

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

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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.

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 m²), the highest (≥ 75 mL/min per 1.73 m²) and lowest (≤ 43 mL/min per 1.73 m²) 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 m², and in the multivariate analyses, the lowest quintile of eGFR_{CYS} (< 52 mL/min per 1.73 m²) 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 m²).

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* 60:1201–1207, 2012.

Key words: octogenarians; kidney function; mortality

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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 immunonephelometric 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.

$\text{eGFR}_{\text{CR}} = 141 \times \text{minimum} (\text{Scr}/\kappa, 1)^{\alpha} \times \text{maximum} (\text{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\text{age}} \times 1.018$ [if female] $\times 1.159$ [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 $\text{eGFR}_{\text{Cys}} = 76.7 \times \text{CysC}^{-1.19}$, 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 $\geq 140/90$ 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 \pm 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 m²) was used as the reference group, whereas for $eGFR_{CR}$, the second-highest quintile (64–75 mL/min per 1.73 m²) 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 subgroups: $eGFR_{CYS}$ 75 mL/min per 1.73 m² or greater (reference group), 65 to 74 mL/min per 1.73 m², 52 to 64 mL/min per 1.73 m², and less than 52 mL/min per 1.73 m².

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) $\times 0.91$ (if female) where GFR is expressed as mL/min per 1.73 m² 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 m²) 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 m², 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 m².

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 m²) (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 m²) 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%

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

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

^b Kruskal–Wallis test.

SD = standard deviation.

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 m²), 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 octogenarians⁸ 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 m² was not associated with a greater risk of death than in the reference group (eGFR ≥ 60 mL/min

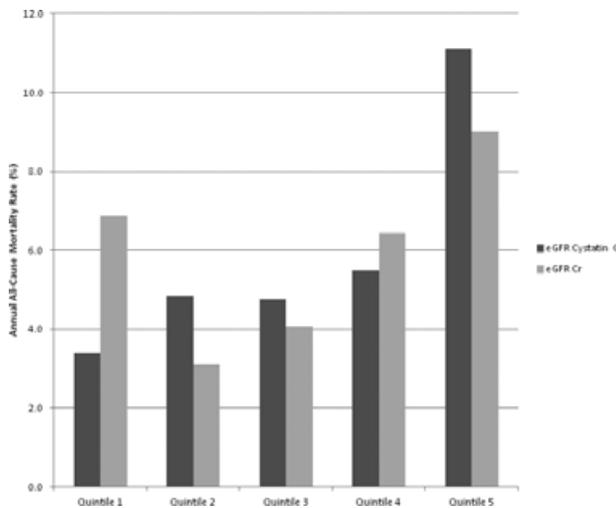


Figure 1. All-cause mortality according to quintile of kidney function measure. eGFR = estimated glomerular filtration rate (mL/min per 1.73 m^2).

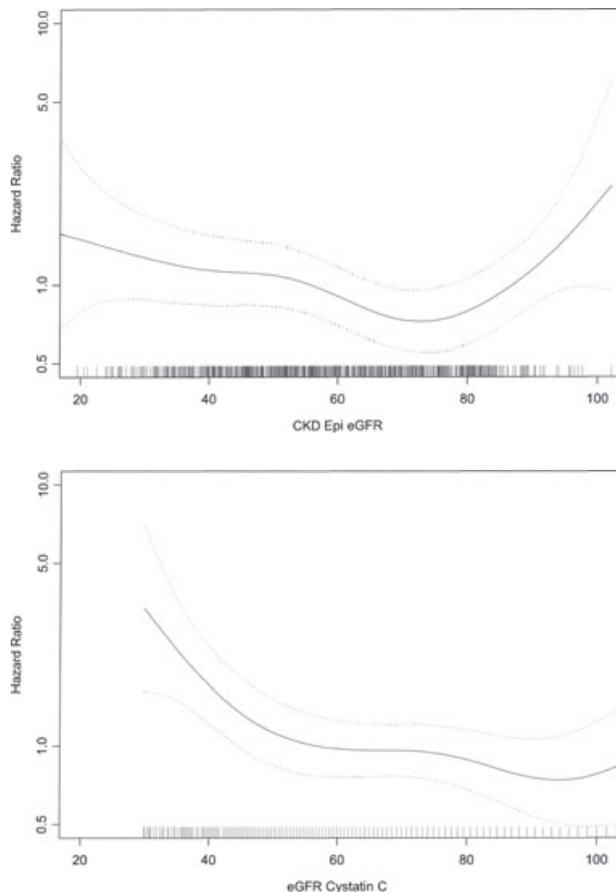


Figure 2. Spline evaluating relationship between kidney function measures and all-cause mortality adjusting for age, sex, and race and excluding the top and bottom 2.5%. CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate (mL/min per 1.73 m^2).

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} \geq 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

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)

^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.

eGFR = estimated glomerular filtration rate.

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)

^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.

eGFR = estimated glomerular filtration rate.

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 m². 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 impaired kidney function are needed in the oldest old.

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