The role of cystatin-C in the confirmation of reduced glomerular filtration rate among the oldest old

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Abstract

Introduction: Current guidelines suggest using cystatin-C to confirm a reduced creatinine-based estimated glomerular filtration rate ($eGFR_{cr}$) when the latter is thought to be inaccurate. Older adults have reduced muscle mass, which may affect the accuracy of $eGFR_{cr}$. We evaluated the use of cystatin-C-based eGFR ($eGFR_{cys}$) to confirm reduced $eGFR_{cr}$ among adults ≥ 80 years of age and, for comparison, younger adults.
Material and methods: We analyzed data from 3,059 REasons for Geographic And Racial Differences in Stroke (REGARDS) study participants with reduced $eGFR_{cr}$ (< 60 ml/min/1.73 m^2) enrolled in 2003–2007 who were not on dialysis. $eGFR_{cr}$ and $eGFR_{cys}$ were calculated using age, sex and race-adjusted equations. Confirmed reduced $eGFR_{cr}$ was defined as $eGFR_{cys}$ < 60 ml/min/1.73 m^2. Prevalence of chronic kidney disease complications at baseline and all-cause mortality up to March 2012 were calculated. Analyses were stratified by age: < 65, 65–79 and ≥ 80 years.
Results: Among participants < 65, 65–79 and ≥ 80 years of age, 76.5%, 85.7% and 92.5%, respectively, had reduced $eGFR_{cr}$ confirmed with $eGFR_{cys}$ (p < 0.001). Among participants ≥ 80 years of age, those with reduced $eGFR_{cr}$ confirmed with $eGFR_{cys}$ had higher prevalence of hypertension (79.1% vs. 65.1%, p = 0.03) and albuminuria (38.3% vs. 22.7%, p = 0.04) and higher risk for all-cause mortality (hazard ratio: 2.43; 95% confidence interval: 1.19–5.01) as compared with those in whom reduced $eGFR_{cr}$ was not confirmed by $eGFR_{cys}$.
Conclusions: Reduced $eGFR_{cr}$ was confirmed using $eGFR_{cys}$ for the vast majority of adults ≥ 80 years. These results suggest that using cystatin-C to confirm a reduced $eGFR_{cr}$ may not be necessary among the oldest old.

Key words: aged, 80 and over, kidney function tests, renal insufficiency, chronic, mortality.

Introduction

The number of US adults 80 years and older (hereafter, the oldest old) with reduced estimated glomerular filtration rate (eGFR, < 60 ml/min/1.73 m^2) has increased over the last 20 years and is expected to

more than double to 9.9 million people by 2030 [1, 2]. Despite studies showing associations of reduced eGFR with increased risk for mortality, cardiovascular disease and concurrent chronic kidney disease (CKD) complications [3–7], questions remain about the use of creatinine-based equations alone to estimate GFR and define CKD in this population [8].

The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Evaluation and Management of CKD recommends using creatinine-based equations for initial assessment of CKD [9]. The guideline also suggests using serum cystatin-C as an additional test in circumstances when estimations based on serum creatinine are thought to be inaccurate [9]. Sarcopenia, defined as a progressive loss of skeletal muscle mass, is more common at older age [10, 11]. Because serum creatinine is a product of muscle metabolism, sarcopenia could affect the accuracy of serum creatinine-based equations to estimate GFR [9]. Therefore, there may be a greater need to confirm reduced eGFR based on serum creatinine among the oldest old.

In the current study, we estimated the percentage of the oldest old with reduced eGFR calculated using serum creatinine confirmed with serum cystatin-C eGFR. For comparison, this percentage was also calculated for younger adults. We hypothesized that among individuals with reduced serum creatinine-based eGFR, the percentage with reduced eGFR based on serum cystatin-C would be lower among the oldest old compared with younger adults. In addition, we compared the prevalence of concurrent CKD complications and risk for all-cause mortality among adults with serum creatinine-based reduced eGFR confirmed versus not confirmed by serum cystatin-C-based eGFR by age group. For completeness, we also analyzed the use of serum cystatin-C for the confirmation of a preserved eGFR based on serum creatinine.

Material and methods

Study population

We used data from the REasons for Geographic And Racial Differences in Stroke (REGARDS) study, a US population-based prospective cohort study designed to investigate reasons underlying the higher rate of stroke mortality among blacks compared with whites and residents of the Southeastern US compared with the rest of the continental US [12]. A total of 30,239 black and white men and women aged 45 years or older were recruited from all 48 contiguous US states and the District of Columbia between January 2003 and October 2007. Blacks and residents of the Southeastern US were oversampled by design. For the present analysis, we included participants who were not on dialysis, had measurements of serum creatinine and cystatin-C at baseline, and follow-up information on all-cause mortality. A total of 27,528 REGARDS participants met the inclusion criteria (Figure 1). The REGARDS study was approved by the institutional review boards at the participating centers and all participants provided written informed consent.

Baseline assessment

REGARDS baseline data were collected through a telephone interview followed by an in-home examination, each performed by trained staff and following standardized protocols. Self-reported information collected during the telephone interview at baseline included age, race, gender, education, physical activity, current cigarette smoking,

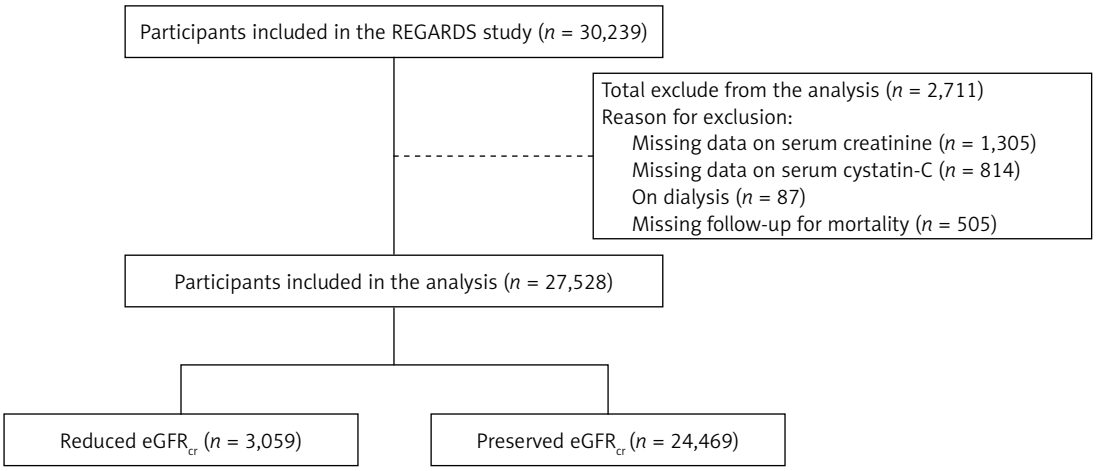

Figure 1. Flow-chart of REGARDS participants included in the study

$eGFR_{cr}$ – estimated glomerular filtration rate using serum creatinine, REGARDS – REasons for Geographic And Racial Differences in Stroke. Reduced $eGFR_{cr}$ was defined as $eGFR_{cr}$ < 60 ml/min/1.73 m². Preserved $eGFR_{cr}$ was defined as $eGFR_{cr} \geq 60$ ml/min/1.73 m².

history of stroke and use of antihypertensive medications. During the in-home examination, blood pressure, weight, height and waist circumference were measured, an electrocardiogram was recorded, and blood and urine samples were collected. Prescription and over-the-counter medications used in the 2 weeks prior to the in-home examination were reviewed and recorded.

History of coronary heart disease (CHD) was defined by self-report of a prior diagnosis or evidence of a previous myocardial infarction (MI) on the study electrocardiogram, coronary bypass, coronary angioplasty, or coronary stenting. Diabetes was defined as self-reported treatment with oral antidiabetes medication or insulin, fasting (≥ 8 h) serum glucose ≥ 126 mg/dl or non-fasting serum glucose ≥ 200 mg/dl. High waist circumference was defined as > 102 cm among males and > 88 cm among females. Body mass index (BMI) was calculated as weight in kg/(height in meters)^2, and categorized as < 18.5, 18.5 to < 25.0, 25.0 to < 30.0 and ≥ 30.0 kg/m^2. Use of statins was defined based on the in-home review of medications.

Glomerular filtration rate

Serum creatinine and cystatin-C were measured using blood samples collected during the baseline in-home assessment. Serum creatinine was measured and calibrated using an isotope-dilution mass spectrometry traceable method [4]. Cystatin-C was measured using a particle-enhanced immunonephelometric assay (N Latex Cystatin C, formerly Dade Behring, now Siemens AG, Munich, Germany). For each participant, eGFR was calculated using serum creatinine ($eGFR_{cr}$) and, separately, using serum cystatin-C ($eGFR_{cys}$) and the age, race, sex Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations [13]. $eGFR_{cr}$ and $eGFR_{cys}$ were each categorized as preserved (GFR ≥ 60 ml/min/1.73 m^2) or reduced (< 60 ml/min/1.73 m^2). Also, we calculated eGFR using a CKD-EPI equation that includes the combination of serum creatinine and cystatin-C ($eGFR_{cr,cys}$) and the two versions of the Berlin Initiative Study (BIS) equation ($eGFR_{BIS1}$ and $eGFR_{BIS2}$) [13, 14]. Table I shows the equations used for the present analysis.

Concurrent CKD complications and all-cause mortality

Concurrent CKD complications considered for the present analysis included hypertension, serum albumin concentration < 3.8 g/dl, anemia, high-sensitivity C-reactive protein (hsCRP) > 3 mg/l and urinary albumin-to-creatinine ratio (ACR) > 30 mg/g. Blood pressure was measured

Table I. Equations used to calculate estimated glomerular filtration rate

eGFR	Gender	Scys [mg/l]	Scr [mg/dl]	Equation
$eGFR_{cr}$ [13][a]	Female	–	≤ 0.7	$144 \times (Scr/0.7)^{-0.329} \times 0.993^{Age}$ [× 1.159 if black]
	Female	–	> 0.7	$144 \times (Scr/0.7)^{-1.209} \times 0.993^{Age}$ [× 1.159 if black]
	Male	–	≤ 0.9	$141 \times (Scr/0.9)^{-0.411} \times 0.993^{Age}$ [× 1.159 if black]
	Male	–	> 0.9	$141 \times (Scr/0.9)^{-1.209} \times 0.993^{Age}$ [× 1.159 if black]
$eGFR_{cys}$ [13]	–	≤ 0.8	–	$133 \times (Scys/0.8)^{-0.499} \times 0.996^{Age}$ [× 0.932 if female]
	–	> 0.8	–	$133 \times (Scys/0.8)^{-1.328} \times 0.996^{Age}$ [× 0.932 if female]
$eGFR_{cr,cys}$ [13]	Female	≤ 0.8	≤ 0.7	$130 \times (Scr/0.7)^{-0.248} \times (Scys/0.8)^{-0.375} \times 0.995^{Age}$ [× 1.08 if black]
	Female	≤ 0.8	> 0.7	$130 \times (Scr/0.7)^{-0.601} \times (Scys/0.8)^{-0.375} \times 0.995^{Age}$ [× 1.08 if black]
	Female	> 0.8	≤ 0.7	$130 \times (Scr/0.7)^{-0.248} \times (Scys/0.8)^{-0.711} \times 0.995^{Age}$ [× 1.08 if black]
	Female	> 0.8	> 0.7	$130 \times (Scr/0.7)^{-0.601} \times (Scys/0.8)^{-0.711} \times 0.995^{Age}$ [× 1.08 if black]
	Male	≤ 0.8	≤ 0.9	$135 \times (Scr/0.9)^{-0.207} \times (Scys/0.8)^{-0.375} \times 0.995^{Age}$ [× 1.08 if black]
	Male	≤ 0.8	> 0.9	$135 \times (Scr/0.9)^{-0.601} \times (Scys/0.8)^{-0.375} \times 0.995^{Age}$ [× 1.08 if black]
	Male	> 0.8	≤ 0.9	$135 \times (Scr/0.9)^{-0.207} \times (Scys/0.8)^{-0.711} \times 0.995^{Age}$ [× 1.08 if black]
	Male	> 0.8	> 0.9	$135 \times (Scr/0.9)^{-0.601} \times (Scys/0.8)^{-0.711} \times 0.995^{Age}$ [× 1.08 if black]
$eGFR_{BIS1}$ [14]	–	–	–	$3736 \times Scr^{-0.87} \times Age^{-0.95}$ [× 0.82 if female]
$eGFR_{BIS2}$ [14]	–	–	–	$767 \times Scys^{-0.61} \times Scr^{-0.40} \times Age^{-0.57}$ [× 0.87 if female]

BIS – Berlin Initiative Study, eGFR – estimated glomerular filtration rate, Scr – serum creatinine, Scys – serum cystatin-C. [a]This equation is also known as the CKD-EPI equation.

twice during the in-home study visit following a 5-minute rest. Based on the average of the two measurements, hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or self-reported use of antihypertensive medications. Anemia was defined as hemoglobin concentration < 13.0 and < 12.0 g/dl for males and females, respectively [15].

REGARDS participants or their proxies are contacted by telephone every 6 months following the baseline study visit to determine vital status. Reported deaths and the date of death were confirmed through the Social Security Death Index, death certificates, or the National Death Index. For the current analysis, data on mortality for REGARDS participants up to March 29, 2012 were analyzed.

Statistical analysis

All analyses were conducted stratified by age: (1) < 65 years, (2) 65 to 79 years, and (3) ≥ 80 years of age. The main analyses were limited to participants with reduced $eGFR_{cr}$. Among this group, participants with $eGFR_{cys}$ < 60 ml/min/1.73 m^2 were considered to have confirmed reduced $eGFR_{cr}$. We calculated baseline characteristics of participants whose reduced $eGFR_{cr}$ was confirmed and not confirmed using $eGFR_{cys}$. The percentage of participants with confirmed reduced $eGFR_{cr}$ across age strata was compared using a χ^2 test.

Table II. Missing data among REGARDS participants included in the analysis (*n* = 27,528). These data were imputed using chained equations

Variable[a]	*N* missing (%)
Less than high school	21 (0.1)
No physical activity	417 (1.5)
Current smoking	101 (0.4)
History of CHD	493 (1.8)
History of stroke	90 (0.3)
Diabetes	140 (0.5)
Waist circumference	150 (0.5)
Concurrent CKD complications:	
Hypertension	67 (0.2)
Serum albumin < 3.8 g/dl	7,561 (27.5)
Anemia	8,438 (30.7)
hsCRP > 3 mg/l	12 (< 0.1)
ACR > 30 mg/g	898 (3.3)

ACR – albumin : creatinine ratio, CHD – coronary heart disease, hsCRP – high sensibility C-reactive protein, REGARDS – REasons for Geographic And Racial Differences in Stroke. [a]Only variables with missing data are listed. The remainder of variables studied had no missing data. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or self-reported use of antihypertensive medications. Anemia was defined as hemoglobin concentration < 13.0 g/dl and < 12.0 g/dl for males and females, respectively [15].

In addition, we calculated the percentage of participants whose reduced $eGFR_{cr}$ was confirmed using $eGFR_{cr,cys}$, $eGFR_{BIS1}$ and $eGFR_{BIS2}$. Among participants ≥ 80 years of age, we calculated the percentage whose reduced $eGFR_{cr}$ was confirmed using $eGFR_{cys}$ by level of waist circumference and, separately, BMI.

We calculated the prevalence of concurrent CKD complications among participants with and without confirmed reduced $eGFR_{cr}$, separately. Differences in the prevalence of concurrent CKD complications across these categories were determined using maximum likelihood. We used the Kaplan-Meier method to estimate cumulative mortality for participants with and without confirmed $eGFR_{cr}$ with the statistical significance of differences determined using log-rank tests. Hazard ratios (HRs) for all-cause mortality comparing participants with versus without confirmed $eGFR_{cr}$ were estimated using Cox proportional hazard models. Three progressively multivariable adjusted Cox proportional hazard models were used. Model 1 included adjustment for age, race, gender, region of residence and $eGFR_{cr}$. Model 2 included adjustment for variables in Model 1 plus education level, physical activity, smoking, history of CHD, history of stroke, diabetes, waist circumference and statin use. Model 3 included adjustment for variables in Model 2 and hypertension, serum albumin < 3.8 g/dl, anemia, hsCRP > 3 mg/l and ACR > 30 mg/g. In a regression model including all age groups and interaction terms, we assessed whether the HRs for all-cause mortality were different across age groups.

For completeness, we conducted analyses to confirm preserved $eGFR_{cr}$. For this secondary analysis, the percentage of participants whose preserved $eGFR_{cr}$ (i.e., $eGFR_{cr}$ ≥ 60 ml/min/1.73 m^2) was confirmed using $eGFR_{cys}$ (i.e., $eGFR_{cys}$ ≥ 60 ml/min/1.73 m^2), and separately using $eGFR_{cr,cys}$, $eGFR_{BIS1}$ and $eGFR_{BIS2}$, was calculated by age group. Among participants ≥ 80 years of age, we calculated the percentage whose preserved $eGFR_{cr}$ was confirmed using $eGFR_{cys}$ by waist circumference and BMI, separately. Also, prevalence of concurrent CKD complications and HRs for all-cause mortality were estimated comparing participants whose preserved $eGFR_{cr}$ was confirmed versus not confirmed using $eGFR_{cys}$.

Because a substantial proportion of REGARDS participants do not have baseline information on serum albumin and hemoglobin (Table II), we used multiple imputation when estimating the prevalence of concurrent CKD complications as well as multivariable adjusted HRs for all-cause mortality. For these analyses, we imputed 10 data sets using chained equations. Multiple imputation was based on observed values from all the variables included in the fully adjusted Cox regression model (Model 3) and all-cause mortality [16, 17].

All analyses were conducted using Stata/I.C. 13.1 (Stata Corporation, College Station, TX) and a 2-sided level of significance of $\alpha < 0.05$.

Results

Confirmation of reduced $eGFR_{cr}$

A total of 3,059 (11.1%) participants included in the analysis had reduced $eGFR_{cr}$ at baseline. Among participants with reduced $eGFR_{cr}$, a higher percentage was confirmed using $eGFR_{cys}$ among those ≥ 80 years of age as compared with younger adults (Figure 2). The percentage whose reduced $eGFR_{cr}$ was confirmed using $eGFR_{cr,cys}$, $eGFR_{BIS1}$ and $eGFR_{BIS2}$ was also higher among those ≥ 80 years of age (Table III). Among those ≥ 80 years of age, the percentage whose reduced $eGFR_{cr}$ was confirmed by $eGFR_{cys}$ was similar when stratified by waist circumference or BMI (Figure 3). Baseline characteristics of REGARDS participants whose reduced $eGFR_{cr}$ was confirmed versus not confirmed using $eGFR_{cys}$ are provided by age in Table IV.

Among participants ≥ 80 years of age, those whose reduced $eGFR_{cr}$ was confirmed using $eGFR_{cys}$ had a higher prevalence of hypertension and ACR > 30 mg/g (Table V). Although presence of serum albumin < 3.8 g/dl, anemia and hsCRP > 3 mg/l were each more common among individuals whose reduced $eGFR_{cr}$ was confirmed versus not confirmed using $eGFR_{cys}$, these differences were

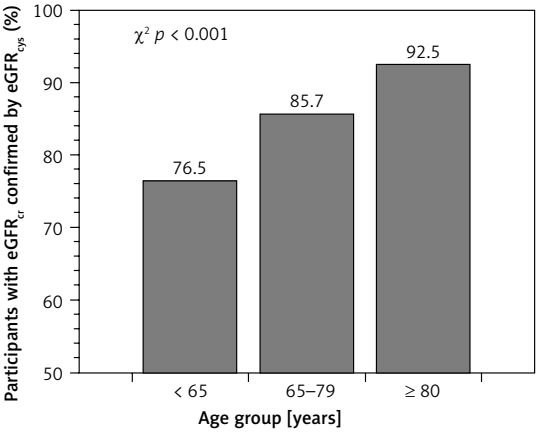

Figure 2. Percentage of REGARDS participants with reduced $eGFR_{cr}$ for whom this result was confirmed using $eGFR_{cys}$ stratified by age

$eGFR_{cr}$ – estimated glomerular filtration rate using serum creatinine, $eGFR_{cys}$ – estimated glomerular filtration rate using serum cystatin-C, REGARDS – REasons for Geographic And Racial Differences in Stroke. Reduced eGFR was defined as eGFR < 60 ml/min/1.73 m².

Table III. Percentage of REGARDS participants whose reduced $eGFR_{cr}$ was confirmed using $eGFR_{cr,cys}$, $eGFR_{BIS1}$ or $eGFR_{BIS2}$ stratified by age

eGFR	< 65 years (*n* = 599)	65 to 79 years (*n* = 1,805)	≥ 80 years (*n* = 655)	*P*-value
	N (%)	*N* (%)	*N* (%)	
$eGFR_{cr,cys}$	506 (84.5)	1,631 (90.4)	629 (96.0)	< 0.001
$eGFR_{BIS1}$	555 (92.7)	1,805 (100.0)	655 (100.0)	< 0.001
$eGFR_{BIS2}$	359 (59.9)	1,670 (92.5)	655 (100.0)	< 0.001

eGFR – estimated glomerular filtration rate. REGARDS – Reasons for Geographic And Racial Differences in Stroke. Reduced $eGFR_{cr}$ confirmed using $eGFR_{cr,cys}$, $eGFR_{BIS1}$ or $eGFR_{BIS2}$ were defined as $eGFR_{cr}$ and $eGFR_{cr,cys}$, $eGFR_{BIS1}$ or $eGFR_{BIS2}$ < 60 ml/min/1.73 m², respectively. Equations for $eGFR_{cr}$, $eGFR_{cys}$, $eGFR_{cr,cys}$, $eGFR_{BIS1}$ and $eGFR_{BIS2}$ are shown in Table I.

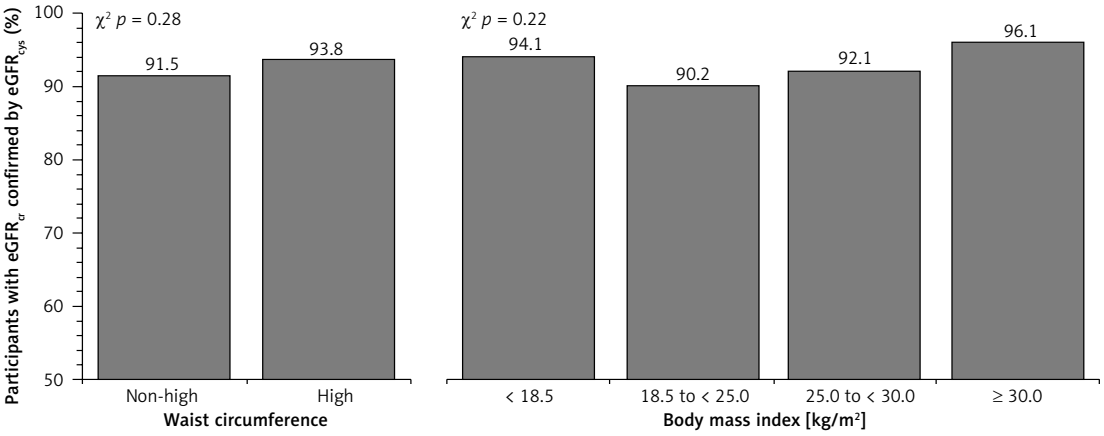

Figure 3. Percentage of REGARDS participants ≥ 80 years of age with reduced $eGFR_{cr}$ for whom this result was confirmed using $eGFR_{cys}$ stratified by waist circumference and body mass index

$eGFR_{cr}$ – estimated glomerular filtration rate using serum creatinine, $eGFR_{cys}$ – estimated glomerular filtration rate using serum cystatin-C, REGARDS – REasons for Geographic And Racial Differences in Stroke. Reduced eGFR was defined as eGFR < 60 ml/min/1.73 m².

Table IV. Baseline characteristics of REGARDS participants whose reduced $eGFR_{cr}$ was confirmed versus not confirmed using $eGFR_{cys}$ stratified by age

Parameter	< 65 years		65 to 79 years		≥ 80 years	
	Reduced $eGFR_{cr}$ confirmed using $eGFR_{cys}$	Reduced $eGFR_{cr}$ not confirmed using $eGFR_{cys}$	Reduced $eGFR_{cr}$ confirmed using $eGFR_{cys}$	Reduced $eGFR_{cr}$ not confirmed using $eGFR_{cys}$	Reduced $eGFR_{cr}$ confirmed using $eGFR_{cys}$	Reduced $eGFR_{cr}$ not confirmed using $eGFR_{cys}$
Number of participants (%)[a]	458 (76.5)	141 (23.5)	1,547 (85.7)	258 (14.3)	606 (92.5)	49 (7.5)
Age, mean (SD) [years]	59.3 (4.0)	59.2 (4.3)	72.4 (4.2)	72.0 (4.11)	83.6 (3.2)	83.3 (3.0)
Men, *n* (%)	189 (41.3)	73 (51.8)	677 (43.8)	122 (47.3)	295 (48.7)	25 (51.0)
Black, *n* (%)	277 (60.5)	63 (44.7)	616 (39.8)	108 (41.9)	199 (32.8)	19 (38.8)
Region of residence, *n* (%):						
Stroke belt (buckle states)	110 (24.0)	26 (18.4)	340 (22.0)	42 (16.3)	122 (20.1)	8 (16.3)
Stroke belt (non-buckle states)	166 (36.3)	44 (31.2)	525 (33.9)	78 (30.2)	175 (28.9)	13 (26.5)
Other contiguous US states	182 (39.7)	71 (50.4)	682 (44.1)	138 (53.5)	309 (51.0)	28 (57.2)
Less than high school, *n* (%)	68 (14.9)	9 (6.4)	316 (20.4)	36 (14.0)	136 (22.6)	9 (18.4)
No physical activity, *n* (%)	215 (47.4)	41 (29.5)	727 (48.2)	70 (27.7)	317 (53.6)	15 (30.6)
Current smoking, *n* (%)	87 (19.0)	13 (9.3)	181 (11.7)	13 (5.0)	25 (4.1)	1 (2.1)
History of CHD, *n* (%)	136 (30.4)	26 (18.8)	543 (35.9)	50 (19.9)	201 (34.0)	9 (18.4)
History of stroke, *n* (%)	67 (14.8)	5 (3.6)	222 (14.4)	17 (6.6)	71 (11.8)	7 (14.3)
Diabetes, *n* (%)	234 (51.3)	30 (21.4)	564 (36.6)	55 (21.5)	165 (27.2)	4 (8.2)
High waist circumference, *n* (%)	316 (70.2)	64 (46.0)	918 (59.6)	100 (39.1)	270 (44.8)	18 (36.7)
Body mass index, *n* (%) [kg/m^2]:						
< 18.5	1 (0.2)	1 (0.7)	17 (1.1)	4 (1.6)	16 (2.7)	1 (2.0)
18.5 to < 25.0	55 (12.4)	18 (13.0)	331 (21.5)	62 (24.2)	194 (32.2)	21 (42.8)
25.0 to < 30.0	115 (25.9)	56 (40.6)	550 (35.7)	121 (47.3)	246 (40.9)	21 (42.8)
≥ 30.0	273 (61.5)	63 (45.7)	643 (41.7)	69 (16.9)	146 (24.2)	6 (4.4)
Taking statins, *n* (%)	213 (46.5)	54 (38.3)	734 (47.5)	116 (45.0)	254 (41.9)	11 (22.5)

CHD – coronary heart disease, eGFR – estimated glomerular filtration rate, REGARDS – REasons for Geographic And Racial Differences in Stroke, SD – standard deviation, US – United States. [a]Percentage within age group. Reduced $eGFR_{cr}$ confirmed using $eGFR_{cys}$ was defined as $eGFR_{cr}$ and $eGFR_{cys}$ < 60 ml/min/1.73 m^2. Reduced $eGFR_{cr}$ not confirmed using $eGFR_{cys}$ was defined as $eGFR_{cr}$ < 60 ml/min/1.73 m^2 and $eGFR_{cys}$ ≥ 60 ml/min/1.73 m^2. Equations for $eGFR_{cr}$ and $eGFR_{cys}$ are shown in Table I.

Table V. Prevalence of concurrent CKD complications among REGARDS participants whose reduced $eGFR_{cr}$ was confirmed versus not confirmed using $eGFR_{cys}$ stratified by age

Parameter	< 65 years			65 to 79 years			≥ 80 years		*P*-value
	Reduced $eGFR_{cr}$ confirmed using $eGFR_{cys}$	Reduced $eGFR_{cr}$ not confirmed using $eGFR_{cys}$	*P*-value	Reduced $eGFR_{cr}$ confirmed using $eGFR_{cys}$	Reduced $eGFR_{cr}$ not confirmed using $eGFR_{cys}$	*P*-value	Reduced $eGFR_{cr}$ confirmed using $eGFR_{cys}$	Reduced $eGFR_{cr}$ not confirmed using $eGFR_{cys}$	
Number of participants:	458	141		1,547	258		606	49	
Hypertension	90.6%	58.0%	< 0.001	83.4%	68.4%	< 0.001	79.1%	65.1%	0.03
Serum albumin < 3.8 g/dl	23.5%	4.2%	0.005	18.8%	9.2%	0.007	22.1%	8.6%	0.19
Anemia	45.3%	14.5%	< 0.001	36.8%	17.3%	< 0.001	35.3%	20.2%	0.08
hsCRP > 3 mg/l	60.9%	39.7%	< 0.001	51.6%	27.5%	< 0.001	40.4%	28.6%	0.11
ACR > 30 mg/g	50.5%	14.7%	< 0.001	37.1%	9.9%	< 0.001	38.3%	22.7%	0.04

ACR – albumin : creatinine ratio, CKD – chronic kidney disease, eGFR – estimated glomerular filtration rate, hsCRP – high-sensitivity C-reactive protein, REGARDS: REasons for Geographic And Racial Differences in Stroke. Reduced $eGFR_{cr}$ confirmed using $eGFR_{cys}$ was defined as $eGFR_{cr}$ and $eGFR_{cys}$ < 60 ml/min/1.73 m². Reduced $eGFR_{cr}$ not confirmed using $eGFR_{cys}$ was defined as $eGFR_{cr}$ < 60 ml/min/1.73 m² and $eGFR_{cys}$ ≥ 60 ml/min/1.73 m². Equations for $eGFR_{cr}$ and $eGFR_{cys}$ are shown in Table I. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or self-reported use of antihypertensive medications. Anemia was defined as hemoglobin concentration < 13.0 and < 12.0 g/dl for males and females, respectively [15].

not statistically significant. Among participants < 65 and 65 to 79 years, those whose reduced $eGFR_{cr}$ was confirmed with $eGFR_{cys}$ were more likely to have each concurrent CKD complication.

There were 878 deaths over 15,874 person-years of follow-up (median follow-up of 5.4 years) among REGARDS participants with reduced $eGFR_{cr}$. Within each age group, participants whose reduced $eGFR_{cr}$ was confirmed using $eGFR_{cys}$ had higher risk for all-cause mortality as compared with their counterparts whose $eGFR_{cr}$ was not confirmed by $eGFR_{cys}$ (Figure 4). The multivariable

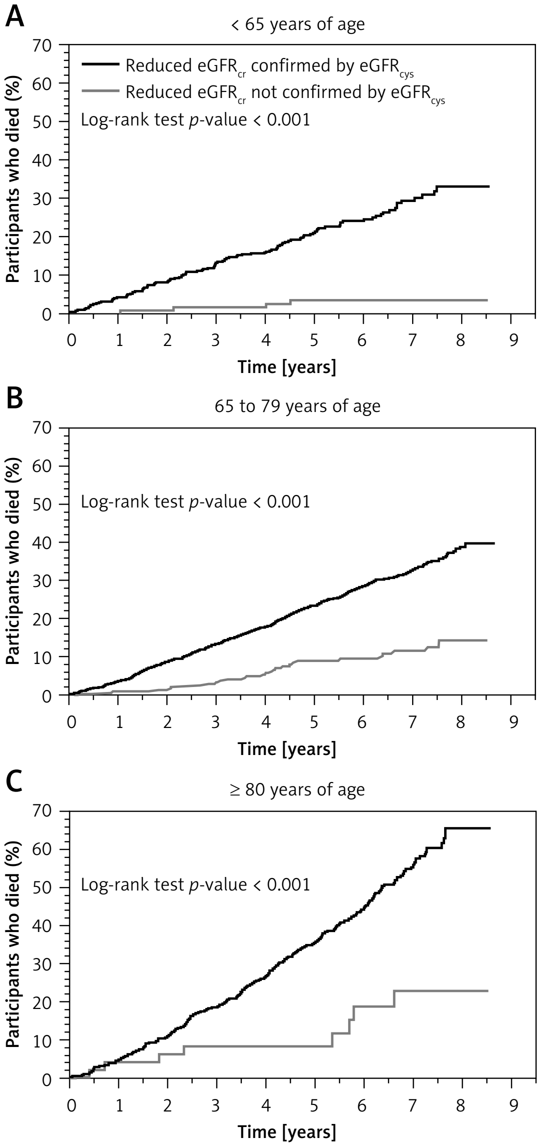

Figure 4. Cumulative mortality (Kaplan-Meier method) for REGARDS participants whose reduced $eGFR_{cr}$ was confirmed versus not confirmed using $eGFR_{cys}$ stratified by age

$eGFR_{cr}$ – estimated glomerular filtration rate using serum creatinine, $eGFR_{cys}$ – estimated glomerular filtration rate using serum cystatin-C, REGARDS – REasons for Geographic And Racial Differences in Stroke. Reduced eGFR was defined as eGFR < 60 ml/min/1.73 m².

Table VI. Age specific hazard ratios (95%CI) for all-cause mortality associated with reduced $eGFR_{cr}$ confirmed versus not confirmed using $eGFR_{cys}$

Parameter	< 65 years		65 to 79 years		≥ 80 years		*P*-value[a]
	Reduced $eGFR_{cr}$ confirmed using $eGFR_{cys}$	Reduced $eGFR_{cr}$ not confirmed using $eGFR_{cys}$	Reduced $eGFR_{cr}$ confirmed using $eGFR_{cys}$	Reduced $eGFR_{cr}$ not confirmed using $eGFR_{cys}$	Reduced $eGFR_{cr}$ confirmed using $eGFR_{cys}$	Reduced $eGFR_{cr}$ not confirmed using $eGFR_{cys}$	
Deaths/participants	115/599		472/1,805		291/655		
Hazard ratio (95% CI):							
Model 1	7.67 (2.78–21.17)	1 (ref)	2.36 (1.58–3.51)	1 (ref)	3.07 (1.51–6.25)	1 (ref)	0.18
Model 2	5.54 (1.99–15.45)	1 (ref)	1.83 (1.22–2.74)	1 (ref)	2.61 (1.28–2.34)	1 (ref)	0.29
Model 3	4.48 (1.55–12.90)	1 (ref)	1.59 (1.06–2.40)	1 (ref)	2.43 (1.19–5.01)	1 (ref)	0.44

95% CI – 95% confidence interval, ACR – albumin : creatinine ratio, CHD – coronary heart disease, eGFR – estimated glomerular filtration rate, hsCRP – high-sensitivity C-reactive protein. [a]Test for homogeneity of hazard ratios across age strata. Preserved eGFR was defined as eGFR ≥ 60 ml/min/1.73 m². Reduced eGFR was defined as eGFR < 60 ml/min/1.73 m². Equations for $eGFR_{cr}$ and $eGFR_{cys}$ are shown in Table I. Model 1: Includes adjustment for age, race, gender, region of residence and $eGFR_{cr}$. Model 2: Includes adjustments in Model 1 plus adjustment for education level, physical activity, smoking, history of CHD, stroke, diabetes, waist circumference and statin use. Model 3: Includes adjustments in Model 2 plus adjustment for hypertension, serum albumin < 3.8 g/dl, anemia, hsCRP > 3 mg/l and ACR > 30 mg/g.

adjusted HRs (95% CI) for all-cause mortality for those whose reduced $eGFR_{cr}$ was confirmed versus not confirmed by $eGFR_{cys}$ were 4.48 (1.55–12.90), 1.59 (1.06–2.40), and 2.43 (1.19–5.01), for those < 65 years, 65 to 79 years, and ≥ 80 years old, respectively (Table VI; *p*-value for homogeneity of HRs across age strata: 0.44).

Confirmation of preserved $eGFR_{cr}$

Among those < 65 years, 65 to 79 years, and ≥ 80 years old, 12,534 (93.7%), 7,930 (80.7%) and 687 (54.6%) participants, respectively, had their preserved $eGFR_{cr}$ confirmed using $eGFR_{cys}$ (Table VII; *p*-value for homogeneity across age strata < 0.001). The percentage of those whose preserved $eGFR_{cr}$ was confirmed using $eGFR_{cr,cys}$, $eGFR_{BIS1}$ and $eGFR_{BIS2}$ was also lower among participants ≥ 80 years of age (Table VIII). Among those ≥ 80 years of age, the percentage whose preserved $eGFR_{cr}$ was confirmed by $eGFR_{cys}$ was lower with higher waist circumference or BMI (Figure 5). Among participants ≥ 80 years of age, those whose preserved $eGFR_{cr}$ was confirmed using $eGFR_{cys}$ had a lower prevalence of anemia, elevated hsCRP, and albuminuria (Table IX). In the younger age groups, those with preserved $eGFR_{cr}$ confirmed using $eGFR_{cys}$ had a lower prevalence of each concurrent CKD complication. Within each age group, a preserved $eGFR_{cr}$ confirmed versus not confirmed using $eGFR_{cys}$ was associated with a lower HR for all-cause mortality (Table X).

Discussion

In the current study, 92.5% of participants ≥ 80 years of age with reduced $eGFR_{cr}$ had reduced $eGFR_{cys}$, as compared with 85.7% and 76.5% of those 65 to 79 and < 65 years of age, respectively. Among participants ≥ 80 years of age, those in whom reduced $eGFR_{cr}$ was confirmed by $eGFR_{cys}$ had a higher prevalence of several concurrent CKD complications and increased risk for all-cause mortality as compared with those in whom reduced $eGFR_{cr}$ was not confirmed. These data suggest that additional testing with cystatin-C to confirm reduced $eGFR_{cr}$ may not be needed among the oldest old, since the vast majority of these individuals have reduced $eGFR_{cys}$.

The 2012 KDIGO Clinical Practice Guideline for the Evaluation and Management of CKD recommends using serum creatinine in calculating eGFR in clinical practice to identify individuals at high risk for concurrent CKD complications, renal disease progression, and all-cause mortality [9]. In the general population, both $eGFR_{cr}$ and $eGFR_{cys}$ show similar performance for estimating measured GFR [13]. However, among the oldest old, $eGFR_{cr}$ may overestimate measured GFR while $eGFR_{cys}$ may underestimate it. For example, in

Table VII. Baseline characteristics of REGARDS participants whose preserved $eGFR_{cr}$ was confirmed versus not confirmed using $eGFR_{cys}$ stratified by age

Parameter	< 65 years		65 to 79 years		≥ 80 years	
	Preserved $eGFR_{cr}$ not confirmed using $eGFR_{cys}$	Preserved $eGFR_{cr}$ confirmed using $eGFR_{cys}$	Preserved $eGFR_{cr}$ not confirmed using $eGFR_{cys}$	Preserved $eGFR_{cr}$ confirmed using $eGFR_{cys}$	Preserved $eGFR_{cr}$ not confirmed using $eGFR_{cys}$	Preserved $eGFR_{cr}$ confirmed using $eGFR_{cys}$
Number of participants (%)[a]	847 (6.3)	12,534 (93.7)	1,899 (19.3)	7,930 (80.7)	572 (45.4)	687 (54.6)
Age, mean (SD) [years]	59.2 (4.0)	57.0 (5.0)	72.0 (4.1)	70.3 (4.0)	83.2 (3.0)	82.7 (2.7)
Men, *n* (%)	259 (30.6)	5,481 (43.7)	769 (40.5)	4,002 (50.5)	269 (47.0)	365 (53.1)
Black, *n* (%)	378 (44.6)	5,327 (42.5)	646 (34.0)	3,067 (38.7)	167 (29.2)	252 (36.7)
Region of residence, *n* (%):						
Stroke belt (buckle states)	200 (23.6)	2,701 (21.5)	420 (22.1)	1,559 (19.7)	99 (17.3)	123 (17.9)
Stroke belt (non-buckle states)	314 (37.1)	4,540 (36.2)	658 (34.7)	2,690 (33.9)	169 (29.6)	212 (30.9)
Other contiguous US states	333 (39.3)	5,293 (42.2)	821 (43.2)	3,681 (46.4)	304 (53.1)	352 (51.2)
Less than high school, *n* (%)	119 (14.1)	980 (7.8)	344 (18.1)	1,118 (14.1)	98 (17.2)	126 (18.4)
No physical activity, *n* (%)	382 (45.9)	3,712 (30.0)	831 (44.5)	2,368 (30.4)	268 (47.8)	262 (39.0)
Current smoking, *n* (%)	248 (29.4)	2,266 (18.2)	279 (14.8)	803 (10.2)	29 (5.1)	16 (2.4)
History of CHD, *n* (%)	187 (22.6)	1,312 (10.7)	532 (28.5)	1,472 (18.9)	175 (31.3)	161 (24.0)
History of stroke, *n* (%)	72 (8.5)	485 (3.9)	192 (10.2)	440 (5.6)	52 (9.2)	58 (8.5)
Diabetes, *n* (%)	277 (32.9)	2,145 (17.2)	534 (28.3)	1,542 (19.6)	108 (19.0)	92 (13.4)
High waist circumference, *n* (%)	623 (74.3)	5,924 (47.5)	1,157 (61.3)	3,462 (43.9)	223 (39.3)	231 (33.8)
Body mass index, *n* (%) [kg/m^2]:						
< 18.5	6 (0.7)	113 (0.9)	23 (1.2)	83 (1.1)	7 (1.2)	13 (1.9)
18.5 to < 25.0	84 (10.3)	2,725 (21.9)	360 (19.1)	2,152 (27.2)	210 (37.0)	282 (41.3)
25.0 to < 30.0	201 (24.5)	4,444 (35.6)	636 (33.7)	3,263 (41.3)	233 (41.0)	289 (42.3)
≥ 30.0	528 (64.5)	5,183 (41.6)	866 (46.0)	2,405 (30.4)	118 (20.8)	99 (14.5)
Taking statins, *n* (%)	268 (31.6)	3,100 (24.7)	710 (37.4)	2,820 (35.6)	175 (30.6)	204 (29.7)

CHD – coronary heart disease, eGFR – estimated glomerular filtration rate, REGARDS – REasons for Geographic And Racial Differences in Stroke, SD – standard deviation, US – United States. [a]Percentage within age group. Preserved $eGFR_{cr}$ confirmed using $eGFR_{cys}$ was defined as $eGFR_{cr}$ and $eGFR_{cys}$ ≥ 60 ml/min/1.73 m^2. Preserved $eGFR_{cr}$ not confirmed using $eGFR_{cys}$ was defined as $eGFR_{cr}$ ≥ 60 ml/min/1.73 m^2 and $eGFR_{cys}$ < 60 ml/min/1.73 m^2. Equations for $eGFR_{cr}$ and $eGFR_{cys}$ are shown in Table I.

Table VIII. Percentage of REGARDS participants whose preserved $eGFR_{cr}$ was confirmed using $eGFR_{cr,cys}$, $eGFR_{BIS1}$ or $eGFR_{BIS2}$ stratified by age

eGFR	< 65 years (*n* = 13,381)	65 to 79 years (*n* = 9,829)	≥ 80 years (*n* = 1,259)	*P*-value
	N (%)	*N* (%)	*N* (%)	
$eGFR_{cr,cys}$	13,077 (97.7)	9,088 (92.5)	963 (76.5)	< 0.001
$eGFR_{BIS1}$	13,211 (98.7)	8,106 (82.5)	554 (44.0)	< 0.001
$eGFR_{BIS2}$	13,366 (99.9)	9,236 (94.0)	775 (61.6)	< 0.001

eGFR – estimated glomerular filtration rate, REGARDS – Reasons for Geographic And Racial Differences in Stroke. Preserved $eGFR_{cr}$ confirmed using $eGFR_{cr,cys}$, $eGFR_{BIS1}$ or $eGFR_{BIS2}$ were defined as $eGFR_{cr}$ and $eGFR_{cr,cys}$, $eGFR_{BIS1}$ or $eGFR_{BIS2}$ ≥ 60 ml/min/1.73 m², respectively. Equations for $eGFR_{cr}$, $eGFR_{cys}$, $eGFR_{cr,cys}$, $eGFR_{BIS1}$ and $eGFR_{BIS2}$ are shown in Table I.

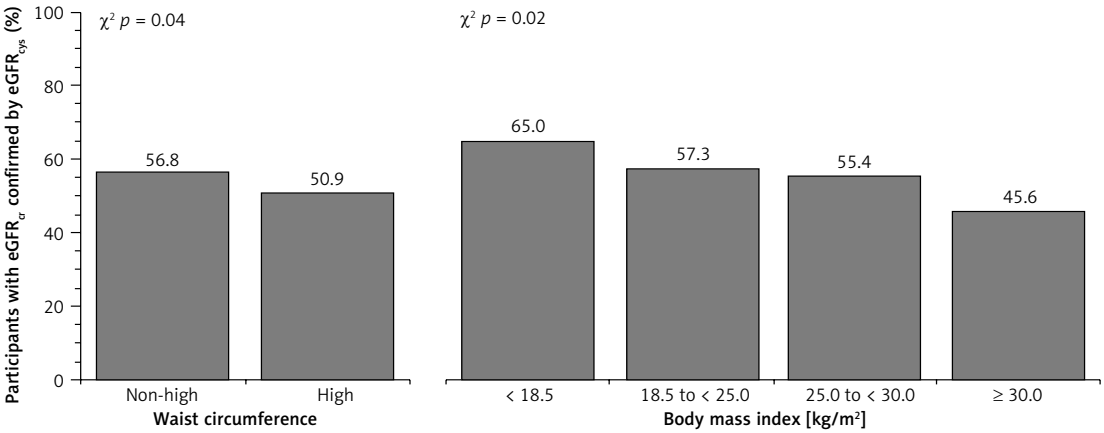

Figure 5. Percentage of REGARDS participants ≥ 80 years of age with preserved $eGFR_{cr}$ for whom this result was confirmed using $eGFR_{cys}$ stratified by waist circumference and body mass index

$eGFR_{cr}$ – estimated glomerular filtration rate using serum creatinine, $eGFR_{cys}$ – estimated glomerular filtration rate using serum cystatin-C, REGARDS – REasons for Geographic And Racial Differences in Stroke. Preserved eGFR was defined as eGFR ≥ 60 ml/min/1.73 m². High waist circumference was defined as > 102 cm among males and > 88 cm among females.

a cohort of 805 old adults (mean age: 80.3 years) from Iceland with a mean measured GFR of 64 ml/min/1.73 m², the mean $eGFR_{cr}$ and $eGFR_{cys}$ were 68 and 61 ml/min/1.73 m², respectively [18]. Additionally, in a prior study of adults ≥ 80 years of age, Van Pottelbergh *et al.* reported that the mean eGFR was lower when calculated using serum cystatin-C (54 ml/min/1.73 m²) as compared with using serum creatinine in conjunction with the CKD-EPI equation (61 ml/min/1.73 m²) [19]. Our results are consistent with these prior studies and demonstrate that a very high percentage of individuals ≥ 80 years of age have reduced eGFR based on serum creatinine confirmed when using cystatin-C-based eGFR.

Prior studies have reported that cystatin-C could be used as an additional test to identify a sub-group of individuals with reduced $eGFR_{cr}$ who have lower risk for all-cause mortality and CKD complications [13, 20, 21]. Peralta *et al.* reported that reduced $eGFR_{cr}$ is only associated with higher risk for all-cause mortality if confirmed using serum cystatin-C [20]. Shlipak *et al.* reported that using cystatin-C as a confirmatory test may rule out reduced eGFR in about 42% of individuals with $eGFR_{cr}$ 45 to 59 ml/min/1.73 m², and that these individuals have a 34% and 80% lower risk for all-cause mortality and end stage renal disease, respectively, as compared to those for whom a reduced eGFR is confirmed via cystatin-C [21]. However, the analysis conducted by Shlipak *et al.* included a small proportion of oldest old (the mean age was 60 years), and the results were not reported stratified by age. Using cystatin-C for the confirmation of a reduced $eGFR_{cr}$ could be important in circumstances when serum creatinine-based estimations are less accurate (e.g., in those with reduced muscle mass), as suggested by the 2012 KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease [9]. There is concern that serum creatinine may be a poor marker of renal function among the oldest old as they may be more likely to have reduced muscle mass or sarcopenia. Unlike serum creatinine, serum cystatin-C is independent of muscle mass and may provide a better estimate for GFR among the oldest old [22]. However, results from the current analysis suggest that measuring cystatin-C for the confirmation of reduced $eGFR_{cr}$ is not needed in this population, regardless of their waist circumference or BMI. This is important considering the high prevalence

Table IX. Prevalence of concurrent CKD complications among participants whose preserved $eGFR_{cr}$ was confirmed versus not confirmed using $eGFR_{cys}$ stratified by age

Parameter	< 65 years		*P*-value	65 to 79 years		*P*-value	≥ 80 years		*P*-value
	Preserved $eGFR_{cr}$ not confirmed using $eGFR_{cys}$	Preserved $eGFR_{cr}$ confirmed using $eGFR_{cys}$		Preserved $eGFR_{cr}$ not confirmed using $eGFR_{cys}$	Preserved $eGFR_{cr}$ confirmed using $eGFR_{cys}$		Preserved $eGFR_{cr}$ not confirmed using $eGFR_{cys}$	Preserved $eGFR_{cr}$ confirmed using $eGFR_{cys}$	
Number of participants:	847	12,534		1,899	7,930		572	687	
Hypertension	77.6%	49.3%	< 0.001	73.5%	59.5%	< 0.001	64.7%	62.4%	0.42
Serum albumin < 3.8 g/dl	19.4%	7.0%	< 0.001	18.1%	9.6%	< 0.001	20.0%	15.4%	0.07
Anemia	23.5%	9.2%	< 0.001	20.6%	11.3%	< 0.001	23.3%	15.1%	0.008
hsCRP > 3 mg/l	64.5%	39.8%	< 0.001	50.9%	34.5%	< 0.001	43.2%	26.1%	< 0.001
ACR > 30 mg/g	25.9%	9.5%	< 0.001	22.6%	11.8%	< 0.001	23.9%	15.3%	0.001

ACR – albumin : creatinine ratio, CKD – chronic kidney disease, eGFR – estimated glomerular filtration rate, hsCRP – high sensibility C-reactive protein. Preserved $eGFR_{cr}$ confirmed using $eGFR_{cys}$ was defined as $eGFR_{cr}$ and $eGFR_{cys}$ ≥ 60 ml/min/1.73 m². Preserved $eGFR_{cr}$ not confirmed using $eGFR_{cys}$ was defined as $eGFR_{cr}$ ≥ 60 ml/min/1.73 m² and $eGFR_{cys}$ < 60 ml/min/1.73 m². Equations for $eGFR_{cr}$ and $eGFR_{cys}$ are shown in Table I. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or self-reported use of antihypertensive medications. Anemia was defined as hemoglobin concentration < 13.0 g/dl and < 12.0 g/dl for males and females, respectively [15].

Table X. Age specific hazard ratios (95%CI) for all-cause mortality associated with preserved $eGFR_{cr}$ confirmed versus not confirmed using $eGFR_{cys}$

Parameter	< 65 years		65 to 79 years		≥ 80 years		*P*-value[a]
	Preserved $eGFR_{cr}$ not confirmed using $eGFR_{cys}$	Preserved $eGFR_{cr}$ confirmed using $eGFR_{cys}$	Preserved $eGFR_{cr}$ not confirmed using $eGFR_{cys}$	Preserved $eGFR_{cr}$ confirmed using $eGFR_{cys}$	Preserved $eGFR_{cr}$ not confirmed using $eGFR_{cys}$	Preserved $eGFR_{cr}$ confirmed using $eGFR_{cys}$	
Deaths/participants	600/13,381		1,237/9,829		376/1,259		
Hazard ratio (95% CI):							
Model 1	1 (ref)	0.21 (0.17–0.26)	1 (ref)	0.43 (0.37–0.49)	1 (ref)	0.50 (0.40–0.63)	< 0.001
Model 2	1 (ref)	0.32 (0.25–0.41)	1 (ref)	0.57 (0.50–0.66)	1 (ref)	0.54 (0.43–0.69)	< 0.001
Model 3	1 (ref)	0.41 (0.32–0.53)	1 (ref)	0.66 (0.57–0.76)	1 (ref)	0.61 (0.48–0.78)	0.001

95% CI – 95% confidence interval, ACR – albumin : creatinine ratio, CHD – coronary heart disease, eGFR – estimated glomerular filtration rate, hsCRP – high sensibility C-reactive protein. [a]Test for interaction for consistency of hazard ratios across age strata. Preserved eGFR was defined as eGFR ≥ 60 ml/min/1.73 m². Reduced eGFR was defined as eGFR < 60 ml/min/1.73 m². Calculations for $eGFR_{cr}$ and $egFR_{cys}$ are shown in Table I. Model 1: Includes adjustment for age, race, gender, region of residence and $eGFR_{cr}$, Model 2: Includes adjustments in Model 1 plus adjustment for education level, physical activity, smoking, history of CHD, stroke, diabetes, waist circumference and statin use. Model 3: Includes adjustments in Model 2 plus adjustment for hypertension, serum albumin < 3.8 g/dl, anemia, hsCRP > 3 mg/l and ACR > 30 mg/g.

of reduced $eGFR_{cr}$ among the oldest old [9, 23] and the relatively high cost of measuring serum cystatin-C [24].

In secondary analyses, we found that 45.4% of participants ≥ 80 years of age with preserved $eGFR_{cr}$ had reduced $eGFR_{cys}$ and this proportion was higher as compared with younger adults. Individuals ≥ 80 years of age with preserved $eGFR_{cr}$ but reduced $eGFR_{cys}$ had a higher prevalence of anemia, elevated hsCRP, and albuminuria and an increased risk for all-cause mortality compared to those whose preserved $eGFR_{cr}$ was confirmed using $eGFR_{cys}$. Future studies should assess the costs and benefits of measuring cystatin-C among the oldest old with preserved $eGFR_{cr}$.

Results from the present study should be interpreted in the context of known and potential limitations. First, eGFR was calculated using data from a single study visit. This may have led to potential misclassification of participants. Second, the observational study design prevents inferring a causal relationship. This is especially important for the cross-sectional analysis of concurrent CKD complications where some conditions may have preceded kidney function impairment. Finally, the REGARDS study excluded individuals residing in nursing homes, which may reduce the generalizability of our results, particularly among the oldest old. Strengths of the current analysis include the large number of participants ≥ 80 years of age with serum creatinine and cystatin-C measured at baseline. Additionally, the REGARDS study enrolled participants residing in all 48 contiguous states and the District of Columbia.

In conclusion, serum creatinine is recommended to routinely evaluate renal function in clinical practice. However, there is concern that serum creatinine may be a poor marker of renal function at older ages. In the current study, the vast majority of participants ≥ 80 years of age with reduced $eGFR_{cr}$ also had reduced $eGFR_{cys}$. These results suggest that cystatin-C does not need to be measured to confirm reduced $eGFR_{cr}$ among the oldest old.

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Conflict of interest

DGW and PM have received grant support from Amgen Inc. LDC, RMT, OMG, SJ and CBB have no conflicts of interest to disclose.

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