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Level of Kidney Function as a Risk Factor for Atherosclerotic Cardiovascular Outcomes in the Community

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OBJECTIVES The goal of this study was to determine whether the level of kidney function is an independent risk factor for atherosclerotic cardiovascular disease (ASCVD) outcomes in the Atherosclerosis Risk in Communities (ARIC) study, a prospective cohort study of subjects aged 45 to 64 years.

BACKGROUND The level of kidney function is now recognized as a risk factor for ASCVD outcomes in patients at high risk for ASCVD, but it remains unknown whether the level of kidney function is a risk factor for ASCVD outcomes in the community.

METHODS Cox proportional-hazards regression was used to evaluate the association of glomerular filtration rate (GFR) with ASCVD after adjustment for the major ASCVD risk factors in 15,350 subjects. We searched for nonlinear relationships between GFR and ASCVD.

RESULTS During a mean follow-up time of 6.2 years, 965 (6.3%) of subjects had ASCVD events. Subjects with GFR of 15 to 59 ml/min/1.73 m^2 (n = 444, hazard ratio 1.38 [1.02, 1.87]) and 60 to 89 ml/min/1.73 m^2 (n = 7,665, hazard ratio 1.16 [1.00, 1.34]) had an increased adjusted risk of ASCVD compared with subjects with GFR of 90 to 150 ml/min/1.73 m^2. Each 10 ml/min/1.73 m^2 lower GFR was associated with an adjusted hazard ratio of 1.05 (1.02, 1.09), 1.07 (1.01, 1.12), and 1.06 (0.99, 1.13) for ASCVD, de novo ASCVD, and recurrent ASCVD, respectively. A nonlinear model did not fit the data better than a linear model.

CONCLUSIONS The level of GFR is an independent risk factor for ASCVD and de novo ASCVD in the ARIC study. (J Am Coll Cardiol 2003;41:47–55) © 2003 by the American College of Cardiology Foundation

It has recently been recognized that a decreased level of kidney function is an independent risk factor for all-cause mortality as well as adverse cardiovascular disease (CVD) outcomes including myocardial infarction, stroke, and progression of heart failure (1–4). This risk has, in particular, been noted in subjects who already have some form of CVD (1–3) or in subjects at high risk for the development of CVD (4).

There is conflicting data, however, as to whether the level of kidney function is an independent risk factor for CVD outcomes in a community cohort of subjects who were not selected for being at high risk for CVD. The level of kidney function was not found to be a risk factor for CVD outcomes in the Framingham cohort (5) or for CVD death in the National Health and Nutrition Examination Survey (NHANES) I (6), but was found to be a risk factor for CVD death in an analysis of the NHANES II (7).

In the current analysis, we evaluated the relationship between level of kidney function and atherosclerotic CVD (ASCVD) in the Atherosclerosis Risk in Communities (ARIC) Study. Although data from ARIC are limited by the absence of urinalyses, the current analysis overcomes many of the limitations of prior studies that have assessed the relationship between level of kidney function and CVD outcomes by estimating kidney function both as a continuous as well as a categorical variable, evaluating both de novo and recurrent ASCVD, and using estimated glomerular filtration rate (GFR) rather than serum creatinine to assess level of kidney function. We also explore the possibility of nonlinear relationships between GFR and the risk of ASCVD, and search for potential interactions between level of kidney function and traditional CVD risk factors.

METHODS

Design. ARIC is a community-based longitudinal study of coronary heart disease (CHD) and stroke in persons ages 45 to 64 years. A total of 15,792 study participants were recruited from the city of Jackson, Mississippi; Forsyth

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Abbreviations and Acronyms

ARIC	= Atherosclerosis Risk in Communities Study
ASCVD	= atherosclerotic cardiovascular disease
CHD	= coronary heart disease
CVD	= cardiovascular disease
GFR	= glomerular filtration rate
HDL	= high-density lipoprotein
K/DOQI	= Kidney Disease Outcomes Quality Initiative
LDL	= low-density lipoprotein
LVH	= left ventricular hypertrophy
MDRD	= Modification of Diet in Renal Disease
NHANES	= National Health and Nutrition Examination Survey
NKF	= National Kidney Foundation

County, North Carolina; the northwestern suburbs of Minneapolis, Minnesota; and Washington County, Maryland. There is an extensive follow-up for ascertainment of ASCVD events (defined by myocardial infarction, cardiac procedure, CHD death, and stroke). Details of recruitment and the study have been extensively described elsewhere (8). The present study is a secondary analysis of the ARIC public use data to ascertain the relationship of baseline kidney function to ASCVD outcomes.

Ascertainment of the level of kidney function. Serum creatinine was measured using the modified kinetic Jaffe method in 15,582 subjects at baseline. Level of GFR is usually regarded as the best overall index of the level of kidney function because serum creatinine is determined by a number of factors other than GFR, such as gender, age, muscle mass, and ethnicity. Glomerular filtration rate was, therefore, estimated using a formula developed and validated in the Modification of Diet in Renal Disease (MDRD) study (9,10) as follows:

$$\text{GFR} = 186.3 \times (\text{serum creatinine}^{-1.154}) \times (\text{age}^{-0.203}) \times 1.212\ (\text{if black}) \times 0.742\ (\text{if female}) \quad [1]$$

Serum creatinine is measured in mg/dl, age in years, and GFR is expressed as ml/min/1.73 m^2. Because serum creatinine values may vary between different labs, and in order to more accurately use the formula developed in the MDRD study, we indirectly calibrated ARIC serum creatinine values to the Cleveland Clinic Laboratory (where serum creatinine was measured in the MDRD study) by using NHANES III data. Because both NHANES III and ARIC were designed as representative samples of the population, and NHANES III data have been directly compared with the MDRD samples (11), it was assumed that the mean serum creatinine for a given age, gender, and race should be comparable in the two studies. A linear regression of data combining the two studies showed that serum creatinine levels were 0.24 mg/dl higher among ARIC participants during the baseline examination than among NHANES III participants after adjustment for age, gender, and race and limiting the analysis to individuals age 45 to 65 years who were white or black and had a serum creatinine <2.0 mg/dl at baseline. This value was subtracted from serum creatinine before application of the MDRD equation (as shown earlier) in order to obtain a more valid estimate of GFR.

Our objective was to evaluate the association of kidney function with ASCVD in subjects with GFR between 15 to 150 ml/min/1.73 m^2. We chose this range for two reasons. First, a GFR of 15 ml/min/1.73 m^2 is defined as kidney failure in the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines (12). A total of 20 subjects had estimated GFR values <15 ml/min/1.73 m^2. Second, a GFR of 150 ml/min/1.73 m^2 is approximately the upper limit of most normal GFR measurements in this age group (2 SD above the mean) (13), and values above this range (n = 212 [1.4%] of ARIC participants) are potentially less accurate estimates of level of kidney function. The study population, therefore, included 15,350 subjects (15,582 − 20 − 212).

Baseline variables. Baseline characteristics included demographics (age, ethnicity, gender, and educational level); lifestyle (smoking, alcohol intake, and exercise intensity); past medical history (baseline ASCVD, diabetes mellitus, hypertension, left ventricular hypertrophy [LVH] defined by voltage in AVL being >11 mm by electrocardiogram); laboratory variables (albumin, creatinine, total cholesterol, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, triglycerides, fibrinogen, uric acid, and hematocrit); physical examination (weight, body mass index, waist-to-hip ratio, systolic and diastolic blood pressure); and medication use as grouped in the public use database (vasodilating agents, cardiac agents, aspirin/nonsteroidals, lipid-lowering agents, and diuretics). Of note, <4% of subjects in ARIC were receiving angiotensin-converting enzyme inhibitors at baseline (14). Urinalyses were not performed in ARIC. The methods employed by the ARIC investigators for the surveillance and ascertainment of ASCVD events have been described elsewhere (15).

Outcomes. We evaluated four outcomes: 1) ASCVD, 2) de novo ASCVD (defined as an ASCVD event in subjects without ASCVD at baseline), 3) recurrent ASCVD (defined as ASCVD in patients with baseline ASCVD), and 4) all-cause mortality.

For de novo disease, because there were missing baseline data on cerebrovascular disease in 3,093 subjects, we performed analyses both by using the data available as well as using multiple imputation techniques for missing data (16). For all-cause mortality, we present the data as the proportion of deaths in the groups stratified by level of kidney function.

Statistical analysis. Means, SD, and percentages were used to describe the baseline characteristics. Data were stratified into three groups by level of kidney function, namely, GFR of 15 to 59 ml/min/1.73 m^2, 60 to 89 ml/min/1.73 m^2, and GFR of 90 to 150 ml/min/1.73 m^2. These cut-points were chosen as an estimated GFR of 90 ml/min/1.73 m^2 or

greater represents a normal GFR at any age, while a GFR of 60 to 89 ml/min/1.73 m^2 represents a mild decrease in GFR, and a GFR of 15 to 59 ml/min/1.73 m^2 represents a moderate to severe decrease in GFR as defined by the NKF K/DOQI guidelines (12). We did not include a separate group with GFR between 15 to 30 ml/min/1.73 m^2 as only 12 subjects had GFR within this range. Chi-squared tests and the analysis of variance were used to compare baseline data between these groups.

Kaplan-Meier survival analysis was used to compare survival time among the three groups stratified by level of kidney function. The log-rank statistic was used to test for differences between groups. Cox proportional hazards regression was used to adjust for covariates. Multivariable stepwise selection models were constructed and estimated GFR modeled as a continuous variable and as a categorical variable, with the cut-points as described above. All analyses adjusted for traditional CVD risk factors as defined in the Framingham population, including age, gender, smoking status, diabetes, systolic blood pressure, total cholesterol, HDL and LDL cholesterol, and LVH by electrocardiogram, as well as baseline variables that were significantly and independently related to ASCVD, de novo ASCVD, and recurrent ASCVD in univariate analyses ($p < 0.05$). The proportional hazard assumption was tested using a time-varying coefficient model testing for global and individual covariates.

We then repeated the above analyses first by including patients with GFR >150 ml/min/1.73 m^2 and second by using serum creatinine (rather than estimated GFR) as the continuous variable of interest. These additional analyses were performed primarily to confirm the internal consistency of our results.

We then performed analyses to define the best form of the relationship between level of kidney function and ASCVD. Curvilinear associations of GFR were tested by including a quadratic term and retaining it when significant ($p < 0.05$), and by fitting parametric smoothing splines with five knots (at 0.05, 0.275, 0.5, 0.725, 0.95 quantiles of GFR) to determine the functional form of GFR that best explained its relationship to ASCVD. The results were displayed by graphing the five-year predicted probability of ASCVD versus GFR. Because the prediction for each individual includes their 19 baseline covariates, it is considered unadjusted. Adjusted predicted probabilities at a given GFR were obtained by assuming all cohort members had this given GFR (for example 60 ml/min/1.73 m^2) and calculating the average five-year predicted probability across the entire cohort (17). Values were calculated in 5 ml/min/1.73 m^2 increments and the results graphed versus GFR using a smoothing function. Adjusted values for a linear model and a cubic spline model were compared graphically to each other and the unadjusted risk.

We tested for interactions between estimated GFR and traditional ASCVD risk factors with ASCVD as the outcome of interest.

Data was analyzed using the SAS version 8.1 (SAS Institute, Cary, North Carolina). S-Plus (MathSoft, Seattle, Washington) was used to explore nonlinear associations in these models. Testing was two sided, and p values <0.05 were considered statistically significant.

RESULTS

Baseline characteristics. The baseline characteristics of the 15,350 subjects are given in Table 1. The baseline serum creatinine was 1.1 mg/dl with a range of 1.0 to 5.0 mg/dl, and the baseline estimated GFR was 92 ml/min/1.73 m^2 with a range of 16 to 149 ml/min/1.73 m^2. The mean age was 54.2 years, and 45% and 26% were men and African Americans, respectively. A total of 5% and 4.8% of the subjects had CHD and cerebrovascular disease at baseline, respectively.

Association of reduced kidney function with other baseline factors. A total of 444 individuals (2.8%) had a GFR of 15 to 59 ml/min/1.73 m^2 with the mean GFR being 52.3 ml/min/1.73 m^2. A total of 7,665 individuals (49.9%) had a GFR of 60 to 89 ml/min/1.73 m^2 with the mean GFR being 79.3 ml/min/1.73 m^2.

The prevalence of baseline ASCVD and risk factors for ASCVD tended to be higher in the group with lower baseline GFR (Table 1). For example, subjects with lower GFR had a higher prevalence of CHD, cerebrovascular disease, diabetes mellitus, and hypertension, as well as higher mean serum total cholesterol, LDL cholesterol, and triglycerides.

Outcomes. The maximum duration of follow-up in the public use data was 8.1 years with a mean follow-up of 6.2 years. There were 775 (5%) deaths (Table 2). A total of 174 (22.4%) of the deaths were directly attributable to ASCVD. A total of 965 (6.3%) of subjects experienced ASCVD events. Of these events, 767 (79.4%) were due to CHD, and 198 (20.6%) were due to cerebrovascular disease.

Kaplan-Meier survival analysis showed a greater probability of ASCVD ($p < 0.001$), de novo ASCVD ($p < 0.001$), and recurrent ASCVD ($p = 0.02$) events and all-cause mortality ($p < 0.001$) in subjects with lower GFR (Figs. 1 and 2, Table 2).

Multivariable models. After adjusting for traditional ASCVD risk factors as well as variables significant in univariate analysis in the Cox proportional hazards models, the hazard ratios for ASCVD and de novo ASCVD were significantly higher in subjects with GFR of 15 to 59 ml/min/1.73 m^2 and GFR of 60 to 89 ml/min/1.73 m^2 compared with subjects with GFR of 90 to 150 ml/min/1.73 m^2 (the reference group) (Table 3). Similar results were obtained when subjects with estimated GFRs >150 ml/min/1.73 m^2 were included in the analyses.

Expressing GFR as a continuous variable, and after adjusting for traditional ASCVD risk factors as well as variables significant in univariate analysis in the Cox proportional hazards models, GFR remained a significant risk

Table 1. Baseline Characteristics of Study Population

Baseline Variables	GFR 15–150 (Total) ml/min/1.73 m^2 (N = 15,350) 92 ± 18.9	GFR 15–59 ml/min/1.73 m^2 (N = 444) 52.3 ± 7.9	GFR 60–89 ml/min/1.73 m^2 (N = 7,665) 79.3 ± 7.6	GFR 90–150 ml/min/1.73 m^2 (N = 7,241) 108 ± 13.1	p Value
Demographic data					
Age (yrs)	54.2 ± 5.7	56.7 ± 5.8	54.6 ± 5.6	53.6 ± 5.8	< 0.001
Male	45.2	37.2	47.0	43.8	< 0.001
African American	25.9	22.3	15.1	37.6	< 0.001
Education (high school and lower)	44.0	37.8	45.6	42.6	< 0.001
Physical characteristics					
Weight (kgs)	78.7 ± 16.6	80.3 ± 16.1	78.9 ± 16.3	78.5 ± 16.9	0.03
Waist/hip ratio	0.93 ± 0.1	0.94 ± 0.1	0.93 ± 0.1	0.92 ± 0.1	0.001
Body mass index	27.7 ± 5.3	28.8 ± 5.5	27.6 ± 5.0	27.8 ± 5.7	0.001
Lifestyle characteristics					
Current smokers	26.0	21.2	22.0	30.6	< 0.001
Smoking (pack yrs)	16.1 ± 21.8	18.7 ± 23.5	15.2 ± 21.2	16.9 ± 22.3	< 0.001
Current drinkers	56.1	47.7	59.2	53.4	0.001
Alcohol (g/week)	42.4 ± 95.8	25.1 ± 58.5	39.9 ± 85.3	46.1 ± 107.4	< 0.001
Exercise (low- vs. high-intensity)	79.8	84.6	76.6	82.9	0.001
Baseline past medical history					
Diabetes mellitus	11.6	24.3	9.6	12.8	< 0.001
Hypertension	34.6	58.0	33.6	34.3	< 0.001
Coronary heart disease	5.0	11.4	5.5	4.1	< 0.001
Cerebrovascular disease	4.8	9.8	4.9	4.4	< 0.001
Atherosclerotic cardiovascular disease*	9	19.1	10.0	8.2	< 0.001
Left ventricular hypertrophy by ECG†	4.8	4.7	4.3	5.4	0.007
Clinical exam					
Systolic blood pressure (mm Hg)	121.2 ± 18.8	125.8 ± 22.8	120.1 ± 18.3	122.0 ± 18.9	< 0.001
Diastolic blood pressure (mm Hg)	73.66 ± 11.2	74.07 ± 11.6	73.19 ± 10.8	74.13 ± 11.6	< 0.001
Laboratory measurements					
Albumin (mg/dl)	3.87 ± 0.3	3.82 ± 0.3	3.89 ± 0.3	3.86 ± 0.3	< 0.001
Creatinine (mg/dl)	1.1 ± 0.2	1.6 ± 0.4	1.2 ± 0.2	1.0 ± 0.1	< 0.001
Total cholesterol (mg/dl)	215.1 ± 42.0	224.3 ± 48.4	216.2 ± 41.6	213.4 ± 41.9	< 0.001
HDL cholesterol (mg/dl)	51.6 ± 17.0	48.8 ± 17.5	50.4 ± 16.7	52.9 ± 17.3	< 0.001
LDL cholesterol (mg/dl)	137.9 ± 39.3	145.0 ± 44.2	139.4 ± 39.0	135.8 ± 39.1	< 0.001
Triglycerides (mg/dl)	131.6 ± 89.3	160.6 ± 111.1	134.6 ± 87.4	126.7 ± 89.3	< 0.001
Fibrinogen (mg/dl)	303.2 ± 65.0	331.8 ± 77.7	299.4 ± 63.2	305.4 ± 65.4	< 0.001
Uric acid (mg/dl)	6.1 ± 1.6	7.4 ± 2.0	6.2 ± 1.5	5.8 ± 1.5	< 0.001
Hematocrit (%)	41.7 ± 4.0	40.8 ± 4.8	42.1 ± 3.9	41.4 ± 4.0	< 0.001
Medications:					
Vasodilating agents	3.8	11.5	3.9	3.2	< 0.001
Diuretics	17.4	42.3	17.3	16.0	< 0.001
Cardiac agents‡	12.5	28.4	13.9	10.1	< 0.001
Aspirin/nonsteroidals	40.6	49.8	42.8	37.7	< 0.001
Lipid-lowering medications	1.3	2.5	1.6	0.9	< 0.001

Continuous variables are presented as mean ± SD while categorical variables are expressed as percent. P values are for the analysis of variance for continuous and chi-square for categorical variables for differences between glomerular filtration rate (GFR) groups (columns 3, 4, and 5). *Atherosclerotic cardiovascular disease is a composite of coronary disease and cerebrovascular disease; †Left ventricular hypertrophy (LVH) defined by voltage in AVL being >11 mm by electrocardiogram (ECG); ‡Cardiac agents not including vasodilator agents, diuretics, aspirin/nonsteroidals, or lipid-lowering medications.

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

factor for ASCVD and de novo ASCVD and showed a trend towards being a risk factor for recurrent ASCVD (Table 3). That is, a 10 ml/min/1.73 m^2 lower GFR was associated with an adjusted hazard ratio of 1.05 (1.02, 1.09), 1.07 (1.01, 1.12), and 1.06 (0.99, 1.13), for total ASCVD, de novo ASCVD, and recurrent ASCVD, respectively.

The results were essentially identical when subjects with estimated GFRs >150 ml/min/1.73 m^2 were included in the analyses. For example, for every 10 ml/min/1.73 m^2 lower estimated GFR, the hazard ratio for ASCVD was 1.05 (1.02, 1.09; p = 0.002).

When serum creatinine was used as the primary measure of level of kidney function, each 0.1 mg/dl increase in serum creatinine was associated with a 1.04 (1.01, 1.07; p = 0.003) increase in hazard ratio for development of ASCVD.

The test for assumption of proportional hazards was met for ASCVD, de novo ASCVD, and recurrent ASCVD. For the de novo analysis, data using multiple imputation techniques (for cerebrovascular disease prevalence) showed similar results to that using the data available.

Nonlinear associations with ASCVD. The five-year probability of ASCVD events as a function of baseline GFR is shown in Figure 2. Without adjustment for covariates, the

Table 2. All-Cause Mortality, ASCVD, De Novo ASCVD, and Recurrent ASCVD Events and Rates, Stratified by Level of Kidney Function

	GFR 15–150 (Total) ml/min/1.73 m^2	GFR 15–59 ml/min/1.73 m^2	GFR 60–89 ml/min/1.73 m^2	GFR 90–150 ml/min/1.73 m^2	Log-Rank p Value‡
All-cause mortality					
% Events	5.0% (775/15,350)	16.7% (74/444)	4.4% (337/7,665)	5.0% (364/7,241)	< 0.001
Person-years at risk	95,411	2,554	47,631	45,226	
Events per 1,000 person-years	8.1	29.0	7.1	7.7	
ASCVD events					
% Events	6.3% (965/15,350)	14.2% (63/444)	6.6% (507/7,665)	5.5% (395/7,241)	< 0.001
Person-years at risk	93,172	2,465	46,445	44,262	
Events per 1,000 person-years	10.4	25.6	10.9	8.9	
De novo ASCVD*					
% Events	4.5% (471/10,420)	9.3% (26/280)	4.8% (253/5,232)	3.9% (192/4,908)	< 0.001
Person-years at risk	60,615	1,546	30,432	28,637	
Events per 1,000 person-years	7.8	16.8	8.3	6.7	
Recurrent ASCVD†					
% Events	19.7% (275/1,393)	28.4% (23/81)	20.4% (151/739)	17.6% (101/573)	0.02
Person-years at risk	7,461	378	3,966	3,117	
Events per 1,000 person-years	36.9	60.8	38.1	32.4	

*De novo ASCVD = events in subjects without baseline ASCVD; †Recurrent ASCVD = events in subjects with baseline ASCVD; ‡p values are for the log-rank for the Kaplan-Meier differences between GFR groups (columns 3, 4, and 5). Note: Events in subjects with de novo and recurrent ASCVD do not add up to the total ASCVD because of subjects with missing data regarding baseline cerebrovascular status.

ASCVD = atherosclerotic cardiovascular disease, de novo ASCVD plus recurrent ASCVD; GFR = glomerular filtration rate.

probability of developing ASCVD increases markedly below a GFR of approximately 75 ml/min/1.73 m^2. After adjustment for covariates, the effect of GFR on ASCVD is diminished but remains present. For example, the five-year probability of ASCVD increases from approximately 4% to 6% with a decrease in GFR from 150 ml/min/1.73 m^2 to 30 ml/min/1.73 m^2. The nonparametric smoothing method led us to explore both linear and piecewise linear forms for GFR. The quadratic term was not significant. A GFR value of 78 ml/min/1.73 m^2 was found to be the optimum knot point of a two-slope model based on maximizing the log likelihood. The resulting two-slope model (relative hazard of 1.03 for every 10 ml/min/1.73 m^2 decrease in GFR above 78 ml/min/1.73 m^2, and 1.11 for every 10 ml/min/1.73 m^2 decrease in GFR above 78 ml/min/1.73 m^2) was not, however, statistically better than a one-slope linear model. Figure 2 is consistent with the latter in that it demonstrates the similarity between the adjusted cubic spline with one knot and linear models.

Interactions. There was a significant interaction between GFR and the presence of LVH. That is, in subjects with LVH, a 10 ml/min/1.73 m^2 lower GFR was associated with a hazard ratio of 1.19 for ASCVD, while in subjects without LVH, the hazard ratio was 1.03 (p for the interaction 0.007). This interaction was also present in exclusively de novo ASCVD (p = 0.013). We noted a trend towards an interaction (p = 0.08) between GFR and race with regard to ASCVD outcomes (a decreased GFR being a stronger risk factor in African Americans than whites). There was no significant interaction between level of kidney function measured as a continuous variable (and using a linear model), with age, gender, presence of diabetes mellitus, systolic and diastolic blood pressure, smoking, and LDL and HDL cholesterol for ASCVD outcomes.

DISCUSSION

Kidney function declines by approximately 10 ml/min/1.73 m^2 per decade, even in the absence of chronic kidney disease. Normal GFR in young adults is approximately 90 to 125 ml/min/1.73 m^2. Recently published clinical practice guidelines by the NKF define a GFR <60 ml/min/1.73 m^2 for three months or more as chronic kidney disease (12). Individuals with GFR 60 to 89 ml/min/1.73 m^2 do not have chronic kidney disease unless there is also a marker of kidney damage, for example, proteinuria.

Our results demonstrate that a lower level of kidney function is associated with a marked increase in the probability of ASCVD over five years. We also found that level of kidney function (even in the range of 60 to 89 ml/min/1.73 m^2, approximately equivalent to a calibrated creatinine as low as 0.9 to 1.1 mg/dl in a white man of age 55) is an independent risk factor for ASCVD and de novo ASCVD outcomes. Finally, we noted that ASCVD risk may increase more sharply at lower levels of GFR, but a nonlinear model was not significantly better than a linear model.

Prior studies of patients with CVD or subjects at high risk for CVD have generally been consistent in showing an independent association between decreased level of kidney function and increased CVD outcomes (1–4). Studies of lower or intermediate-risk populations have not been conclusive. For example, the Hypertension Detection and Follow-up Program (HDFP) found an association between higher serum creatinine and CVD mortality (18), while the Multiple Risk Factor Intervention trial (19) and the Framingham study (5) did not.

Our study demonstrates that the level of kidney function is an independent risk factor for ASCVD outcomes in the community. The only prior studies that we are aware of that

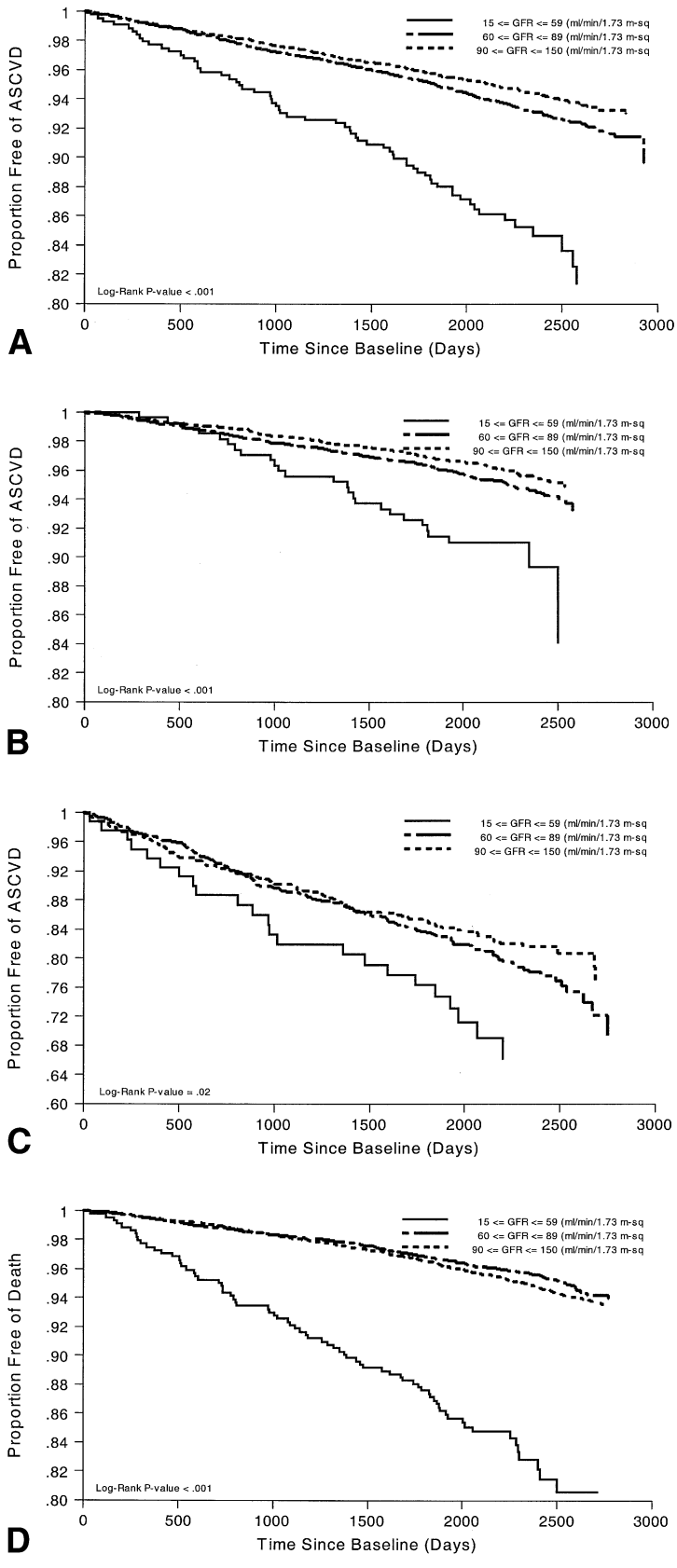

Figure 1. **(A)** Kaplan-Meier survival analysis for atherosclerotic cardiovascular disease (ASCVD) stratified by level of glomerular filtration rate (GFR). **(B)** Kaplan-Meier survival analysis for de novo ASCVD stratified by level of GFR. **(C)** Kaplan-Meier survival analysis for recurrent ASCVD stratified by level of GFR. **(D)** Kaplan-Meier survival analysis for all-cause mortality stratified by level of GFR.

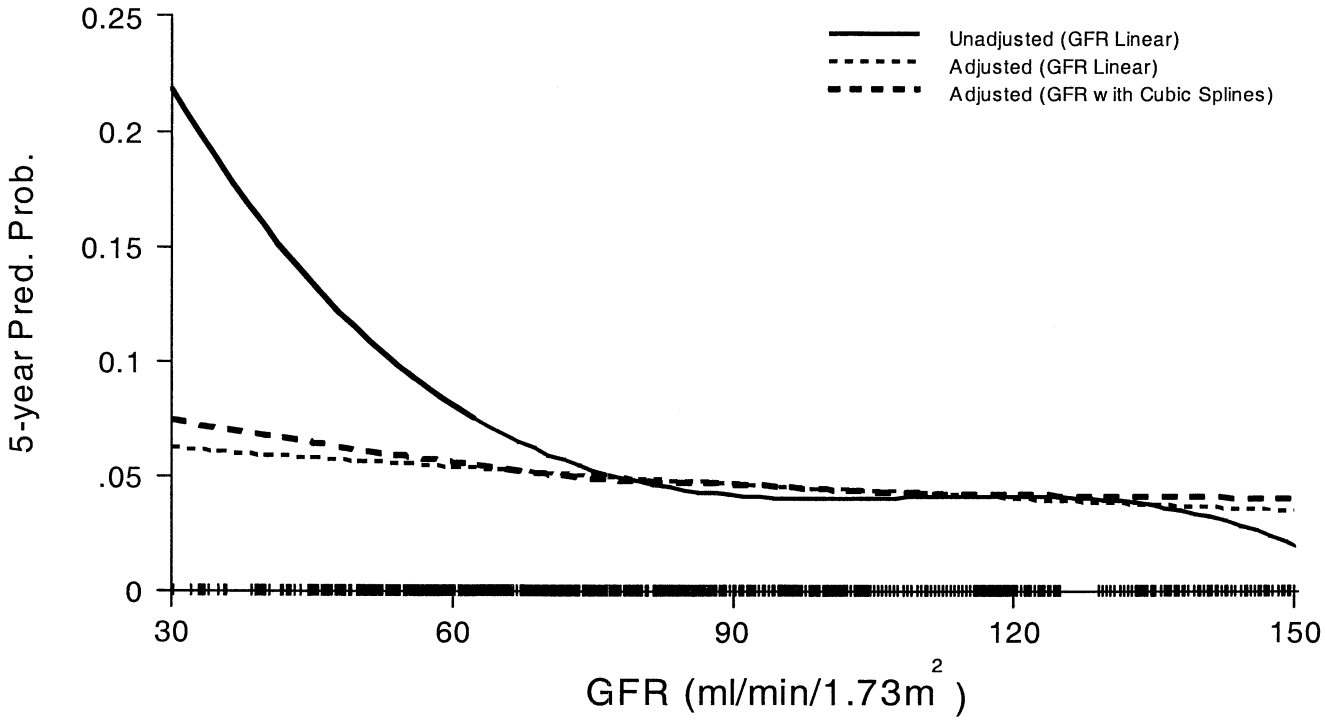

Figure 2. Smoothed five-year predicted probability of developing atherosclerotic cardiovascular disease by level of glomerular filtration rate (GFR). Unadjusted curve shows the risk incorporating each individual's value for 19 covariates in Table 3. Adjusted curve shows the average risk in the Atherosclerosis Risk in Communities study population if everyone had the GFR value on the X-axis. The linear model includes GFR as a continuous variable in a Cox regression while the cubic spline includes a cubic transition between linear segments with knots (at 0.05, 0.275, 0.5, 0.725, 0.95 quantiles of GFR) corresponding to GFR values of 63.7, 81.7, 88.2, 101.1, and 123.7 ml/min/1.73 m^2, respectively. Tick marks along the X-axis indicate GFR values for individual participants (the marks form a solid bar in GFR regions with many individuals). A lower GFR cut-off of 30 ml/min/1.73 m^2 was chosen because only 12 subjects had GFR values between 15 and 30 ml/min/1.73 m^2; therefore, the data was less precise in the latter range.

have evaluated the association of level of kidney function with CVD outcomes in the community are NHANES I and II (6,7) and the Framingham study (5). The results from the NHANES studies gave conflicting results, with NHANES II (7) noting an association between level of kidney function and CVD death and NHANES I noting no association between level of kidney function and CVD death (6). The current analysis of the ARIC cohort adds to those studies by having prospective standardized ASCVD event ascertainment (8,15), rather than relying on death certificate data as the primary outcome (6,7). In addition to reliance on death certificate data, the lack of association in NHANES I may at least be partly due to a small number of events (n = 197 cardiovascular deaths) and reliance on serum creatinine rather than estimated GFR.

Culleton et al. (5) evaluated the relationship of elevated serum creatinine, defined by serum creatinine of 1.5 to 3.0 mg/dl in men and 1.4 to 3.0 mg/dl in women, to CVD and all-cause mortality in 6,233 subjects in the Framingham study. Results showed that an elevated serum creatinine was associated with a higher prevalence of CVD and CVD risk factors at baseline. However, in multivariable analysis, elevated serum creatinine was not independently associated with a higher risk for CVD in either men or women.

Our results confirm the findings of Culleton et al. (5) with regard to a higher prevalence of CVD and CVD risk factors in patients with reduced GFR. In addition, we demonstrate that the increased prevalence of CVD and CVD risk factors likely play a major role in promoting an increased risk for ASCVD in patients with decreased GFR (comparison between unadjusted and adjusted models, Fig. 2).

Our results, however, differ from those of the Framingham population in that we found an independent association of level of kidney function to ASCVD outcomes. There are two potential explanations for the differences between our results and those of the Framingham study. First, the ARIC cohort is larger, and although the number of events is similar, with very long duration from measurement of serum creatinine and no African American participants, the Framingham study may have had lower power. We noted a trend towards an interaction ($p = 0.08$) between GFR and race with regard to ASCVD outcomes, a topic worth further study. Second, equations that estimate GFR may provide greater power than serum creatinine alone. These equations appropriately take into account how gender, age, and race modify the association between creatinine and GFR. The association between estimated GFR and ASCVD still needs to be adjusted for age, gender, and race to avoid confounding by these factors, but the analysis benefits from examining the predictive power of a much better estimate of GFR than serum creatinine alone.

Table 3. The Association of Level of Kidney Function on ASCVD, De Novo ASCVD, and Recurrent ASCVD

Outcomes	GFR Stratified Into Three Groups	
	Unadjusted Hazard Ratio (95% CI) p Value	**Adjusted Hazard Ratio (95% CI) p Value**
ASCVD*		
15–59 ml/min/1.73 m^2	2.89 (2.22, 3.77), <0.001	1.38 (1.02, 1.87), 0.038
60–89 ml/min/1.73 m^2	1.22 (1.07, 1.40), 0.003	1.16 (1.00, 1.34), 0.045
90–150 ml/min/1.73 m^2	1.0 (reference)	1.0 (reference)
De novo ASCVD†		
15–59 ml/min/1.73 m^2	2.55 (1.69, 3.84), <0.001	1.58 (1.01, 2.47), 0.047
60–89 ml/min/1.73 m^2	1.24 (1.03, 1.50), 0.023	1.25 (1.02, 1.52), 0.031
90–150 ml/min/1.73 m^2	1.0 (reference)	1.0 (reference)
Recurrent ASCVD‡		
15–59 ml/min/1.73 m^2	1.88 (1.20, 2.96), 0.006	1.53 (0.95, 2.47), 0.079
60–89 ml/min/1.73 m^2	1.18 (0.92, 1.52), 0.201	1.12 (0.85, 1.48), 0.409
90–150 ml/min/1.73 m^2	1.0 (reference)	1.0 (reference)
Outcomes	**GFR as a Continuous Variable**	
ASCVD* (per 10 ml/min/1.73 m^2 lower GFR)	1.14 (1.10, 1.18), <0.001	1.05 (1.02, 1.09), 0.006
De novo ASCVD† (per 10 ml/min/1.73 m^2 lower GFR)	1.11 (1.06, 1.17), < 0.001	1.07 (1.01, 1.12), 0.015
Recurrent ASCVD‡ (per 10 ml/min/1.73 m^2 lower GFR)	1.11 (1.04, 1.18), 0.001	1.06 (0.99, 1.13), 0.114

*Adjusted model with age, gender, race, baseline coronary heart disease, baseline stroke/transient ischemic attack, hypertension, diabetes mellitus, left ventricular hypertrophy by electrocardiogram (ECG), smoking status, pack years, body mass index, waist/hip ratio, activity level, systolic blood pressure, total cholesterol, high-density lipoprotein (HDL), cholesterol, albumin, fibrinogen, and vasodilating agents; †Adjusted model with age, gender, race, hypertension, diabetes mellitus, left ventricular hypertrophy by ECG, smoking status, systolic blood pressure, total cholesterol, HDL cholesterol, albumin, fibrinogen, cardiac agents, vasodilating agents; ‡Adjusted model with age, gender, race, systolic blood pressure, low-density lipoprotein cholesterol, HDL cholesterol, albumin, smoking status, vasodilating agents, cardiac agents, left ventricular hypertrophy by ECG, total cholesterol, and diabetes.

ASCVD = atherosclerotic cardiovascular disease; CI = confidence interval; GFR = glomerular filtration rate.

Interactions. The significant interaction between LVH and GFR on ASCVD outcomes is consistent with prior studies that have demonstrated that level of kidney function is an independent risk factor for outcomes in individuals who already have CVD (1–4). The interaction should, however, be interpreted with caution. First, the method used to define the presence of LVH is insensitive, and, second, the interaction was not one of our a priori hypotheses.

Potential explanations as to why level of kidney function may be a risk factor for outcomes. There are several theoretical but unproven explanations as to why the level of kidney function may be an independent risk factor for ASCVD outcomes. First, a decrease in the level of kidney function may be associated with increased levels of nontraditional CVD risk factors, such as elevated homocysteine levels, oxidative stress, and remnant cholesterol particles, that were not measured in the study and, therefore, not adjusted for in our analysis. Second, there may be residual confounding from variables for which we have adjusted. For example, a decrease in level of kidney function at baseline may be a marker of the severity of prior vascular damage (including subclinical cardiac disease) due to hypertension. Third, reduced kidney function itself may be a risk factor for progression of ventricular remodeling and cardiac dysfunction.

Nonlinear versus linear association of GFR with ASCVD. Our results show that, although we were able to establish an optimum GFR cut-point (78 ml/min/1.73 m^2), a two-slope model did not fit the data better than a one-slope linear model. Therefore, in the ARIC study, there is no clear threshold level of GFR above which the adjusted risk for ASCVD is not lower at a higher GFR.

Study limitations. There are three potential limitations of our analyses. First, recent studies have shown that albuminuria, an alternate marker for the presence of kidney disease, may be an independent risk factor for CVD outcomes (20). Unfortunately, urinalyses were not performed in ARIC, and we, therefore, could not adjust for the presence of albuminuria. Second, we are unable to account for differences or clustering of outcomes due to the center effect. This is due to the fact that the public use database does not provide center information because of concern of confidentiality. Although we are unable to completely overcome this limitation, we have endeavored to control for all variables that may track with center location such as education, ethnicity, and numerous other comorbidities. Third, indirect calibration of serum creatinine to the NHANES III study is not as precise as a direct comparison. However, this calibration resulted in GFR estimates that are more similar to direct inulin measurements supporting its use.

Conclusions. The level of kidney function is an independent risk factor for ASCVD in middle-aged subjects who are not selected for being at higher risk for CVD.

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