

Chronic Kidney Disease in Octogenarians

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Summary

Background and objectives There are limited data on the prevalence of chronic kidney disease (CKD) and its clinical importance in the very old. We examined the prevalence of CKD in octogenarians and its association with cardiovascular disease (CVD).

Design, setting, participants, & measurements In a cross-sectional analysis of 1028 participants from the Cardiovascular Health Study All Stars, we evaluated association of prevalent CKD with CVD using multivariable logistic regression. CKD was defined as eGFR of <60 ml/min per 1.73 m². GFR was estimated using CKD-Epi creatinine and cystatin C equations that incorporate coefficients for age, gender, and race (eGFR_{EPI}, eGFR_{CYS3var}) and the one-variable cystatin C equation (eGFR_{CYS1var}). Prevalent CVD was defined as a composite of coronary heart disease, heart failure, and stroke.

Results Mean age was 86 years, 64% were women, 86% were Caucasians, 14% had diabetes, and 39% had prevalent CVD. Mean eGFR_{EPI}, eGFR_{CYS3var}, and eGFR_{CYS1var} were 59, 62, and 70 ml/min per 1.73 m², and 51%, 46%, and 33% had CKD, respectively. Associations of CKD with CVD varied by equation in adjusted analyses: CKD_{EPI} (OR, 1.53; 95% CI, 1.15 to 2.03), CKD_{CYS3var} (OR, 1.67; 95% CI, 1.25, 2.23), and CKD_{CYS1var} (OR, 2.09; 95% CI, 1.55, 2.83).

Conclusions Reduced eGFR is highly prevalent in octogenarians, and the eGFR_{CYS1var} equation yielded the lowest prevalence of CKD but the strongest association with prevalent CVD. Because there are no validated estimating equations in the elderly, estimation of kidney function on the basis of on any one equation should be interpreted with caution.

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Introduction

Chronic kidney disease (CKD) is a major public health problem disproportionately affecting the elderly. In various epidemiologic studies, approximately one-third to one-half of the individuals older than 70 years have CKD (1–3). Age was also the leading risk factor for incident CKD in the Framingham Heart Study (4). Thus, older individuals are most likely both to have CKD and to develop CKD over time. According to the United States Census Bureau, 8 million persons were 80 years or older in 2000, and by 2040 this will increase to 27 million when the “baby boomers” reach old age (5). Given the projected growth of the elderly population, understanding the prevalence and associations of CKD in octogenarians has important clinical and economic consequences.

Most prior studies that have evaluated the prevalence of CKD in the elderly have focused on individuals between the ages of 65 and 80 years (2,3). Many have utilized estimating equations on the basis of serum creatinine, but equations using serum creatinine may be particularly limited as a measure of estimated GFR (eGFR) in older adults in whom

there may be a high prevalence of chronic disease associated with alterations in muscle mass and diet. Cystatin C, an alternative marker of GFR, may be less influenced by muscle mass (6,7) and has advantages as a marker of kidney function in the elderly where muscle mass is unpredictable. Conversely, cystatin C may be more affected by inflammatory status than serum creatinine (8,9).

The presence of CKD is recognized as an important, independent risk factor for all-cause mortality and cardiovascular disease (CVD) in most (10–16), but not all, longitudinal studies (17,18). Furthermore, most longitudinal studies suggest that cystatin C is more strongly associated with CVD than serum creatinine (15,19). However, few studies have evaluated the association of kidney function with CVD in octogenarians (20–22). The latter is important given the high prevalence of CKD in the elderly as well as the recognition that CKD may carry less prognostic importance as one ages (1).

We used data from Cardiovascular Health Study All Stars participants, survivors of at least 17 years from enrollment into the Cardiovascular Health Study (CHS), to assess the prevalence of CKD using

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different estimating equations on the basis of serum creatinine and cystatin C in octogenarians and the association of CKD with CVD in cross-sectional analyses.

Materials and Methods

Study Population

The CHS is a longitudinal study of community-dwelling adults aged 65 years and older recruited from Medicare eligibility lists in four United States communities (Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Pittsburgh, PA) that was designed to examine subclinical and clinical CVD risk factors in older adults. Sampling and recruitment procedures have been described in detail elsewhere (23). An initial 5201 participants were recruited between 1989 and 1990, and an additional 687 black participants were added to the study between 1992 and 1993.

Until 1999, semiannual contact with participants alternated between clinic examinations and telephone contacts, during which time information about hospitalizations and potential CVD events were collected. Subsequently, participants were contacted twice a year by telephone to collect data, including use of various medications, and to identify all hospitalizations and potential cardiovascular events that were adjudicated by committee. During the seventeenth year of follow-up (April 2005 to May 2006), the CHS cohort was re-recruited for the CHS All Stars Study (24). The flow of patients is shown in Figure 1.

Exposure Variable

Serum creatinine was measured using a colorimetric method (Ektachem 700; Eastman Kodak, Rochester, NY), which was calibrated to isotope dilution mass spectrometry (IDMS). The intra-assay coefficient of variation for creatinine was 1.94%. Cystatin C was measured using a BN II nephelometer (Siemens) by a particle-enhanced immunonephelometric assay (N Latex Cystatin-C) on frozen serum samples stored at -70°C . The intra-assay coefficient of variation for cystatin C ranged from 2.0 to 2.8%. Estimated GFR was calculated using the Chronic Kidney Disease Epidemiology (CKD-Epi) equation because it may be more accurate and less biased than the Modification of Diet in Renal Disease (MDRD) Study equation at higher levels of GFR. $\text{eGFR}_{\text{EPI}} = 141 \times \text{minimum}(\text{Scr}/\kappa, 1)^{\alpha} \times \text{maximum}(\text{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$ (if female) $\times 1.159$ (if black), where κ is 0.7 for women and 0.9 for men, and α is -0.329 for women and -0.411 for men (25). eGFR_{EPI} is expressed in ml/min per 1.73 m^2 of body surface area.

Most prior studies that have utilized a GFR estimate from cystatin C have chosen a single variable GFR equation (26). The cystatin C demographic equation had slightly higher accuracy and precision and lower bias when compared with the cystatin C one-variable equation in a pooled study of patients with established CKD with mean age of 52 years (8). We estimated GFR using both equations,

$$\text{eGFR}_{\text{CYS1var}} = 76.7 \times \text{CysC}^{-1.19}$$

$\text{eGFR}_{\text{CYS3var}} = 127.7 \times \text{CysC}^{-1.17} \times \text{age}^{-0.13} \times 1.06$ (if black) $\times 0.91$ (if female)

where eGFR is expressed as ml/min per 1.73 m^2 of body surface area, and CysC is serum cystatin C expressed in mg/L (8).

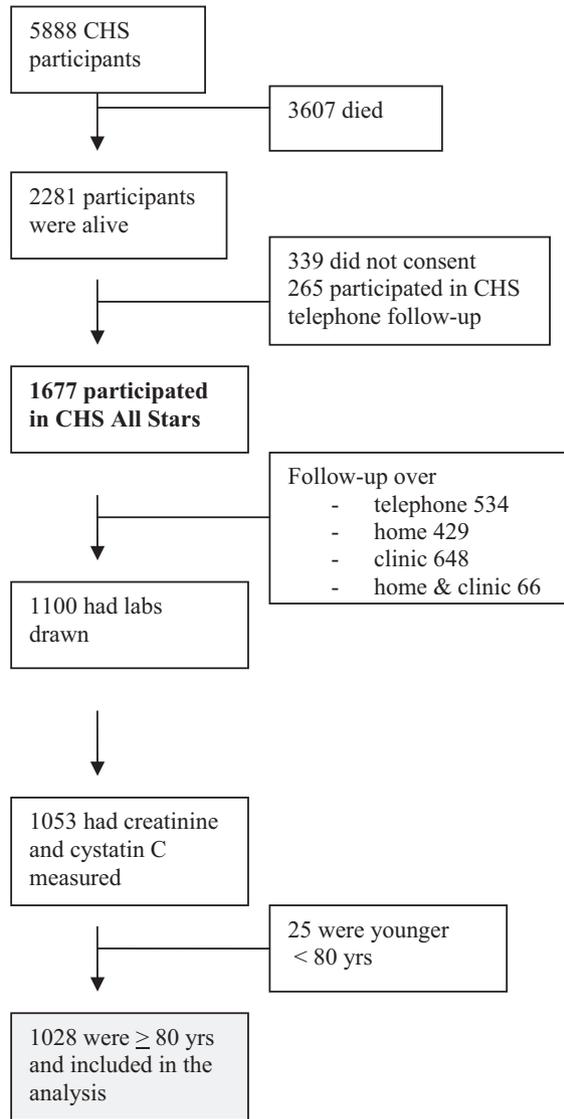


Figure 1. | Flow diagram of cardiovascular health study participants.

For ease of interpretation, comparison with other studies, and consistency with kidney disease guidelines, CKD was defined as $\text{eGFR} < 60 \text{ ml/min per } 1.73 \text{ m}^2$ using any of the three equations. CKD stages 3 and stage 4 were defined as $\text{eGFR} 30 \text{ to } 60 \text{ ml/min per } 1.73 \text{ m}^2$ and $\text{eGFR} < 30 \text{ ml/min per } 1.73 \text{ m}^2$, respectively (27). We recognize that despite recent studies demonstrating an association of eGFR below $60 \text{ ml/min per } 1.73 \text{ m}^2$ (even in the absence of albuminuria) with adverse outcomes (16), there continues to be debate as to whether reduced GFR in the elderly is due to a normal decline associated with aging *versus* whether it meets criteria to define a disease state (28,29).

Study Outcome

The primary study outcome was prevalent clinical CVD, defined as a composite of history of coronary heart disease, heart failure, or stroke, at the time of initiation of CHS All Stars. Coronary heart disease was defined as history of angina, myocardial infarction, angioplasty, or

coronary bypass surgery. Potential events were identified through contact with participants or proxies. Reports not confirmed by examination or medication use were investigated by review of medical records. All of the events were adjudicated by a committee as described previously (30).

Covariates

Covariates were chosen for multivariate analyses on the basis of prior studies or the biologic plausibility of variables that may confound the association between decreased kidney function and presence of CVD. These included: (1) demographic variables (age, gender, and race); (2) cardiovascular risk factors (body mass index calculated as weight in kilograms/height in meters squared, hypertension [defined as self-reported history or an average of three BP measurements $\geq 140/90$ mmHg], diabetes [defined as self-reported history of diabetes, use of insulin, or oral hypoglycemic agent or fasting glucose value ≥ 126 mg/dl], systolic BP, diastolic BP, smoking, LDL cholesterol, and HDL cholesterol); and (3) novel cardiovascular risk factors (C-reactive protein, vitamin D₂₅).

Statistical Analyses

Descriptive analyses were used to summarize baseline characteristics of the study participants according to stages of CKD. Continuous data are presented as means \pm SD, and categorical variables are presented as proportions. ANOVA (31) and Pearson chi-squared test (32) with trend *P* values were used to compare the stages of CKD across continuous and categorical variables, respectively. Because the distribution of C-reactive protein is skewed, the data are presented as median and interquartile ranges, and the Kruskal-Wallis test (33) was used to compare this variable across the stages of CKD. Pearson correlation was used to assess the correlation between creatinine and cystatin C-based estimates of GFR. The overlap of CKD groups on the basis of creatinine (CKD_{EPI}) and cystatin C three (CKD_{CYS3var}) and cystatin C one-variable (CKD_{CYS1var}) eGFR was evaluated, and the degree of agreement between the two was assessed using weighted kappa statistics (32). Logistic regression analyses were used to examine the association of kidney function with CVD (34). Separate models were constructed for eGFR defined either by creatinine or cystatin C. Creatinine- and cystatin C-based eGFR were initially modeled as continuous variables, and a piecewise linear model was used because of nonlinearity, where eGFR was modeled in 10 ml/min per 1.73 m² increments for those with eGFR <60 ml/min per 1.73 m² and ≥ 60 ml/min per 1.73 m². Analyses were repeated for cystatin C and creatinine CKD stages with the reference group being those without CKD.

Initial analyses were unadjusted, and subsequent analyses were adjusted for demographic factors and CVD risk factors with the same variables in each model. Interactions were assessed *a priori*, between CKD and diabetes and CKD and gender, given that nephropathy in diabetes is a particularly high risk state, and there are known differences between men and women in nontraditional CVD risk factors in patients with CKD (35). To assess whether the addition of CKD defined by cystatin C added prognostic

information to CKD defined by creatinine, participants were categorized into four mutually exclusive groups: eGFR_{EPI} < 60 ml/min per 1.73 m² only, eGFR_{CYS3var} < 60 ml/min per 1.73 m² only, eGFR_{EPI} and eGFR_{CYS3var} < 60 ml/min per 1.73 m², and eGFR_{EPI} and eGFR_{CYS3var} ≥ 60 ml/min per 1.73 m² (reference group). A similar analysis was repeated using the cystatin C one-variable equation.

Sensitivity Analyses. Several sensitivity analyses were performed to assess the consistency of our results. Analyses were repeated using the four-variable MDRD Study equation given that it is currently the most commonly used estimating equation ($eGFR = 175 \times \text{standardized Scr}^{-1.154} \times \text{age}^{-0.203} \times 1.212$ [if black] $\times 0.742$ [if female]), in which eGFR is expressed as ml/min per 1.73 m² of body surface area and where Scr is serum creatinine expressed in mg/dL (36). Because prior studies have shown that kidney function may have different relationships with atherosclerotic CVD and heart failure (37), repeat analyses were performed by excluding those individuals with a history of heart failure, but with no other form of atherosclerotic CVD, from our working definition of CVD. Finally, because high GFR, a marker of low creatinine and malnutrition, has also been associated with CVD and mortality (14), we repeated the CKD_{EPI} analyses with eGFR_{EPI} of 60 to 90 ml/min per 1.73 m² as the reference group, rather than eGFR_{EPI} >60 ml/min per 1.73 m². Analyses were performed using SAS software (9.2; SAS, Cary, NC). We considered two-tailed *P* < 0.05 as statistically significant.

Results

Characteristics of Study Participants

Of the 1053 CHS All Stars participants in whom creatinine and cystatin C was measured, 25 were excluded because they were younger than 80 years old, resulting in a sample of 1028 participants for these analyses. Participants who were alive but did not have laboratory data available were more likely to be women, to be older, and to have a higher prevalence of myocardial infarction and stroke compared with those included in the analysis.

The average age of the study sample was 86 years, and 64% were women, 86% were Caucasians, two-thirds had hypertension, and 14% had diabetes. Mean eGFR_{EPI}, eGFR_{CYS3var}, and eGFR_{CYS} were 59, 62, and 70 ml/min per 1.73 m², respectively (Table 1). The Pearson correlation between eGFR_{EPI} and eGFR_{CYS3var} was 0.75 (*p* = <0.01), and that between eGFR_{EPI} and eGFR_{CYS1var} was 0.74 (*p* = <0.01). Compared with participants without CKD, those with CKD were more likely to be older and have a history of hypertension and diabetes, higher C-reactive protein levels, and lower HDL cholesterol and LDL cholesterol levels. Similar results were obtained when CKD was considered using cystatin C.

Prevalence of CKD

On the basis of eGFR_{EPI}, eGFR_{CYS3var}, and eGFR_{CYS1var} equations, 51.3, 46.1, and 33.0% participants, respectively, had CKD. There was moderate agreement between both the CKD_{EPI} and CKD_{CYS3var} stages and the CKD_{EPI} and CKD_{CYS1var} stages, and the weighted kappa statistic was 0.58 (95% CI, 0.53 to 0.62) and 0.51 (95% CI, 0.46 to 0.55), respectively (Table 2).

Table 1. Baseline characteristics by level of kidney function using the CKD-Epi equation

Characteristics	Total	eGFR _{EPI} (ml/min per 1.73 m ²)			P ^a
		>60	30 to 59	<30	
<i>n</i>	1028	501	477	50	
Age	85.5 (3.5)	85.2 (3.4)	85.7 (3.6)	86.2 (3.7)	<0.01
Women	63.8	62.7	66.5	50.0	0.89
White race	85.9	83.2	88.5	88.0	0.03
Body mass index (kg/m ²)	26.8 (4.7)	26.6 (4.6)	26.8 (4.7)	27.8 (5.0)	0.22
Ever smoked	49.2	50.2	48.2	48.0	0.54
Diabetes	14.4	13.1	13.9	32.0	0.02
Hypertension	65.6	60	69.5	84.0	<0.01
Systolic blood pressure (mmHg)	132.7 (21.1)	133.7 (20.8)	131.4 (20.9)	135.7 (25.9)	0.19
HDL cholesterol (mg/dl)	54.3 (15.3)	55.7 (15.2)	53.7 (15.3)	44.9 (12.3)	<0.01
LDL cholesterol (mg/dl)	101.3 (31.5)	104.0 (32.0)	99.0 (30.5)	96.0 (33.7)	<0.01
Vitamin D ₂₅ (ng/ml)	25.9 (10.4)	24.8 (9.1)	27.2 (11.5)	25.1 (11.3)	<0.01
C-reactive protein (mg/L) ^b	2.0 (1.0, 4.5)	1.8 (0.9, 4.1)	2.1 (1.0, 5.0)	3.0 (1.8, 7.8)	<0.01
Creatinine (mg/dl)	1.1 (0.5)	0.8 (0.1)	1.2 (0.2)	2.7 (1.4)	<0.01
Cystatin C (mg/L)	1.2 (0.5)	1.0 (0.2)	1.3 (0.3)	2.4 (1.0)	<0.01
MDRD eGFR	61.8 (19.1)	77.0 (12.9)	49.8 (8.2)	23.7 (7.4)	<0.01
CKD-Epi eGFR	58.8 (17.0)	72.9 (8.5)	47.7 (8.1)	21.9 (7.1)	<0.01
Cystatin C eGFR using one- variable equation	69.8 (21.7)	82.6 (17.7)	60.3 (15.9)	31.2 (10.6)	<0.01
Cystatin C eGFR using three- variable equation	61.9 (19.2)	73.4 (15.9)	53.4 (13.7)	28.3 (9.5)	<0.01

The data are presented either as means (SD) or percentages. Represent $P = 0.0000$ as $P < 0.01$.

^aTrend P values.

^bMedian [IQR] with Kruskal-Wallis test.

Cross-sectional Association of CVD with CKD

The overall prevalence of CVD in this study sample was 38.5%, of which 30.5% had a history of coronary heart disease, 14.5% had heart failure, and 8.1% had stroke. A piecewise linear form with cut-point of 60 ml/min per 1.73 m² was chosen for the continuous models on the basis of current definition of CKD (Table 3). In these analyses, eGFR <60ml/min per 1.73 m² was associated with CVD with the strongest relationship in eGFR_{CYS1var} analysis. There was no significant relationship between CVD and eGFR >60 ml/min per 1.73 m². In both unadjusted and adjusted analyses, associations of CKD with CVD varied by the equation with increased odds of CVD in those with CKD stage 4 compared with stage 3 (Table 3). CKD when defined by cystatin C was associated with higher odds of CVD compared with CKD_{EPI}. There was no interaction between CKD with diabetes or gender ($P = 0.7$ for both).

When participants were categorized into four mutually exclusive groups using eGFR_{EPI} and eGFR_{CYS}, CKD was associated with CVD only in those participants who were identified as having CKD by both measures when eGFR_{CYS3var} was used (Table 4). In comparison, when CKD was defined using the eGFR_{CYS1var} equation, there was a significant association with CVD, irrespective of CKD on the basis of eGFR_{EPI}.

Sensitivity Analyses

The prevalence of CKD using MDRD equation was 47.3%, which is very similar to that obtained using CKD_{EPI} and CKD_{CYS3var}. In multivariable analyses, the presence of CKD was also associated with similar odds of CVD (OR, 1.57; 95% CI, 1.18 to 2.10). The results were essentially unchanged when the 36 participants with heart failure and

no other atherosclerotic CVD were excluded from the definition of CVD. That is, CKD was associated with a higher odds of CVD using CKD_{EPI} (OR, 1.54; 95% CI, 1.15 to 2.06) and CKD_{CYS3var} (OR, 1.56; 95% CI, 1.16 to 2.09). Finally, when eGFR_{EPI} 60 to 90 ml/min per 1.73 m² was used as the reference group, the results were similar. Those with CKD_{EPI} stage 3 (OR, 1.39; 95% CI, 1.04 to 1.87) and stage 4 (OR, 4.12; 95% CI, 2.02 to 8.43) had higher odds of CVD when compared with eGFR_{EPI} 60 to 90 ml/min per 1.73 m².

Discussion

In this community-based cohort of octogenarians, we observed a high prevalence of CKD. Although the prevalence of CKD and strength of the association between CKD and CVD varied depending on the estimating equation used, the association was significant across all of our analyses.

There was a very high prevalence of CKD in our population, and our findings are consistent with those previously reported in the elderly (1,38,39). The prevalence of CKD was 40% among a national cohort of veterans aged 75 to 84 years (1); in the Kidney Early Evaluation Program, a high risk population, the prevalence of CKD was 60% in individuals over 80 years (38); and in the National Health and National Examination Survey, which oversamples minorities, the prevalence of CKD was 68% (38). Differences in the prevalence of CKD may be due to differences in the clinical and demographic characteristics of the study population, criteria used to define CKD, age of subjects, and measurement of serum creatinine (calibrated *versus* uncalibrated). Also, most studies have used serum creatinine-based estimating equations. This is one of the first studies in patients over 80 years of age where GFR was

Table 2. Agreement between CKD_{EPI} and CKD_{Cys} stages

eGFR _{EPI} (ml/min per 1.73 m ²)	eGFR _{CYS3var} (ml/min per 1.73 m ²) (n) (%) ^a		Total patients (n) (%)		eGFR _{CYS1var} (ml/min per 1.73 m ²) (n) (%) ^b		Total patients (n) (%)	
	eGFR >60	eGFR 30 to 59	eGFR <30	eGFR <30	eGFR >60	eGFR 30 to 59		eGFR <30
eGFR >60	416 (40.5)	85 (8.3)	0	501 (48.7)	465 (45.2)	36 (3.5)	0	501 (48.7)
eGFR 30 to 59	138 (13.4)	328 (31.9)	11 (1.1)	477 (46.4)	224 (21.8)	248 (24.1)	5 (0.5)	477 (46.4)
eGFR <30	0	20 (2.0)	30 (2.9)	50 (4.9)	0	28 (2.7)	22 (2.1)	50 (4.9)
Total	554 (53.9)	433 (42.1)	41 (4.0)	1028 (100)	689 (67.0)	312 (30.4)	27 (2.6)	1028 (100)

The cell percentages may not total to margin percentages because of rounding. Cells with bold type represent agreement. Cells above the cells with bold represent disagreements in which estimated GFR category was higher with the CKD-Epi equation than with the cystatin C equation; cells below the cells with bold represent disagreements in which estimated GFR category was lower with the CKD-Epi equation than with the cystatin C equation. Parentheses = percentages of total participants (n = 1028). To calculate the percentage of agreement in a particular row, divide the value in bold into the total in that row. To calculate the percentage of agreement in a particular column, divide the value in bold into the total in that column. For example, in patients with eGFR using CKD_{EPI} of <30 ml/min per 1.73 m², the percentage of agreement in rows = 30/50 and percentage of agreement in columns = 30/41.

^aWeighted kappa statistics: 0.58 (95% CI, 0.53 to 0.62).
^bWeighted kappa statistics: 0.51 (95% CI, 0.46 to 0.55).

Table 3. Association of CKD with CVD based on serum creatinine and cystatin C estimates

eGFR (ml/min per 1.73 m ²)	CKD-Epi		Cystatin C Three-variable Equation		Cystatin C One-variable Equation	
	n (%)	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI) ^a	n (%)	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI) ^a
Piecewise linear analysis						
>60 ^b	501 (49)	1.06 (0.89, 1.26)	1.07 (0.88, 1.29)	554 (54)	0.98 (0.88, 1.11)	0.98 (0.86, 1.11)
<60 ^b	527 (51)	1.35 (1.18, 1.55)	1.31 (1.12, 1.53)	474 (46)	1.53 (1.33, 1.77)	1.48 (1.25, 1.75)
CKD 3 groups						
>60	501 (49)	1.00 (ref)	1.00 (ref)	554 (54)	1.00 (ref)	1.00 (ref)
30 to 59	477 (46)	1.45 (1.11, 1.88)	1.40 (1.04, 1.87)	433 (42)	1.63 (1.26, 2.12)	1.54 (1.15, 2.07)
<30	50 (5)	4.79 (2.55, 9.03)	4.16 (2.03, 8.49)	41 (4.0)	6.60 (3.17, 13.76)	5.68 (2.42, 13.34)
CKD 2 groups						
>60	501 (49)	1.00 (ref)	1.00 (ref)	554 (54)	1.00 (ref)	1.00 (ref)
<60	527 (51)	1.62 (1.25, 2.08)	1.53 (1.15, 2.03)	474 (46)	1.83 (1.42, 2.36)	1.67 (1.25, 2.23)

ref, referent group.

^a Adjusted for age, gender, race, body mass index, smoking, diabetes, hypertension, systolic blood pressure, low density lipoprotein cholesterol, high density lipoprotein cholesterol, vitamin D, and log C-reactive protein. The sample sizes are based on the complete case data for all variables used in the multivariable models.

^b Values per 10 ml/min per 1.73 m² lower eGFR.

Table 4. Association of chronic kidney disease with cardiovascular disease using four mutually exclusive groups based CKD-Epi and cystatin C equations

eGFR (ml/min per 1.73 m ²)	Cystatin C Three-variable Equation		Cystatin C One-variable Equation	
	n (%)	Adjusted Odds Ratio (95% CI) ^a	n (%)	Adjusted Odds Ratio (95% CI) ^a
eGFR _{CKD-Epi} and eGFR _{CYS} >60	385 (41)	1.00 (ref)	430 (46)	1.00 (ref)
eGFR _{CKD-Epi} <60/eGFR _{CYS} >60	130 (14)	1.31 (0.84, 2.02)	212 (23)	1.18 (0.81, 1.70)
eGFR _{CKD-Epi} >60/eGFR _{CYS} <60	78 (8)	1.59 (0.94, 2.69)	33 (4)	2.58 (1.22, 5.43)
eGFR _{CKD-Epi} and eGFR _{CYS} <60	349 (37)	1.85 (1.33, 2.57)	267 (28)	2.18 (1.55, 3.06)

ref, referent group.

^aAdjusted for age, gender, race, body mass index, smoking, diabetes, hypertension, systolic blood pressure, low density lipoprotein cholesterol, high density lipoprotein cholesterol, vitamin D, and log C-reactive protein.

estimated using both CKD-Epi and cystatin C equations. We noted that the prevalence of CKD was significantly lower when the cystatin C one-variable equation was used to estimate kidney function. Therefore, although the prevalence of CKD remained very high in the elderly, the prevalence differs depending upon the equation used, despite a strong correlation between creatinine and cystatin C-based estimates of kidney function. Further studies in older adults with actual GFR measurements are needed to evaluate the validity of these estimating equations.

The clinical significance of CKD has been questioned in the elderly (28). Prior studies had conflicting results, with some suggesting that CKD is associated with all-cause (21) and CVD mortality (20,21), whereas others noted an attenuation of this effect with advancing age (1,40). Our results demonstrate that CKD defined using either creatinine or cystatin was independently associated with prevalent CVD in the very old. In addition, an incremental association of CKD with CVD with decreasing kidney function was observed. The reasons why CKD is independently associated with a higher prevalence of CVD are unknown. Among the possibilities are that CKD is a marker of the severity of traditional risk factors, such as hypertension, a measure of nontraditional CVD risk factors, a causal risk factor through promotion of volume retention, anemia, and abnormalities in mineral metabolism, or because of therapeutic nihilism whereby those with CKD are not treated with medications that are known to prevent CVD (41). We also noted that participants identified as having CKD using the cystatin one-variable equation had higher odds of CVD compared with those defined by eGFR_{EPI}. The cystatin one-variable equation therefore identifies a smaller but higher risk group. Follow-up of our cohort will allow assessment of the consistency of these differences in longitudinal analyses.

We were particularly interested in evaluating whether a more specific definition of CKD requiring the presence of both CKD_{CYS} and CKD_{EPI} would identify a higher risk group.

Our results demonstrated that when CKD was defined using the eGFR_{CYS3var} equation, the presence of CKD by eGFR_{EPI} was also required for a significant association with CVD. In comparison, when CKD was defined using

the eGFR_{CYS1var} equation, there was a significant association with CVD, irrespective of CKD on the basis of eGFR_{EPI}. The latter is consistent with combined analyses from Multi-Ethnic Study of Atherosclerosis and CHS (participants were at baseline and therefore of a younger age than in this work), where in patients with a diagnosis of CKD using the creatinine-based CKD-Epi equation, risks for adverse outcomes (death, CVD events, heart failure, and end stage renal disease) were limited to the subset who also have CKD according to the cystatin C-based equation (42). Therefore, cystatin C could in theory be used to distinguish high and low risk individuals defined by CKD_{EPI}.

The results of this study may have particular relevance in the context of the increasing prevalence of CKD in octogenarians. The discrepancies in GFR estimates between different creatinine and cystatin C-based equations must be taken into consideration if cystatin C-based equations become a method for assessing kidney function in the elderly. These differences in estimation of kidney function may affect clinical decision making at an individual level (such as risk/benefit decisions regarding medication dosing and assessing risk of contrast-induced nephropathy), as well as in estimating the burden of CKD in the elderly.

The strengths of our study include the use of data from a well characterized cohort of older men and women. In addition, this is one of the largest cohorts of octogenarians with detailed ascertainment of covariates and CVD. Most prior studies in octogenarians have only used estimating equations on the basis of serum creatinine to assess kidney function, whereas we used IDMS calibrated creatinine as well as cystatin C. Furthermore, we used the CKD-Epi equation, which is more accurate than the MDRD equation at higher levels of GFR, in women, and in persons of white race.

Several limitations need to be considered in interpreting our findings. The CHS All Stars Study lacks direct measurement of GFR, and therefore we cannot comment on discrepancies between creatinine and cystatin C measurements and true GFR. It is possible that some participants with reduced eGFR (e.g. 45 to 59 ml/min per 1.73 m²) may not meet the criteria for CKD, given that the equations have not been validated in this age group. Unfortunately, there are no large studies that have measured GFR or

validated estimating equations in the elderly. Therefore, at the present time and into the foreseeable future, indirect estimates of GFR will be used to assess kidney function, and the limitations of this approach need to be recognized. Urinary protein was not collected in the CHS All Stars study; therefore, we were unable to adjust for the presence of albuminuria or define individuals in CKD stages 1 to 2. Furthermore, in those individuals with eGFR just below the threshold of 60 ml/min per 1.73 m², we had no supportive data to strengthen or weaken the diagnosis of kidney disease. We may also have underestimated the prevalence of CKD, because the participants who did not provide blood samples were in general sicker. This is a cross-sectional analysis; therefore, cause or effect could not be established, and indeed recent data suggest that CVD may contribute to the progression of kidney disease (43). As opposed to the IDMS creatinine reference standard, a cystatin C reference standard is not yet available, and prevalence data may vary depending on its calibration. In addition, cystatin C may be influenced somewhat by factors other than GFR such as age, gender, body fat, smoking, and inflammation; despite adjustment for these variables, residual confounding may have remained (8,9).

In summary, there is a high prevalence of reduced eGFR in octogenarians, and the prevalence of CKD and its relationship with CVD differed depending on the estimating equation used to assess kidney function. Because there are no validated estimating equations in the elderly, estimation on the basis of any one equation should be interpreted with caution. Although octogenarians are survivors, those with CKD defined by either creatinine or cystatin C remain a high risk group. Longitudinal studies in octogenarians are needed to assess the importance of CKD, defined by either eGFR_{EPI} or eGFR_{CYS}, for prognosis and clinical decision making.

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Disclosures

None.

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