Title
Kidney function and mortality in octogenarians: Cardiovascular Health Study All Stars.

Journal
Journal of the American Geriatrics Society, 60(7)

ISSN
0002-8614

Authors
Shastri, Shani
Katz, Ronit
Rifkin, Dena E
et al.

Publication Date
2012-07-01

DOI
10.1111/j.1532-5415.2012.04046.x

Peer reviewed

Published in final edited form as:
J Am Geriatr Soc. 2012 July ; 60(7): 1201–1207. doi:10.1111/j.1532-5415.2012.04046.x.

Kidney Function and Mortality in Octogenarians: Cardiovascular Health Study All Stars

Shani Shastri, MD, MPH, MS[a], **Ronit Katz, DPhil**[b], **Dena E. Rifkin, MD, MS**[c], **Linda F. Fried, MD, MPH**[d,e], **Michelle C. Odden, PhD**[f], **Carmen A. Peralta, MD, MAS**[g], **Michel Chonchol, MD**[h], **David Siscovick, MD, MPH**[i], **Michael G. Shlipak, MD, MPH**[j], **Anne B. Newman, MD, MPH**[k], and **Mark J. Sarnak, MD, MS**[l]

[a]Division of Nephrology, University of Texas Southwestern, Dallas, Texas

[b]Department of Biostatistics, University of Washington, Seattle, Washington

[c]Division of Nephrology, University of California at San Diego, San Diego, California

[d]Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania

[e]Renal Section, Veterans Affairs Pittsburgh Healthcare System, Pittsburgh, Pennsylvania

[f]Department of Epidemiology, School of Biological and Population Health Sciences, Oregon State University, Corvallis, Oregon

[g]Division of Nephrology, University of California at San Francisco, San Francisco, California

[h]Division of Renal Disease and Hypertension, University of Colorado, Denver, Colorado

[i]Department of Medicine and Epidemiology, University of Washington, Seattle, Washington

[j]Department of Medicine, University of California at San Francisco, San Francisco, California

[k]Division of Geriatric Medicine, Department of Epidemiology, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania

[l]Division of Nephrology, Tufts Medical Center, Boston, Massachusetts.

Abstract

OBJECTIVES: To examine the association between kidney function and all-cause mortality in octogenarians.

DESIGN: Retrospective analysis of prospectively collected data.

SETTING: Community.

PARTICIPANTS: Serum creatinine and cystatin C were measured in 1,053 Cardiovascular Health Study (CHS) All Stars participants.

Address correspondence to Shani Shastri, UT Southwestern, 5323 Harry Hines Blvd, Dallas, TX 75390. Shani.Shastri@UTSouthwestern.edu.

Author Contributions: Study concept and design: Shani Shastri, Ronit Katz, Michael G. Shlipak, Anne B. Newman, Mark J. Sarnak. Acquisition of subjects and/or data: Anne B. Newman. Analysis: Ronit Katz. Interpretation of data: Shani Shastri, Ronit Katz, Michael G. Shlipak, Mark J. Sarnak. Preparation of manuscript: Shani Shastri, Ronit Katz, Dena E. Rifkin, Linda F. Fried, Michelle C. Odden, Carmen A. Peralta, Michel Chonchol, David Siscovick, Michael G. Shlipak, Anne B. Newman, Mark J. Sarnak.

Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

Sponsor's Role: N/A.

MEASUREMENTS: Estimated glomerular filtration rate (eGFR) was determined using the Chronic Kidney Disease Epidemiology Collaboration creatinine ($eGFR_{CR}$) and cystatin C one-variable ($eGFR_{CYS}$) equations. The association between quintiles of kidney function and all-cause mortality was analyzed using unadjusted and adjusted Cox proportional hazards models.

RESULTS: Mean age of the participants was 85, 64% were female, 66% had hypertension, 14% had diabetes mellitus, and 39% had prevalent cardiovascular disease. There were 154 deaths over a median follow-up of 2.6 years. The association between $eGFR_{CR}$ and all-cause mortality was U-shaped. In comparison with the reference quintile (64–75 mL/min per 1.73 m^2), the highest (≥75 mL/min per 1.73 m^2) and lowest (≤43 mL/min per 1.73 m^2) quintiles of $eGFR_{CR}$ were independently associated with mortality (hazard ratio (HR) = 2.49, 95% confidence interval (CI) = 1.36–4.55; HR = 2.28, 95% CI = 1.26–4.10, respectively). The association between $eGFR_{CYS}$ and all-cause mortality was linear in those with $eGFR_{CYS}$ of less than 60 mL/min per 1.73 m^2, and in the multivariate analyses, the lowest quintile of $eGFR_{CYS}$ (<52 mL/min per 1.73 m^2) was significantly associated with mortality (HR = 2.04, 95% CI = 1.12–3.71) compared with the highest quintile (>0.88 mL/min per 1.73 m^2).

CONCLUSION: Moderate reduction in kidney function is a risk factor for all-cause mortality in octogenarians. The association between $eGFR_{CR}$ and all-cause mortality differed from that observed with $eGFR_{CYS}$; the relationship was U-shaped for $eGFR_{CR}$, whereas the risk was primarily present in the lowest quintile for $eGFR_{CYS}$. **J Am Geriatr Soc 2012.**

Keywords

octogenarians; kidney function; mortality

There is a high prevalence of chronic kidney disease (CKD) in elderly adults,[1-3] although there continues to be controversy regarding the importance of low glomerular filtration rate (GFR) in the absence of other markers of kidney disease in this population.[4] Several studies have noted an attenuation of the prognostic importance of kidney function with advancing age,[5-7] and the data in octogenarians are particularly sparse.[8] In a cross-sectional analysis of octogenarians in the Cardiovascular Health Study (CHS) All Stars cohort, it was found that CKD was associated with prevalent cardiovascular disease (CVD), but whether this translates into longitudinal outcomes remains unknown.[9] Examining the relationship between kidney function and mortality in this oldest age group will help clinicians understand the implications of CKD in this growing subgroup of the population.

Use of serum creatinine–based estimating equations may be particularly limited as a measure of kidney function in elderly adults, among whom there is low muscle mass. Cystatin C is a filtration marker that muscle mass influences less than it does creatinine[10,11] and thus may have a particular advantage in elderly adults. Previous studies from the CHS cohort have shown that cystatin C is a stronger predictor of adverse outcomes than creatinine or GFR estimated using creatinine-based equations.[12-14] It remains unclear whether there are similar associations in octogenarians.

Whether reduction in kidney function was associated with mortality in the oldest old was evaluated. To do so, the association between kidney function, using creatinine and cystatin C-based GFR estimated equations, and all-cause and CVD mortality in octogenarian CHS All Stars participants was examined.

METHODS

Study Population

Cardiovascular Health Study All Stars, an ancillary study of CHS, was undertaken to identify factors associated with successful aging. Sampling and recruitment procedures for CHS and CHS All Stars have been described in detail elsewhere.[15,16] Briefly, CHS was a longitudinal study of community-dwelling adults aged 65 and older designed to determine the risk factors, consequences, and natural history of CVD in older adults. Participants were recruited from Medicare eligibility lists in four U.S. communities (Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Pittsburgh, PA). An initial 5,201 participants were recruited between 1989 and 1990, and an additional 687 black participants were added to the study between 1992 and 1993.

During the seventeenth year of follow-up (April 2005–May 2006), the CHS cohort was re-recruited for the CHS All Stars Study.[16] Of the 2,281 participants still alive, 1,677 (73.5%) participated in the CHS All Stars Study, and 265 (11.6%) participated in the CHS telephone follow-up. Of the 1,100 CHS All Stars participants in whom laboratory data were obtained, creatinine and cystatin C were measured in 1,053.

Assessment of Kidney Function

All assays were performed at the CHS Core Laboratory in May and June 2008 on serum stored at −70°C. Serum creatinine, measured using a colorimetric method (Ektachem 700, Eastman Kodak, Rochester, NY) was calibrated to isotope dilution mass spectrometry, and the intra-assay coefficient of variation was 1.9%. Cystatin C was measured using a BN II nephelometer (N Latex cystatin C, Dade Behring, Munich, Germany) using a particle-enhanced immunonepholometric assay, and the intra-assay coefficient of variation for cystatin C ranged from 2.0% to 2.8%. Estimated glomerular filtration rate (eGFR) was determined using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation because it is thought to be more accurate and less biased than the Modification of Diet in Renal Disease (MDRD) equation at higher levels of GFR.

$eGFR_{CR} = 141 \times \text{minimum}(Scr/\kappa, 1)^{\alpha} \times \text{maximum}(Scr/\kappa, 1)^{-1.209} \times 0.993^{age} \times 1.018$ [if female] × 1.159 [if black], where Scr is serum creatinine, κ is 0.7 for women and 0.9 for men, α is −0.329 for women and −0.411 for men, and $eGFR_{CR}$ is expressed in mL/min per 1.73 m^2.[17]

Glomerular filtration rate was estimated from cystatin C using the CKD-EPI equation, with $eGFR_{CYS} = 76.7 \times CysC^{-1.19}$, GFR expressed as mL/min per 1.73 m^2 of body surface area, and CysC is serum cystatin C expressed in mg/L.[18]

Study Outcome

The primary outcome was all-cause mortality. Information regarding death after the CHS All Stars visit was ascertained by review of obituaries, telephone follow-up, and proxy contact and was available through June 2008. The secondary outcome was death from CVD, defined as death caused by atherosclerotic coronary heart disease, cerebrovascular disease, other atherosclerotic disease, or other CVD in participants with and without prevalent CVD. A committee adjudicated all events, as previously described.[19]

Covariates

Covariates that may confound the association between poor kidney function and mortality were chosen for multivariate analyses. These included demographic variables (age, sex, and race), cardiovascular risk factors (body mass index (kg/m^2), hypertension (blood pressure ≥

140/ 90 mmHg or antihypertensive treatment)), diabetes mellitus (use of insulin or oral hypoglycemic agent or fasting glucose value ≥ 126 mg/dL), smoking status (current smoker, former smoker, never smoked), systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), clinical CVD (composite of history of coronary heart disease (angina pectoris, myocardial infarction, angioplasty, coronary bypass surgery) or (stroke at the time of initiation of CHS All Stars or heart failure)), and a novel cardiovascular risk factor (C-reactive protein).

Statistical Analyses

Continuous data are presented as means ± standard deviations and categorical variables as proportions. Analysis of variance and Pearson Chi-square tests with trend *P*-values were used for comparison of quintiles of $eGFR_{CYS}$ for continuous and categorical variables, respectively. Data for C-reactive protein are presented as medians and interquartile ranges because its distribution was skewed, and the Kruskal–Wallis test was used to compare differences between quintiles of $eGFR_{CYS}$. Pearson correlation was used to assess correlation between $eGFR_{CR}$ and $eGFR_{CYS}$.

Age-, sex-, and race-adjusted splines of $eGFR_{CR}$ and $eGFR_{CYS}$ were plotted to evaluate the functional form of their relationship with all-cause mortality. The 2.5% of the extremes were excluded to remove influence from the extremes. Mortality rates per 100 person-years according to quintiles of $eGFR_{CR}$ and $eGFR_{CYS}$ were calculated. Cox proportional hazards models were used to assess associations between kidney disease and all-cause mortality in unadjusted and adjusted models. Covariates were selected for the analyses based on their biologically plausible potential to act as confounders and entered into the models in stages: Model 1, unadjusted; Model 2, demographic factors (age, sex, and race); Model 3, demographic and cardiovascular risk factors and disease. Separate models were constructed for $eGFR_{CR}$ and $eGFR_{CYS}$ quintiles, and the same covariates were entered into the models. Taking the spline into account, for $eGFR_{CYS}$ analyses, the first quintile (>88 mL/min per 1.73 m^2) was used as the reference group, whereas for $eGFR_{CR}$, the second-highest quintile (64–75 mL/min per 1.73 m^2) was used as the reference group.

The association between kidney function and CVD mortality was examined using the same models. Because of the small number of CVD deaths in the highest $eGFR_{CYS}$ quintile (n = 2), the first and second quintiles of $eGFR_{CYS}$ were combined into one group, leading to the following sub-groups: $eGFR_{CYS}$ 75 mL/min per 1.73 m^2 or greater (reference group), 65 to 74 mL/min per 1.73 m^2, 52 to 64 mL/min per 1.73 m^2, and less than 52 mL/min per 1.73 m^2.

Sensitivity Analyses

Two sensitivity analyses were performed to assess the consistency of the results. Most prior studies have used the one-variable cystatin C equation to estimate GFR,[12,20] but in a pooled study of individuals with established CKD with mean age of 52, the cystatin C demographic equation had slightly higher accuracy and precision and lower bias than the cystatin C one-variable equation.[18] Therefore, the analyses were repeated using the cystatin C demographic equation where $eGFR_{CYS\ demo} = 127.7 \times CysC^{-1.17} \times age^{-0.13} \times 1.06$ (if black) × 0.91 (if female) where GFR is expressed as mL/min per 1.73 m^2 of body surface area, and CysC is serum cystatin C expressed in mg/L.[18] Taking the spline into account, for $eGFR_{CYS\ demo}$ analyses, the first quintile (>78 mL/min per 1.73 m^2) was used as the reference group.

Second, because frailty may be an important confounding variable, additional analyses were performed adjusting for the presence of frailty. The presence of frailty has previously been defined as three of the following five characteristics: recent weight loss, self-reported

exhaustion, weakness, slow walking speed, and low physical activity.[21] Information on physical activity was not collected in CHS All Stars, so frailty was defined according to the presence of three of the following: unintentional weight loss, exhaustion, weakness, and walking slowness based on gait speed.

Analyses were performed using S-Plus (release 8.0, Insightful, Inc., Seattle, WA) and SPSS (version 16.0.2, SPSS, Inc., Chicago, IL). Two-tailed $P < .05$ was considered to be statistically significant.

RESULTS

Characteristics of Study Participants

One thousand fifty-three CHS All Stars participants were included in the analyses. Participants who were alive but did not have laboratory data available were more likely to be female and older and to have a higher prevalence of myocardial infarction and stroke than those included in the analyses.

The clinical characteristics of the study population are shown in Table 1 according to $eGFR_{CYS}$ quintile. The average age of the participants was 85, 64% were female, 86% were white, 67% had hypertension, 18% had diabetes mellitus, 35% had prevalent CVD, and 14% had heart failure. Mean $eGFR_{Cr}$ and $eGFR_{CYS}$ were 59 and 70 mL/ min per 1.73 m^2, respectively.

Participants in the lowest $eGFR_{CYS}$ quintiles were more likely to be older, male, and not black than those in the highest $eGFR_{CYS}$ quintiles. Nearly all of the comorbid conditions assessed were more prevalent in those with lower $eGFR_{CYS}$. Also, participants in the lowest $eGFR_{CYS}$ quintiles had higher levels of C-reactive protein and lower levels of HDL-C and LDL-C. The prevalence of diabetes mellitus did not vary significantly between quintiles of $eGFR_{CYS}$.

Association Between Kidney Function and Mortality

All-Cause Mortality—During a median follow-up of 2.6 years, there were 154 deaths, of which 64 were due to CVD. Quintiles of $eGFR_{CR}$ had a U-shaped association with mortality. The second, third, and fourth quintiles of $eGFR_{CYS}$ had slightly higher mortality than the first quintile, and the lowest quintile had a three times the mortality (Figure 1).

The age-, sex-, and race-adjusted splines for $eGFR_{CR}$ revealed a more-pronounced U-shaped relationship with all-cause mortality (Figure 2). In contrast, the adjusted splines for $eGFR_{CYS}$ revealed a linear relationship with mortality for participants with eGFR less than 60 mL/min per 1.73 m^2.

The U-shaped association with $eGFR_{CR}$ persisted in the multivariate analyses, with participants in the highest (HR = 2.49, 95% CI = 1.36–4.55) and lowest quintiles (HR = 2.28, 95% CI = 1.26–4.10) having significantly greater risk of mortality than those in the second-highest quintile (64–75 mL/min per 1.73 m^2) (Table 2). In contrast, the lowest $eGFR_{CYS}$ quintile was significantly more associated with death than the highest quintile (HR = 2.04, 95% CI = 1.12–3.71), with the second, third, and fourth quintiles of $eGFR_{CYS}$ having similar mortality rates and not being significantly different from the reference group.

Cardiovascular Mortality—In multivariable analysis, the U-shaped association between $eGFR_{CR}$ quintile and CVD mortality persisted, although none of the differences between $eGFR_{CR}$ quintiles reached statistical significance (Table 3). In contrast, the lowest subgroup

of $eGFR_{CYS}$ (<52 mL/min per 1.73 m^2) was significantly more associated with CVD death than the highest subgroup (HR = 1.66, 95% CI = 1.06–2.60).

Sensitivity Analyses

When the analyses were repeated using quintiles of $eGFR_{CYS\ demo}$, results were similar to those with $eGFR_{CYS}$, with only the lowest $eGFR_{CYS\ demo}$ quintile being significantly more associated with all-cause (HR = 2.01, 95% CI = 1.16–3.50) and CVD mortality (HR = 3.67, 95% CI = 1.45–9.28) than the highest quintile.

One hundred seven (10%) CHS All Stars participants met the definition of frailty. Similar results were obtained when adjusted for frailty, with the relationship being U-shaped for $eGFR_{CR}$, whereas for $eGFR_{CYS}$, the risk was primarily present in the lowest quintile. That is, the highest (HR = 2.43, 95% CI = 1.33–4.44) and lowest (HR = 2.19, 95% CI = 1.21–3.95) quintiles of $eGFR_{CR}$ were independently associated more with all-cause mortality than the reference quintile (64–75 mL/min per 1.73 m^2), and in contrast, only the lowest $eGFR_{CYS}$ quintile was significantly associated more with death than the highest quintile (HR = 1.88, 95% CI = 1.03–3.43).

DISCUSSION

Impaired kidney function assessed using $eGFR_{CR}$ or $eGFR_{CYS}$ was a significant risk factor for all-cause mortality in this community-based cohort of octogenarians.

The association between $eGFR_{CR}$ and all-cause mortality differed from that observed with $eGFR_{CYS}$, for which the relationship was U-shaped for $eGFR_{CR}$, whereas for cystatin C, the risk was primarily in the lowest quintile. Although a similar relationship was noted with CVD mortality, $eGFR_{CR}$ was not associated with CVD mortality, and only the lowest $eGFR_{CYS}$ subgroup had a greater risk of CVD mortality.

Whereas the association between impaired kidney function and outcomes has been clearly described in middle-aged and elderly adults,[22-24] few studies have evaluated whether impaired kidney function is associated with mortality in octogenarians[8] and whether any thresholds regarding this association exist. In the National Cohort of Veterans Study that compared mortality risk associated with CKD across all ages, the relative risk for death associated with each level of kidney function decreased markedly with age, and creatinine-based eGFR of 50 to 59 mL/ min per 1.73 m^2 was not associated with a greater risk of death than in the reference group (eGFR ≥ 60 mL/min per 1.73 m^2) in those aged 65 and older.[5] Similar findings were reported in a community-based cohort, in which those aged 75 and older with $eGFR_{CR}$ between 45 and 59 mL/min per 1.73 m^2 did not have a greater relative risk of death than those with eGFR of 60 mL/min per 1.73 m^2 or greater.[6] In an analysis of a representative sample of adults aged 75 and older drawn from primary care practices across Britain, $eGFR_{CR}$ less than 45 mL/min per 1.73 m^2 was an independent predictor of mortality compared with the reference group ($eGFR_{CR}$ ≥ 60 mL/min per 1.73 m^2), especially in the first 2 years of follow-up, and there was greater risk of CVD mortality in those with $eGFR_{CR}$ of 45 to 59 mL/min per 1.73 m^2.[7] In octogenarians in Japan, CKD defined as $eGFR_{CR}$ less than 60 mL/ min per 1.73 m^2 was associated with greater CVD mortality but not all-cause mortality compared with eGFR greater than 60 mL/min per 1.73 m^2.[8] These studies are all partially limited by lack of consideration of the appropriate reference group for $eGFR_{CR}$ given that $eGFR_{CR}$ greater than 60 mL/min per 1.73 m^2 includes some individuals at low risk ($eGFR_{CR}$ 60–75 mL/min per 1.73 m^2) and others at higher mortality risk ($eGFR_{CR}$ >75 mL/min per 1.73 m^2). Furthermore, except for the Japanese study, there was not a focus on octogenarians, and none evaluated the importance of cystatin C.

When kidney function was assessed using $eGFR_{CR}$, the lowest and highest quintiles were associated with greater mortality than in the lowest-risk group (second-highest quintile). The association between high $eGFR_{CR}$ or low serum creatinine and mortality has been noted previously in the CHS,[22] although the U-shape appears to be more prominent in octogenarians, as noted in the current study. This is probably not because higher eGFR is a risk factor for death but because higher eGFR partly reflects those with lower muscle mass and malnutrition, who are thus more likely to die.[24] The inability to distinguish whether low creatinine primarily reflects low muscle mass (a proxy of frailty) rather than very high GFR remains a limitation of $eGFR_{CR}$ in elderly adults. The finding that only those with $eGFR_{CR}$ below 44 mL/min per 1.73 m^2 were at greater risk of mortality is consistent with several of the studies noted above[5-8] and suggests that, in octogenarians, the threshold at which kidney function becomes a risk factor may be lower than in younger individuals. The lower relative risk for death attributable to impaired kidney function in octogenarians may reflect the higher prevalence of other comorbid conditions, which may lessen the potential for a single condition such as low GFR to affect mortality. The relative risk of two conditions translates into a high absolute risk of mortality given the high mortality in this population. The results were unchanged despite adjusting for frailty, although the prevalence of frailty may have been underestimated which may have limited the ability to adjust for it in this cohort.

When $eGFR_{CYS}$ was used to estimate kidney function, only those in the lowest quintile had greater risk of mortality in adjusted analyses. This is in contrast to prior studies, including earlier analyses from CHS that studied younger cohorts, in which the gradient of risk was more linear.[12-14,22] The reason for these discrepancies is unclear, but possibilities include differences in the relationship between kidney function and mortality in octogenarians, fewer events and therefore less statistical power in the current analysis, variation in the importance of non-GFR determinants of cystatin C in the oldest old, and more importantly survivor bias.

Previous studies have demonstrated that cystatin C is superior to serum creatinine or creatinine-based estimating equations for prediction of CVD events, including CVD mortality.[13,25] In the present study, the lowest subgroup of $eGFR_{CYS}$ had greater risk of CVD mortality than the reference group, whereas $eGFR_{CR}$ quintiles had no statistically significant association with CVD mortality. These relationships are mostly consistent with the all-cause mortality data but are partly limited by insufficient statistical power.

The current study has several strengths. CHS All Stars is one of the largest, best-characterized cohorts of octogenarians, with detailed ascertainment of covariates and CVD risk factors. The CKD-EPI equation, which is thought to be more accurate than the MDRD equation at higher levels of GFR, in women, and in white people, was used to assess kidney function. In addition, this is one of the few studies in which cystatin C was measured, which is relevant because cystatin C is now being considered as an alternative marker of GFR, particular in elderly adults. Finally, thresholds where risk may increase, including appropriate reference groups, were evaluated using $eGFR_{CR}$ and $eGFR_{CYS}$.

There are some limitations to this study. Participants who lacked laboratory data were in general less healthy, so generalizability may be partly limited. Indirect estimates of GFR that have not been validated in octogenarians were used. It was not possible to adjust for proteinuria because urine protein was not measured in this cohort. There was limited statistical power to assess the association between impaired kidney function and CVD mortality and to appreciate an association with mortality in the group with $eGFR_{CR}$ of 45 to 60 mL/min per 1.73 m^2. Factors other than GFR may influence cystatin C; despite adjustment for these variables, residual confounding may have remained.[26,27] Finally, at the

present time cystatin C assays traceable to an accepted reference are not available, unlike the isotope dilution mass spectrometry creatinine reference standard.

In conclusion, even in this oldest subgroup of the population, impaired kidney function is associated with all-cause and CVD mortality, although the risk appears to be greater only in those with moderately impaired kidney function, below the current definition of CKD. Furthermore, this relationship was U-shaped for $eGFR_{CR}$, whereas for $eGFR_{CYS}$, the risk was primarily present in the lowest quintile. Future studies that explore novel therapeutic approaches to reduce CVD and mortality in individuals with imparired kidney function are needed in the oldest old.

Acknowledgments

Participation by patients and staff in the CHS Study is greatly appreciated.

An abstract representing this work was presented at the American Society of Nephrology Annual Meeting in Philadelphia, November 11, 2011.

The research reported in this article was supported by National Institute on Aging (NIA) Grant AG-023629. CHS was supported by National Heart, Lung, and Blood Institute (NHLBI) Contracts N01-HC-85239, N01-HC-85079 through N01-HC-85086, N01-HC-35129, N01 HC-15103, N01 HC-55222, N01-HC-75150, and N01-HC-45133 and NHLBI Grant HL080295, with additional contribution from the National Institute of Neurological Disorders and Stroke. Additional support was provided through AG-023629, AG-15928, AG-20098, and AG-027058 from the NIA. A full list of principal CHS investigators and institutions can be found at http://www.chsnhlbi.org/pi.htm. This material is also based on work supported in part by the Department of Veterans Affairs, Veterans Integrated Service Network 4, R01 HL-075366 from the National Heart, Lung and Blood Institute, and the University of Pittsburgh Claude. D. Pepper Older Americans Independence Center P30-AG-024827. Dr. Sarnak is supported by K24 DK078204.

REFERENCES

1. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. JAMA. 2007; 298:2038–2047. [PubMed: 17986697]
2. Fox CS, Larson MG, Leip EP, et al. Predictors of new-onset kidney disease in a community-based population. JAMA. 2004; 291:844–850. [PubMed: 14970063]
3. Garg AX, Papaioannou A, Ferko N, et al. Estimating the prevalence of renal insufficiency in seniors requiring long-term care. Kidney Int. 2004; 65:649–653. [PubMed: 14717937]
4. Eckardt KU, Berns JS, Rocco MV, et al. Definition and classification of CKD: The debate should be about patient prognosis–a position statement from KDOQI and KDIGO. Am J Kidney Dis. 2009; 53:915–920. [PubMed: 19406541]
5. O'Hare AM, Bertenthal D, Covinsky KE, et al. Mortality risk stratification in chronic kidney disease: One size for all ages? J Am Soc Nephrol. 2006; 17:846–853. [PubMed: 16452492]
6. Raymond NT, Zehnder D, Smith SC, et al. Elevated relative mortality risk with mild-to-moderate chronic kidney disease decreases with age. Nephrol Dial Transplant. 2007; 22:3214–3220. [PubMed: 17631511]
7. Roderick PJ, Atkins RJ, Smeeth L, et al. CKD and mortality risk in older people: a community-based population study in the United Kingdom. Am J Kidney Dis. 2009; 53:950–960. [PubMed: 19394727]
8. Kagiyama S, Matsumura K, Ansai T, et al. Chronic kidney disease increases cardiovascular mortality in 80-year-old subjects in Japan. Hypertens Res. 2008; 31:2053–2058. [PubMed: 19098377]
9. Shastri S, Tighiouart H, Katz R, et al. Chronic kidney disease in octogenarians. Clin J Am Soc Nephrol. 2011; 6:1410–1417. [PubMed: 21511839]
10. Fliser D, Ritz E. Serum cystatin C concentration as a marker of renal dysfunction in the elderly. Am J Kidney Dis. 2001; 37:79–83. [PubMed: 11136171]

11. Newman DJ, Thakkar H, Edwards RG, et al. Serum cystatin C measured by automated immunoassay: A more sensitive marker of changes in GFR than serum creatinine. Kidney Int. 1995; 47:312–318. [PubMed: 7731163]
12. Peralta CA, Katz R, Sarnak MJ, et al. Cystatin C identifies chronic kidney disease patients at higher risk for complications. J Am Soc Nephrol. 2011; 22:147–155. [PubMed: 21164029]
13. Sarnak MJ, Katz R, Stehman-Breen CO, et al. Cystatin C concentration as a risk factor for heart failure in older adults. Ann Intern Med. 2005; 142:497–505. [PubMed: 15809461]
14. Shlipak MG, Katz R, Sarnak MJ, et al. Cystatin C and prognosis for cardiovascular and kidney outcomes in elderly persons without chronic kidney disease. Ann Intern Med. 2006; 145:237–246. [PubMed: 16908914]
15. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: Design and rationale. Ann Epidemiol. 1991; 1:263–276. [PubMed: 1669507]
16. Newman AB, Arnold AM, Sachs MC, et al. Long-term function in an older cohort–the Cardiovascular Health Study All Stars study. J Am Geriatr Soc. 2009; 57:432–440. [PubMed: 19187412]
17. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009; 150:604–612. [PubMed: 19414839]
18. Stevens LA, Coresh J, Schmid CH, et al. Estimating GFR using serum cystatin C alone and in combination with serum creatinine: A pooled analysis of 3,418 individuals with CKD. Am J Kidney Dis. 2008; 51:395–406. [PubMed: 18295055]
19. Ives DG, Fitzpatrick AL, Bild DE, et al. Surveillance and ascertainment of cardiovascular events. The Cardiovascular Health Study. Ann Epidemiol. 1995; 5:278–285.
20. Rifkin DE, Shlipak MG, Katz R, et al. Rapid kidney function decline and mortality risk in older adults. Arch Intern Med. 2008; 168:2212–2218. [PubMed: 19001197]
21. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: Evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001; 56A:M146–M156. [PubMed: 11253156]
22. Shlipak MG, Sarnak MJ, Katz R, et al. Cystatin C and the risk of death and cardiovascular events among elderly persons. N Engl J Med. 2005; 352:2049–2060. [PubMed: 15901858]
23. Shlipak MG, Wassel Fyr CL, Chertow GM, et al. Cystatin C and mortality risk in the elderly: The Health, Aging, and Body Composition Study. J Am Soc Nephrol. 2006; 17:254–261. [PubMed: 16267155]
24. Manjunath G, Tighiouart H, Coresh J, et al. Level of kidney function as a risk factor for cardiovascular outcomes in the elderly. Kidney Int. 2003; 63:1121–1129. [PubMed: 12631096]
25. Ix JH, Shlipak MG, Chertow GM, et al. Association of cystatin C with mortality, cardiovascular events, and incident heart failure among persons with coronary heart disease: Data from the Heart and Soul Study. Circulation. 2007; 115:173–179. [PubMed: 17190862]
26. Knight EL, Verhave JC, Spiegelman D, et al. Factors influencing serum cystatin C levels other than renal function and the impact on renal function measurement. Kidney Int. 2004; 65:1416–1421. [PubMed: 15086483]
27. Stevens LA, Schmid CH, Greene T, et al. Factors other than glomerular filtration rate affect serum cystatin C levels. Kidney Int. 2009; 75:652–660. [PubMed: 19119287]

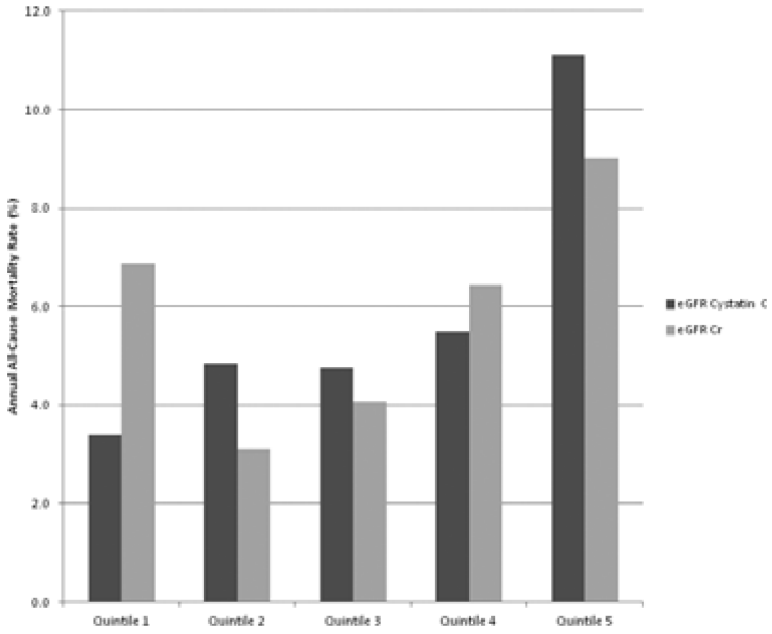

Figure 1.
All-cause mortality according to quintile of kidney function measure. eGFR = estimated glomerular filtration rate (mL/min per 1.73 m^2).

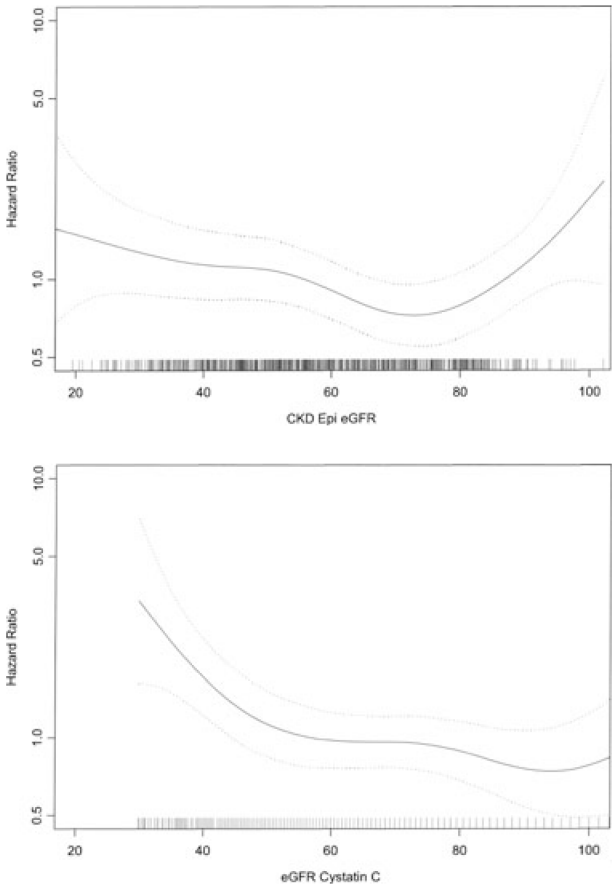

Figure 2.

Spline evaluating relationship between kidney function measures and all-cause mortality adjusting for age, sex, and race and excluding the top and bottom 2.5%. CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate (mL/min per 1.73 m^2).

Table 1

Baseline Characteristics According to Quintile of Cystatin C Estimated Glomerular Filtration Rate (eGFR)

Characteristic	All, N = 1,053	Quintile 1 (>88 mL/min per 1.73 m^2), n = 195	Quintile 2 (75–88 mL/min per 1.73 m^2), n = 213	Quintile 3 (65–74 mL/min per 1.73 m^2), n = 224	Quintile 4 (52–64 mL/min per 1.73 m^2), n = 216	Quintile 5 (<52 mL/min per 1.73 m^2), n = 105	*P*-value
Age, mean ± SD	85 (4)	84 (4)	85 (4)	86 (3)	85 (3)	86 (4)	<.001
Male, n (%)	381 (36)	61 (31)	64 (30)	83 (37)	83 (38)	90 (44)	.002
Black, n (%)	170 (16)	47 (24)	35 (16)	30 (13)	34 (16)	24 (12)	.002
Body mass index, kg/m^2, mean ± SD	26.8 (4.7)	26.3 (4.4)	26.5 (4.2)	26.8 (4.8)	27.2 (4.9)	27.3 (5.0)	.01
Smoking, n (%)							.43
Never	536 (51)	109 (56)	104 (49)	111 (50)	112 (52)	100 (49)	
Former	481 (46)	80 (41)	101 (47)	102 (46)	101 (47)	97 (47)	
Current	36 (3)	6 (3)	8 (4)	11 (5)	3 (1)	8 (4)	
Prevalent heart failure, n (%)	151 (14)	14 (7)	22 (10)	26 (12)	32 (15)	57 (28)	<.001
Prevalent cardiovascular disease, n (%)	363 (35)	53 (27)	64 (30)	63 (28)	81 (38)	102 (50)	<.001
Diabetes mellitus, n (%)	193 (18)	40 (21)	39 (18)	29 (13)	38 (18)	47 (23)	.61
Hypertension, n (%)	710 (67)	117 (60)	136 (64)	151 (67)	151 (70)	155 (76)	<.001
Systolic blood pressure, mmHg, mean ± SD	133 (21)	134 (20)	132 (20)	134 (21)	131 (22)	132 (22)	.38
Diastolic blood pressure, mmHg, mean ± SD	67 (10)	68 (10)	68 (10)	68 (11)	66 (10)	65 (11)	.001
Frailty, n (%)[a]	107 (10)	14 (7)	13 (6)	28 (13)	12 (6)	40 (20)	<.001
Low-density lipoprotein cholesterol, mg/dL	101 (32)	105 (33)	106 (30)	100 (32)	101 (31)	95 (31)	<.001
High-density lipoprotein cholesterol, mg/dL	55 (16)	60 (16)	57 (15)	54 (14)	54 (16)	49 (15)	<.001
C-reactive protein, mg/L, median (interquartile range)[b]	1.96 (0.96–4.59)	1.36 (0.79–3.09)	1.81 (0.85–4.03)	1.79 (0.89–4.71)	2.26 (1.02–5.09)	2.99 (1.41–7.38)	<.001
Cystatin C, mg/L, mean ± SD	1.19 (0.45)	0.79 (0.07)	0.95 (0.04)	1.09 (0.04)	1.26 (0.07)	1.84 (0.62)	<.001
Creatinine, mg/dL, mean ± SD	1.09 (0.53)	0.82 (0.16)	0.88 (0.17)	0.98 (0.19)	1.13 (0.23)	1.66 (0.92)	<.001
Chronic kidney disease epidemiology collaboration eGFR, mL/min per 1.73 m^2, mean ± SD	59 (17)	74 (11)	68 (12)	61 (12)	53 (12)	38 (13)	<.001
Cystatin C eGFR, mL/min per 1.73 m^2, mean ± SD	70 (22)	102 (13)	82 (4)	70 (3)	58 (4)	40 (9)	<.001

SD = standard deviation.

[a] Frailty defined as 3 of unintentional weight loss, weakness, exhaustion, and walking slowness.

[b] Kruskal–Wallis test.

Table 2

Association Between Kidney Function Measures and All-Cause Mortality

Kidney Function Measure, mL/min per 1.73 m^2	Mortality per 100 Person-Years	Unadjusted	Adjusted[a]	Adjusted[b]
		Hazard Ratio (95% Confidence Interval)		
Chronic Kidney Disease Epidemiology eGFR quintile				
>75	6.9	2.32 (1.28–4.20)	2.40 (1.32–4.37)	2.49 (1.36–4.55)
64–75	3.1	1.00 (reference)	1.00 (reference)	1.00 (reference)
55–63	4.1	1.25 (0.64–2.43)	1.22 (0.63–2.38)	1.23 (0.63–2.41)
44–54	6.4	1.99 (1.09–3.66)	1.84 (1.00–3.38)	1.68 (0.91–3.09)
≤ 43	9.0	2.86 (1.60–5.09)	2.71 (1.52–4.83)	2.28 (1.26–4.10)
Cystatin C eGFR quintile				
>88	3.4	1.00 (reference)	1.00 (reference)	1.00 (reference)
75–88	4.9	1.49 (0.80–2.80)	1.45 (0.77–2.72)	1.43 (0.76–2.70)
65–74	4.8	1.43 (0.76–2.67)	1.26 (0.67–2.38)	1.14 (0.60–2.15)
52–64	5.5	1.54 (0.82–2.86)	1.39 (0.74–2.59)	1.21 (0.64–2.27)
<52	11.1	3.33 (1.89–5.87)	2.69 (1.52–4.77)	2.04 (1.12–3.71)

eGFR = estimated glomerular filtration rate.

[a] Adjusted for age, sex, and race.

[b] Additionally adjusted for hypertension, diabetes mellitus, smoking, body mass index, prevalent cardiovascular disease, prevalent heart failure, low- and high-density lipoprotein cholesterol, and C-reactive protein.

Table 3

Association Between Kidney Function Measures and Cardiovascular Mortality

Kidney Function Measure, mL/min per 1.73 m^2	Mortality per 100 Person-Years	Unadjusted	Adjusted[a]	Adjusted[b]
		Hazard Ratio (95% Confidence Interval)		
Chronic Kidney Disease Epidemiology Collaboration eGFR quintile				
≥75	2.6	1.56 (0.67–3.65)	1.51 (0.64–3.55)	1.48 (0.62–3.51)
64–75	1.6	1.00 (reference)	1.00 (reference)	1.00 (reference)
55–63	2.2	1.29 (0.53–3.10)	1.28 (0.53–3.08)	1.19 (0.49–2.90)
44–54	2.1	1.18 (0.48–2.90)	1.10 (0.45–2.70)	0.95 (0.38–2.35)
≤ 43	4.7	2.73 (1.26–5.93)	2.62 (1.21–5.70)	1.98 (0.90–4.37)
eGFR Cystatin C quintile				
≥75	1.6	1.00 (reference)	1.00 (reference)	1.00 (reference)
65–74	2.1	1.14 (0.69–1.87)	1.02 (0.62–1.69)	0.93 (0.56–1.54)
52–64	2.4	1.23 (0.75–2.01)	1.13 (0.69–1.84)	0.98 (0.60–1.62)
<52	5.6	2.66 (1.75–4.04)	2.18 (1.43–3.33)	1.66 (1.06–2.60)

eGFR = estimated glomerular filtration rate.

[a] Adjusted for age, sex, and race.

[b] Additionally adjusted for hypertension, diabetes mellitus, smoking, body mass index, prevalent cardiovascular disease, prevalent heart failure, low- and high-density lipoprotein cholesterol, and C-reactive protein.