study) (6–8). In contrast, in meta-analyses of general population and high-risk cohorts conducted by the Chronic Kidney Disease Prognosis Consortium (CKD-PC), an association was present between eGFR <60 ml/min per 1.73 m^2 and increased all-cause and cardiovascular mortality among adults <65 years of age and their counterparts ≥65 years of age (9,10).

Until recently, there were limited published data on the association of albuminuria with mortality across the full range of age including older adults. In one study of patients with diabetes mellitus from the Veterans Administration Medical Centers, albumin-to-creatinine ratio (ACR) levels ≥30 mg/g were associated with all-cause mortality among adults ≥75 years of age (11). Additionally, in general population and high-risk cohorts included in the CKD-PC, higher levels of albuminuria were associated with increased all-cause mortality for adults <65 and ≥65 years of age (9,10).

Using age-specific estimated GFR (eGFR) cut-points for defining CKD in the National Kidney Foundation guidelines has been proposed (12). Also, most age-specific analyses of eGFR and ACR with outcomes have stratified the population at 65 years of age and have not investigated outcomes associated with reduced eGFR and albuminuria at older ages. Therefore, we evaluated the age-specific association between eGFR and albuminuria levels with all-cause mortality across a wide age distribution among participants in the REasons for Geographic and Racial Differences in Stroke (REGARDS) study. The REGARDS study enrolled U.S. adults ≥45 years of age, including many participants older than 80 years of age, African Americans, and women.

Study Population and Methods

Study Participants

The REGARDS study is a population-based investigation of stroke incidence among U.S. adults ≥45 years of age (13). The study was designed to oversample African Americans, residents of the stroke-belt region of the United States, and to provide approximate equal representation of men and women. Overall, 30,239 African-American and white U.S. adults were enrolled between January 2003 and October 2007. Participants receiving hemodialysis ($n = 54$) or those without urinary albumin and creatinine ($n = 1485$) or serum creatinine ($n = 958$) measurements, those without follow-up data ($n = 498$), or those who were missing covariable information ($n = 2894$) were excluded, leaving 24,350 participants with complete data for the analysis presented here. Compared with participants included in this analysis, those excluded for missing serum creatinine or urinary albumin and creatinine were older (65.6 *versus* 64.8 years) and more likely to be women (64% *versus* 54%) and African American (53% *versus* 40%). However, participants excluded for missing covariables were not markedly different from those included in this analysis with respect to eGFR and ACR levels. The institutional review boards governing research in human subjects at the participating centers approved the REGARDS study protocol, and all participants provided informed consent.

Data Collection

The REGARDS study data were collected through interview- and self-administered questionnaires and during an in-home study visit. The following were obtained via self-report: age, race, gender, education, physical activity, annual household income, cigarette smoking, self-rated health, antihypertensive medication use, and a prior diagnosis of coronary heart disease, stroke, atrial fibrillation, and diabetes mellitus. The in-home examination included clinical measurements, a pill bottle review, an electrocardiogram, and the collection of a fasting blood sample and urine sample. BP was measured two times, and waist circumference was measured midway between the lowest rib and the iliac crest with the participant standing.

Laboratory Measures

Serum creatinine assays were performed at the University of Vermont and calibrated with an isotope dilution mass spectroscopic standard (14). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate eGFR (15). Urinary albumin and creatinine were measured at the Department of Laboratory Medicine and Pathology at the University of Minnesota using the BN ProSpec Nephelometer from Dade Behring (Marburg, Germany) (16). C-reactive protein was measured using a high-sensitivity, particle-enhanced immunonepholometric assay, and levels ≥2 mg/L were defined as elevated. Total and HDL cholesterol and triglycerides were measured, and LDL cholesterol was calculated using the Freidewald equation (17). Diabetes mellitus was defined as fasting glucose ≥126 mg/dl, nonfasting glucose ≥200 mg/dl, or self-report of a prior diagnosis with current use of insulin or antidiabetes medication.

Outcome Assessment—All-Cause Mortality

Mortality, subsequent to the REGARDS study in-home examination and through September 30, 2010, was assessed through contact with proxies provided by the participant upon recruitment or during follow-up. If a proxy reported a participant had died, an interview was conducted with the next of kin listed on study forms. The REGARDS study confirmed dates of death through the Social Security death index, death certificates, or the national death index. Follow-up time was recorded as the number of days from the baseline in-home visit to a participant's confirmed date of death or their last REGARDS study telephone contact before September 30, 2010 for nondeceased participants.

Statistical Analyses

Characteristics of the REGARDS study population included in this analysis were calculated by age group (45 to 59.9, 60 to 69.9, 70 to 79.9, and ≥80 years), within each age group by level of eGFR (≥60, 45 to 59.9, and <45 ml/min per 1.73 m^2), and separately by level of ACR (<10, 10 to 29.9, 30 to 299.9, and ≥300 mg/g). All-cause mortality rates were calculated by age group and level of eGFR and by age group and level of ACR. Using age-stratified Cox proportional hazard models, the hazard ratios for all-cause mortality associated with eGFR and ACR levels, separately, were calculated. Initial models included adjustment for age, race, gender, and region of residence with subsequent models including additional adjustment for education, physical activity, income, current smoking, general health status, waist circumstance, systolic BP, diastolic BP, antihypertensive medicine use, diabetes mellitus, LDL cholesterol, HDL cholesterol, statin use, elevated C-reactive protein, history of coronary heart disease, stroke, atrial fibrillation, and ACR (for the model of eGFR and mortality) or eGFR (for the model of ACR and mortality). Additionally, for each age group separately, the joint effect of eGFR and ACR on all-cause mortality was determined using Cox proportional hazard models with eGFR ≥60 ml/min per 1.73 m^2 and ACR <10 mg/g serving as the referent group. Within each age group, trends in mortality rates and hazard ratios for mortality across eGFR and ACR categories were calculated by assigning the median eGFR or ACR value for participants in the category and modeling these variables as continuous independent variables. Two sensitivity analyses were conducted. First, the multivariable adjusted hazard ratios for all-cause mortality associated with ACR levels were determined by age group for men and women, separately, and participants with and without diabetes mellitus, separately. Second, we calculated age-specific hazard ratios for all-cause mortality associated with urinary albumin concentration rather than ACR. Multiplicative interaction between eGFR and age group, and ACR and age group, was assessed by comparing the log likelihoods for models with and without interaction terms for age group by eGFR categories and age group by ACR categories. Additive interaction was assessed via the relative excess risk due to interaction using the method described by Li and Chambless (18). SAS version 9.2 (SAS Institute, Cary, NC) was used for all analyses.

Results

Participant Characteristics

Participant characteristics are presented by age grouping in Table 1, by age grouping and eGFR level in Supplemental Table 1, and age grouping and ACR level in Supplemental Table 2. Within each age grouping, the prevalence of ACR levels ≥30 mg/g was higher at progressively lower eGFR levels. Also, the prevalence of eGFR <60 ml/min per 1.73 m^2 was higher at higher ACR levels within each age grouping.

Association of Reduced eGFR with Mortality by Age

The number of deaths among REGARDS study participants through September 30, 2010 are provided in Supplemental Table 3. There was a graded increase in crude mortality rates at lower eGFR levels within each age group (Figure 1 and Supplemental Table 4). Within each age grouping, the age, race, gender, and geographic region of residence adjusted hazard ratio for mortality increased progressively at lower eGFR levels (Table 2). The hazard ratios were attenuated, but the overall pattern of higher mortality at lower eGFR levels remained present after further multivariable adjustment. Neither multiplicative nor additive interaction between age and eGFR levels on all-cause mortality were present (each test for *P* interaction >0.1).

Association of Elevated ACR with Mortality by Age

Within each age grouping, the crude mortality rate increased at higher ACR levels (Figure 2 and Supplemental Table 5). After adjustment for age, race, gender, and geographic region of residence, there was a graded relationship between higher ACR levels and higher hazard ratios for all-cause mortality within each age grouping (Table 3). The magnitude of the hazard ratios was similar within each age grouping. This pattern remained present after further multivariable adjustment. Neither multiplicative nor additive interaction between age and ACR levels on all-cause mortality was present (each test for *P* interaction >0.1). Additionally, higher urinary albumin concentration was associated with increased hazard ratios for all-cause mortality in each age group (Supplementary Table 6). When stratified by gender, the association between higher ACR levels and increased hazard ratios for all-cause mortality was similar within each age group for men and women (Supplementary Tables 7 and 8). Also, higher ACR levels were associated with increased multivariable ad-

Table 1. Characteristics of the REasons for Geographic and Racial Differences in Stroke (REGARDS) study population by age group

Participant Characteristic	Age Group, Years			
	45 to 59.9 (*n* = 7630)	60 to 69.9 (*n* = 9228)	70 to 79.9 (*n* = 5823)	≥80 (*n* = 1669)
Age, years	54.3 (4.0)	64.4 (2.8)	73.9 (2.8)	83.1 (3.0)
Women, %	59.2	52.8	49.8	49.7
African American, %	44.4	40.1	36.0	31.5
Less than high school education, %	6.6	11.9	16.1	18.8
Region of residence, %				
nonbelt	41.4	44.2	47.7	52.0
stroke belt	36.1	35.2	32.6	29.6
stroke buckle	22.5	20.7	19.8	18.4
Household income <$20,000, %	14.3	18.8	24.0	28.7
Not physically active, %	30.3	32.2	35.3	45.1
Current smoker, %	19.8	14.6	9.1	3.4
Fair/poor self-rated health, %	17.2	17.0	16.8	18.2
Waist circumstance, cm	95.8 (16.4)	96.9 (15.3)	95.7 (14.7)	92.9 (13.2)
Systolic BP, mmHg	123.8 (16.1)	127.7 (15.8)	130.4 (17.1)	131.4 (17.7)
Diastolic BP, mmHg	77.6 (9.8)	76.8 (9.3)	75.2 (9.5)	73.3 (9.8)
Antihypertension medication use, %	44.6	57.0	61.5	62.4
Diabetes mellitus, %	16.7	22.2	22.1	17.9
LDL cholesterol, mg/dl	118.7 (35.0)	114.4 (34.8)	109.2 (33.4)	107.1 (32.4)
HDL cholesterol, mg/dl	52.1 (15.9)	51.8 (16.1)	51.9 (16.0)	52.8 (16.8)
Statin use, %	21.7	34.6	38.6	33.6
hsCRP ≥ 2 mg/L, %	53.1	54.4	51.5	47.8
History of CHD, %	9.0	16.9	24.8	28.9
History of stroke, %	3.5	5.6	7.9	9.2
Atrial fibrillation, %	5.9	7.7	11.1	14.6
Urine albumin concentration, mg/L	8 (4 to 17)	9 (5 to 19)	11 (6 to 25)	14 (6 to 31)
Urine creatinine concentration, mg/dl	131 (83 to 186)	125 (79 to 177)	117 (75 to 165)	105 (69 - 146)
ACR ≥ 30 mg/g, %	10.9	13.2	18.3	25.0
eGFR < 60 ml/min per 1.73 m^2, %	2.9	7.9	18.9	33.6

Numbers in table are mean (standard deviation) or percentage except for urine albumin concentration and urine creatinine concentration, which are median (25th to 75th percentiles). hsCRP, high sensitivity C-reactive protein; CHD, coronary heart disease; ACR, urinary albumin-to-creatinine ratio; eGFR, estimated GFR.

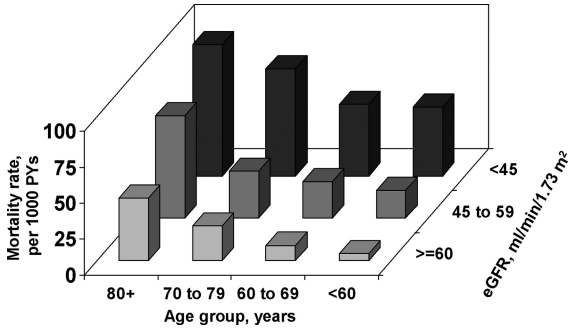

Figure 1. | All-cause mortality rates associated with level of eGFR and age group. eGFR, estimated GFR; PY, person-years; CI, confidence interval. See Supplemental Table 4 for all-cause mortality rates with 95% CIs.

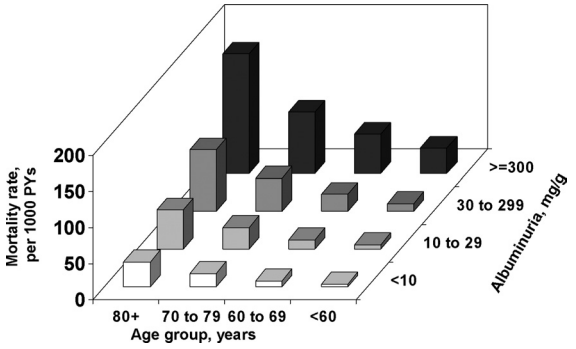

Figure 2. | All-cause mortality rates associated with level of albuminuria and age group. See Supplemental Table 5 for all-cause mortality rates with 95% CIs.

justed hazard ratios for mortality within each age group for participants with and without diabetes (Table 4).

Joint Effect of eGFR and ACR on Mortality by Age

The age-specific joint effect of eGFR and ACR levels on all-cause mortality are presented in Table 5. For each age grouping, higher hazard ratios for mortality were present at lower eGFR levels within each ACR level except 10 to 29.9 mg/g for participants 45 to 59.9 years of age and ≥300 mg/g among participants 70 to 79.9 and ≥80 years of age. When stratified by level of eGFR, higher age, race, gender, and geographic region of residence adjusted hazard ratios for mortality were present at higher ACR levels for participants 60 to 69.9, 70 to 79.9, and ≥80 years of age. Among participants 45 to 59.9 years of age, higher hazard ratios at higher ACR levels were present among individuals with eGFR levels ≥60 ml/min per 1.73 m^2 but not for their peers with eGFR levels of 45 to 59.9 or <45 ml/min per 1.73 m^2.

Discussion

In this population-based study of U.S. adults, reduced eGFR and elevated ACR were associated with higher rates of all-cause mortality in all age groups, including in individuals ≥80 years of age. A substantially increased risk for all-cause mortality was present for individuals with a moderate reduction in eGFR (45 and 59.9 ml/min per 1.73 m^2) and for ACR levels considered within the normal rage (10 to 29.9 mg/g). These results were robust to multivariable adjustment and remained present when the joint effect of eGFR and ACR was assessed.

The finding that reduced eGFR is associated with all-cause mortality regardless of age differs from a prior analysis of U.S. veterans (6). Among U.S. veterans ≥65 years of age in the prior study, the annual mortality rate was only approximately 10% higher among those with eGFR of 50 to 59 *versus* ≥60 ml/min per 1.73 m^2, which was attenuated after adjustment. However, in the meta-analysis of general

Table 2. Age-stratified hazard ratios for all-cause mortality associated with eGFR

	Age Group, Years			
	45 to 59.9	60 to 69.9	70 to 79.9	≥80
Age, race, gender, and region adjusted hazard ratios (95% CI)				
eGFR, ml/min per 1.73 m^2				
≥60	1 (ref)	1 (ref)	1 (ref)	1 (ref)
45 to 59.9	3.9 (2.1 to 7.0)	2.4 (1.8 to 3.1)	1.3 (1.1 to 1.6)	1.6 (1.3 to 2.1)
<45	7.8 (4.5 to 13.6)	4.5 (3.4 to 6.2)	3.1 (2.5 to 3.8)	2.2 (1.7 to 2.9)
P trend	<0.01	<0.01	<0.01	<0.01
Multivariable adjusted hazard ratios (95% CI)				
eGFR, ml/min per 1.73 m^2				
≥60	1 (ref)	1 (ref)	1 (ref)	1 (ref)
45 to 59.9	2.5 (1.3 to 4.6)	1.7 (1.3 to 2.3)	1.1 (0.9 to 1.3)	1.3 (1.0 to 1.7)
<45	3.5 (1.8 to 6.8)	2.2 (1.6 to 3.0)	1.9 (1.5 to 2.4)	1.5 (1.1 to 2.0)
P trend	<0.01	<0.01	<0.01	<0.01

Multivariable adjusted includes age, gender, race, region, education, physical activity, income, current smoking, general health status, waist circumstance, systolic BP, diastolic BP, antihypertensive medication use, diabetes mellitus, LDL cholesterol, HDL cholesterol, statin use, high sensitivity C-reactive protein ≥ 2 mg/L, history of coronary heart disease, self-reported stroke, atrial fibrillation, and albuminuria. CI, confidence interval; eGFR, estimated GFR; ref, reference.

Table 3. Age-stratified hazard ratios for all-cause mortality associated with level of albuminuria

	Age Group, Years			
	45 to 59.9	60 to 69.9	70 to 79.9	≥80
Age, race, gender, region adjusted hazard ratios (95% CI)				
albuminuria, mg/g				
<10	1 (ref)	1 (ref)	1 (ref)	1 (ref)
10 to 29.9	1.7 (1.2 to 2.5)	1.6 (1.3 to 2.0)	1.6 (1.4 to 2.0)	1.7 (1.3 to 2.1)
30 to 299.9	2.5 (1.7 to 3.8)	2.8 (2.2 to 3.5)	2.3 (1.9 to 2.8)	2.5 (1.9 to 3.3)
≥ 300	7.2 (4.4 to 11.8)	5.5 (4.0 to 7.4)	4.4 (3.4 to 5.9)	5.1 (3.6 to 7.4)
P trend	<0.01	<0.01	<0.01	<0.01
Multivariable adjusted hazard ratios (95% CI)				
albuminuria, mg/g				
<10	1 (ref)	1 (ref)	1 (ref)	1 (ref)
10 to 29.9	1.3 (0.9 to 2.0)	1.3 (1.02 to 1.6)	1.4 (1.2 to 1.7)	1.7 (1.3 to 2.2)
30 to 299.9	1.5 (0.98 to 2.4)	1.8 (1.4 to 2.3)	1.5 (1.2 to 1.9)	2.0 (1.5 to 2.7)
≥300	2.7 (1.3 to 5.7)	2.2 (1.5 to 3.2)	2.3 (1.6 to 3.3)	3.9 (2.5 to 6.2)
P trend	<0.01	<0.01	<0.01	<0.01

Multivariable adjusted includes age, gender, race, region, education, physical activity, income, current smoking, general health status, waist circumstance, systolic BP, diastolic BP, antihypertensive medicine use, diabetes mellitus, LDL cholesterol, HDL cholesterol, statin use, C-reactive protein ≥ 2 mg/L, history of coronary heart disease, self-reported stroke, atrial fibrillation, and estimated GFR. CI, confidence interval; ref, reference.

Table 4. Age-stratified hazard ratios of all-cause mortality associated with level of albuminuria for REGARDS study participants with (top panel) and without (bottom panel) diabetes mellitus

	Age Group, Years			
	45 to 59.9	60 to 69.9	70 to 79.9	≥80
Participants with diabetes mellitus				
albuminuria, mg/g				
<10	1 (ref)	1 (ref)	1 (ref)	1 (ref)
10 to 29.9	1.4 (0.6 to 3.48)	1.1 (0.8 to 1.7)	1.4 (0.96 to 2.0)	2.2 (1.1 to 4.4)
30 to 299.9	2.4 (1.00 to 5.8)	1.8 (1.2 to 2.6)	1.7 (1.2 to 2.5)	1.6 (0.8 to 3.2)
≥300	3.3 (1.1 to 10.3)	2.2 (1.3 to 3.9)	3.1 (1.9 to 5.2)	4.0 (1.4 to 11.3)
P trend	0.01	<0.01	<0.01	<0.01
Participants without diabetes mellitus				
albuminuria, mg/g	1 (ref)	1 (ref)	1 (ref)	1 (ref)
<10	1.4 (0.9 to 2.1)	1.4 (1.05 to 1.8)	1.4 (1.1 to 1.7)	1.7 (1.3 to 2.3)
10 to 29.9	1.4 (0.8 to 2.4)	1.9 (1.4 to 2.7)	1.5 (1.1 to 1.9)	2.3 (1.7 to 3.1)
30 to 299.9	3.3 (1.1 to 9.6)	2.1 (1.1 to 3.8)	2.2 (1.3 to 3.7)	4.8 (2.8 to 8.4)
≥300	0.06	<0.01	<0.01	<0.01

Data presented as multivariable adjusted HR (95% CI). Multivariable adjusted includes age, gender, race, region, education, physical activity, income, current smoking, general health status, waist circumstance, systolic BP, diastolic BP, antihypertensive medicine use, LDL cholesterol, HDL cholesterol, statin use, C-reactive protein ≥ 2 mg/L, history of coronary heart disease, self-reported stroke, self-reported or electrocardiogram evidence of atrial fibrillation, and estimated GFR. HR, hazard ratio.

population studies conducted by the CKD-PC, reduced eGFR was associated with increased hazard ratios for all-cause mortality among individuals <65 and ≥65 years of age. The hazard ratio comparing eGFR levels of 45 to 95 ml/min per 1.73 m^2 was 2.14 (95% confidence interval [CI]: 1.56 to 2.92) and 1.60 (95% CI: 1.46 to 1.75) for individuals <65 and ≥65 years of age, respectively (9).

Although the hazard ratios for mortality associated with increased ACR were similar within each age group, consistent with the CKD-PC data cited above, the hazard ratios associated with an eGFR of 45 to 59.9 ml/min per 1.73 m^2 were closer to the null for the older compared with younger age groups in the study presented here. However, the comparison of the magnitude of hazard ratios across subgroups of the population with different baseline risk for outcomes should be undertaken cautiously. As described by Howard, there may be a natural tendency to infer that a smaller hazard ratio among older adults means that a risk factor has decreased importance in this subgroup (19). In fact, a smaller relative increase in a group

Table 5. Age-stratified HR for all-cause mortality associated with level of albuminuria and eGFR

	eGFR, ml/min per 1.73 m^2			*P* Trend
	≥60 years	45 to 59.9 years	<45 years	
Age 45 to 59.9 years				
ACR, mg/g				
<10	1 (ref)	4.5 (1.8 to 11.1)	4.7 (0.7 to 34.2)	<0.01
10 to 29.9	1.8 (1.2 to 2.7)	1.8 (0.3 to 13.0)	NA	0.91
30 to 299.9	2.3 (1.5 to 3.7)	8.4 (2.6 to 26.5)	9.7 (3.0 to 30.9)	<0.01
≥300	4.7 (2.2 to 9.7)	10.5 (3.3 to 33.5)	14.2 (7.3 to 27.7)	0.02
P trend	<0.01	0.18	0.18	–
Age 60 to 69.9 years				
ACR, mg/g				
<10	1 (ref)	1.9 (1.2 to 3.1)	2.5 (1.0 to 6.1)	<0.01
10 to 29.9	1.5 (1.2 to 1.9)	3.5 (2.1 to 5.9)	4.6 (2.1 to 10.5)	<0.01
30 to 299.9	2.6 (2.0 to 3.3)	4.5 (2.7 to 7.3)	5.9 (3.3 to 10.5)	<0.01
≥300	4.0 (2.5 to 6.3)	6.1 (3.1 to 11.9)	9.8 (6.4 to 15.1)	<0.01
P trend	<0.01	<0.01	<0.01	–
Age 70 to 79.9 years				
ACR, mg/g				
<10	1 (ref)	1.1 (0.8 to 1.6)	2.1 (1.2 to 3.6)	0.03
10 to 29.9	1.5 (1.3 to 1.9)	1.8 (1.3 to 2.7)	4.3 (2.8 to 6.4)	<0.01
30 to 299.9	2.1 (1.6 to 2.6)	2.5 (1.7 to 3.6)	5.0 (3.6 to 7.2)	<0.01
≥300	3.8 (2.5 to 5.6)	5.6 (3.3 to 9.4)	5.8 (3.9 to 8.9)	0.12
P trend	<0.01	<0.01	0.02	–
Age ≥ 80 years				
ACR, mg/g				
<10	1 (ref)	1.4 (0.9 to 2.2)	1.6 (0.9 to 2.8)	0.04
10 to 29.9	1.6 (1.2 to 2.3)	2.3 (1.5 to 3.5)	2.2 (1.2 to 3.7)	0.05
30 to 299.9	1.9 (1.3 to 2.7)	3.0 (2.0 to 4.5)	5.2 (3.5 to 7.6)	<0.01
≥300	6.2 (3.5 to 10.9)	5.7 (3.1 to 10.6)	4.9 (2.7 to 8.9)	0.74
P trend	<0.01	<0.01	<0.01	–

P interaction between ACR and eGFR > 0.1 for each age group. HRs are adjusted for age, race, gender, and geographic region of residence. HR, hazard ratio; eGFR, estimated GFR; ACR, albumin-to-creatinine ratio; ref, reference NA, only five participants in this cell with zero deaths.

with a higher base mortality rate may have a higher public health effect. As noted in Figures 1 and 2, despite lower hazard ratios for eGFR levels of 45 to 59.9 *versus* ≥60 ml/min per 1.73 m^2 at older age, the absolute differences in mortality rates by level of eGFR and ACR were similar across age groups. Additionally, even after multivariable adjustment for potential confounders, reduced eGFR and ACR levels were associated with increased hazard ratio for mortality, and additive interaction between age and eGFR and age and ACR with mortality was not present.

Higher levels of albuminuria have been reported to be associated with increased mortality in prior studies of older adults with diabetes mellitus and in the general population (11,20). O'Hare and colleagues reported ACR levels ≥30 mg/g to be associated with increased mortality, regardless of age, among U.S. veterans with diabetes mellitus (11). Also, the hazard ratio for all-cause mortality associated with higher ACR levels (42.5 *versus* 5.1 mg/g) was similar for adults <65 years of age (1.49, 95% CI: 1.40 to 1.59) and ≥65 years of age (1.52, 95% CI: 1.45 to 1.61) in the CKD-PC (9). The study presented here extends the findings from U.S. veterans and the CKD-PC in several important ways. Most notably, all-cause mortality was investigated in narrow age bands (*i.e.*, 45 to 59, 60 to 69, 70 to 79, and ≥80 years of age) in this study. Such data were not reported by the CKD-PC. Compared with the study of U.S. veterans, REGARDS enrolled participants with and without diabetes mellitus and higher ACR was associated with increased hazard ratios for mortality in each of these subgroups. Results were consistent when urine albumin concentration was used in place of ACR, suggesting that the association of ACR with all-cause mortality is not due to reduced urine creatinine concentration.

The use of age-specific cutpoints (*e.g.*, eGFR < 60 ml/min per 1.73 m^2 for adults <65 years of age and <45 ml/min per 1.73 m^2 for adults ≥65 years of age) for defining reduced eGFR has been suggested (4). Additionally, incorporation of ACR level for diagnosing CKD in older adults has also been proposed (21). The argument for age-specific eGFR cutpoints is based partially on the large number of older adults with reduced eGFR but without evidence of kidney damage (5). However, among individuals with eGFR levels of 45 to 59.9 ml/min per 1.73 m^2 in this study, the proportion with ACR ≥30 mg/g was higher for those ≥80 years of age (33.0%) than their younger counterparts (24.4%, 27.9%, and 25.0% for participants 70 to 79.9, 60 to 69.9, and 45 to 59.9 years of age, respectively). Furthermore, within each age group, a graded relationship between lower levels of eGFR and increased mortality was present among individuals with ACR < 10 mg/g. Beyond

these potential implications for CKD diagnosis, the current findings highlight the importance of eGFR and ACR for assessing prognosis in older adults. Although among the "oldest old" a disease-oriented focus on diagnosis becomes less important, eGFR and ACR may serve as important tools for risk assessment, informing broader clinical decisions as part of individually tailored, patient-oriented care plans. Further studies are needed to understand the effect of identifying older adults with reduced eGFR and increased ACR for individual patients and from a public health standpoint; however, the data presented here do not support the need for age-specific eGFR or ACR cutpoints.

The results of this study should be interpreted within the context of certain limitations. Measurements of eGFR and ACR were obtained on a single occasion. Many individuals with high ACR levels may not have persistent albuminuria (22). Although REGARDS study visits were conducted in the morning, the spot urine samples collected were not necessarily obtained from a first void. Another limitation is that the only outcome was all-cause mortality. End-stage renal disease is being identified in the REGARDS study; however, not enough cases have occurred to date to calculate reliable estimates by age and eGFR or ACR level. Although we adjusted for several potential confounders, the possibility of residual confounding remains present. Despite these limitations, the study presented here has many strengths. Most notable are the population-based sample of the REGARDS study, the measurement of serum creatinine and urinary albumin and creatinine following a standardized protocol, and the active follow-up of participants for all-cause mortality. Additionally, there were many REGARDS study participants ≥80 years of age with complete data available for the analysis presented here. This large sample size allowed for the estimation of all-cause mortality by the joint effect of eGFR and ACR levels.

In conclusion, this study identified a strong relationship between reduced eGFR and higher levels of ACR with all-cause mortality across a broad age range, including adults ≥80 years old. Despite a decline in the hazard ratio for all-cause mortality associated with reduced eGFR and higher ACR with age, the difference in absolute risk for all-cause mortality associated with reduced eGFR and increased ACR remained constant across age groupings. Future studies are needed to evaluate the association of reduced eGFR and albuminuria with other outcomes (*e.g.*, cardiovascular disease, end-stage renal disease, and geriatric conditions such as falls, low mobility, and functional decline) across the full range of age. In the interim, these data suggest that age-specific eGFR or ACR cutpoints for identifying high risk for mortality are not needed and may result in the underappreciation of the excess all-cause mortality risk associated with reduced eGFR and increased ACR for all age groups including individuals ≥80 years of age.

Acknowledgments

This research project is supported by a cooperative agreement U01 NS041588 from the National Institute of Neurologic Disorders and Stroke, National Institutes of Health, and the Department of Health and Human Services. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Neurologic Disorders and Stroke or the National Institutes of Health. Representatives of the funding agency have been involved in the review of the manuscript but not directly involved in the collection, management, analysis, or interpretation of the data. Additional funding was provided by an investigator-initiated grant-in-aid from Amgen Corporation. Amgen did not have any role in the design and conduct of the study; the collection, management, analysis, or interpretation of the data; or the preparation or approval of the manuscript. Dr. Muntner and Dr. Gao had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. These results were presented in abstract form at the 2011 World Congress of Nephrology; April 8 through 12, 2011; Vancouver, British Columbia, Canada.

Disclosures

None.

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Received: March 2, 2011 **Accepted:** May 6, 2011

Published online ahead of print. Publication date available at www.cjasn.org.