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Association of Low Glomerular Filtration Rate With Adverse Outcomes at Older Age in a Large Population With Routinely Measured Cystatin C

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Background: The commonly accepted threshold of glomerular filtration rate (GFR) to define chronic kidney disease (CKD) is less than 60 mL/min/1.73 m^2. This threshold is based partly on associations between estimated GFR (eGFR) and the frequency of adverse outcomes. The association is weaker in older adults, which has created disagreement about the appropriateness of the threshold for these persons. In addition, the studies measuring these associations included relatively few outcomes and estimated GFR on the basis of creatinine level ($eGFR_{cr}$), which may be less accurate in older adults.

Objective: To evaluate associations in older adults between $eGFR_{cr}$ versus eGFR based on creatinine and cystatin C levels ($eGFR_{cr\text{-}cys}$) and 8 outcomes.

Design: Population-based cohort study.

Setting: Stockholm, Sweden, 2010 to 2019.

Participants: 82 154 participants aged 65 years or older with outpatient creatinine and cystatin C testing.

Measurements: Hazard ratios for all-cause mortality, cardiovascular mortality, and kidney failure with replacement therapy (KFRT); incidence rate ratios for recurrent hospitalizations, infection, myocardial infarction or stroke, heart failure, and acute kidney injury.

Results: The associations between $eGFR_{cr\text{-}cys}$ and outcomes were monotonic, but most associations for $eGFR_{cr}$ were U-shaped. In addition, $eGFR_{cr\text{-}cys}$ was more strongly associated with outcomes than $eGFR_{cr}$. For example, the adjusted hazard ratios for 60 versus 80 mL/min/1.73 m^2 for all-cause mortality were 1.2 (95% CI, 1.1 to 1.3) for $eGFR_{cr\text{-}cys}$ and 1.0 (CI, 0.9 to 1.0) for $eGFR_{cr}$, and for KFRT they were 2.6 (CI, 1.2 to 5.8) and 1.4 (CI, 0.7 to 2.8), respectively. Similar findings were observed in subgroups, including those with a urinary albumin–creatinine ratio below 30 mg/g.

Limitation: No GFR measurements.

Conclusion: Compared with low $eGFR_{cr}$ in older patients, low $eGFR_{cr\text{-}cys}$ was more strongly associated with adverse outcomes and the associations were more uniform.

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In routine clinical practice, glomerular filtration rate (GFR) is usually estimated from serum creatinine level ($eGFR_{cr}$). An $eGFR_{cr}$ below 60 mL/min/1.73 m^2 is very common in older persons, with prevalence estimates ranging from 23% to 44% for those aged 65 years or older (1–3). The rationale for using a GFR threshold of less than 60 mL/min/1.73 m^2 to define chronic kidney disease (CKD) is that it represents a large decrease in GFR from the normal value in young persons and because of associations between low $eGFR_{cr}$ and adverse outcomes, such as kidney failure and all-cause mortality, in the general population (4, 5). However, $eGFR_{cr}$ levels of 60 mL/min/1.73 m^2 or lower are less strongly associated with adverse outcomes in older adults than in young persons (6–10). This has led to substantial debate about the appropriateness of the current GFR threshold to define CKD in older adults, and several researchers have called for lower thresholds of GFR below 45 mL/min/1.73 m^2 to define CKD in adults aged 65 years or older (6, 11–16).

The weaker associations between $eGFR_{cr}$ and adverse outcomes in older adults may be due in part to the limitations of creatinine for estimating GFR in the older population. Low muscle mass, which is frequently found with chronic disease or inactivity, may lead to low creatinine levels and consequently high $eGFR_{cr}$ that does not accurately represent true GFR (17–19). Patients with $eGFR_{cr}$ above 60 mL/min/1.73 m^2 may therefore disproportionately include persons who

See also:
Editorial comment. 393
Web-Only
Supplement

are at high risk for adverse outcomes because of low muscle mass and frailty, which dilutes risk associations between low $eGFR_{cr}$ and adverse outcomes. Furthermore, previous studies that investigated the risks associated with CKD in older age focused primarily on the outcomes of kidney failure and mortality (8, 10). However, CKD increases the risk for many outcomes that are important to patients, and investigating these additional outcomes is important to appreciate the broad range of risks associated with CKD (20).

The limitations of $eGFR_{cr}$ may be overcome by using more accurate GFR estimates. Using both creatinine and cystatin C to calculate GFR ($eGFR_{cr\text{-}cys}$) is the most accurate estimation method in both younger and older adults (21–23). Recent recommendations suggest that cystatin C testing should be available and widely used in the United States (24). In contrast to creatinine, cystatin C is minimally influenced by muscle mass (17, 18, 25). Consequently, associations between eGFR and outcomes would be expected to be more accurate for $eGFR_{cr\text{-}cys}$ than for $eGFR_{cr}$.

To inform the evidence for the definition and staging of CKD in older adults, we evaluated associations between $eGFR_{cr\text{-}cys}$ versus $eGFR_{cr}$ with 8 outcomes in older adults receiving routine care in Sweden, where use of cystatin C testing as a supportive test in routine clinical practice was implemented more than a decade ago.

METHODS

This study falls into the category of prognostic factor research (26), which studies factors whose values are associated with changes in the outcome's risk. The prognostic factor framework is often used to define diseases (27) and has been a cornerstone in the definition and staging of CKD, on which clinical recommendations are based (5, 28).

Data Source and Study Population

We used data from the SCREAM (Stockholm CREAtinine Measurements) project, which contains health care utilization data from residents of Stockholm, Sweden, between 2006 and 2019 (29). SCREAM contains complete information on demographic characteristics, health care utilization, laboratory tests, dispensed drugs (30), diagnoses (31), and vital status (32). A single health care provider in the Stockholm region provides universal and tax-funded health care to 20% to 25% of the population of Sweden. The Regional Ethical Review Board in Stockholm approved the study (reference 2017/793-31); informed consent was not deemed necessary because all data were deidentified by the Swedish Board of Health and Welfare.

We included all persons aged 65 years or older who had same-day routine outpatient tests for creatinine and cystatin C between 1 January 2010 and 31 December 2018. Persons with a history of kidney failure with replacement therapy (KFRT) were excluded. If persons had multiple pairs of same-day creatinine and cystatin C measurements, we selected the first pair. Creatinine tests were standardized to isotope dilution mass spectrometry–traceable methods, and cystatin C measurements were also standardized (33). Performance of creatinine and cystatin C assays was monitored internally and by an external quality assessment program (Equalis). To investigate whether testing for cystatin C was random or directed at persons with certain characteristics, we also considered baseline characteristics for the complete cohort of older adults with a creatinine test available and compared their characteristics with those of the subset who had both a creatinine test and a cystatin C test.

Study Exposure

The primary study exposures were $eGFR_{cr}$ and $eGFR_{cr\text{-}cys}$, calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021 equations (22, 24). For comparisons with previous studies, we also evaluated eGFR based on cystatin C alone ($eGFR_{cys}$), calculated using the CKD-EPI 2012 equation (34). All 3 CKD-EPI equations included age, sex, and filtration markers and did not include a coefficient for race.

Covariates

Covariates of interest included age, sex, hypertension, diabetes, history of cardiovascular disease, antihypertensive medication use, total and high-density lipoprotein cholesterol level, and urinary albumin–creatinine ratio (UACR) (definitions are provided in **Supplement Table 1**, available at Annals.org). We converted urinary protein–creatinine ratio and urine dipstick protein categories to UACR values using previously published conversion equations (35). We used the most recent value before the index date for laboratory values, with a maximum lookback period of 3 years (results were similar when we used a lookback period of 1 year).

Study Outcomes and Follow-up

The 8 study outcomes were all-cause mortality; cardiovascular mortality (32, 36); KFRT (37, 38); all-cause hospitalization; and hospitalization with infection, myocardial infarction or stroke, heart failure, or acute kidney injury (AKI) (definitions are provided in **Supplement Table 1**). The date of the first concurrent creatinine and cystatin C test after age 65 years was considered the index date and the start of follow-up. For the outcomes of all-cause mortality, cardiovascular mortality, and KFRT, patients were followed until occurrence of the outcome, death, or the end of available data (31 December 2019), whichever occurred first. For the other outcomes, patients were followed until death or 31 December 2019.

Statistical Analysis

We used cause-specific Cox regression models to estimate hazard ratios for the associations between eGFR

and the outcomes of all-cause mortality, cardiovascular mortality, and KFRT. Negative binomial regression was used to estimate incidence rate ratios for the associations between eGFR and the recurrent outcomes, which could occur multiple times during follow-up. We modeled continuous eGFR (the exposure) using linear splines with knots at 30, 45, 60, 75, and 90 mL/min/1.73 m^2. We selected 80 mL/min/1.73 m^2 as the reference (hazard ratio or incidence rate ratio of 1.0), which is consistent with previous studies in older adults (6, 8). Of note, the reference point influences statistical significance at a given eGFR but does not influence the shape of the overall association between eGFR and outcomes. We adjusted for age, sex, hypertension, diabetes, cardiovascular disease, and log-transformed UACR. Analyses for cardiovascular mortality, all-cause hospitalization, myocardial infarction or stroke, and heart failure were also adjusted for total and high-density lipoprotein cholesterol levels and antihypertensive medication use. From the fitted models, we calculated hazard ratios and incidence rate ratios at eGFR values of 30, 45, and 60 mL/min/1.73 m^2 (compared with the reference of 80 mL/min/1.73 m^2), corresponding to current Kidney Disease: Improving Global Outcomes (KDIGO) GFR thresholds for CKD stages G3a, G3b, and G4 (5). Details on handling of missing data are provided in the **Supplement Methods** (available at Annals.org).

We also calculated incidence rates for specific ages (70 and 80 years) at specific $eGFR_{cr\text{-}cys}$ levels (30, 45, and 60 mL/min/1.73 m^2) using Poisson regression for mortality and KFRT and negative binomial regression for the recurrent outcomes. These models included an interaction between the linear eGFR spline and age. To calculate incidence rates at specific ages and $eGFR_{cr\text{-}cys}$ levels, we used the mean value of each covariate in the study population with same-day creatinine and cystatin C measurements.

Many treatment recommendations for kidney disease are based on GFR thresholds (5). Thus, to investigate potential clinical implications of using $eGFR_{cr\text{-}cys}$ versus $eGFR_{cr}$, we assessed reclassification across KDIGO GFR categories by cross-tabulating eGFR categories for $eGFR_{cr}$ versus $eGFR_{cr\text{-}cys}$ (5).

We also performed stratified analyses to assess consistency of associations for the following subgroups: age (≥75 vs. <75 years), sex, presence of cardiovascular disease, presence of diabetes, and UACR below 30 mg/g. In supporting analyses, we calculated $eGFR_{cr}$ and $eGFR_{cr\text{-}cys}$ using the CKD-EPI 2009 and 2012 equations with age, sex, and the non-Black race coefficient for all participants (39), which remain commonly used in Europe. We also calculated $eGFR_{cr}$, $eGFR_{cys}$, and $eGFR_{cr\text{-}cys}$ using the European Kidney Function Consortium (EKFC) equations with age and sex (40, 41), which were specifically developed for a European population. We note that our primary aim was to compare the association with adverse outcomes for eGFR based on different filtration markers (creatinine vs. cystatin C vs. both) rather than to compare newer versus older CKD-EPI equations (39, 42) or to compare CKD-EPI equations with eGFR equations developed by other research groups (21, 40, 41, 43–45). Finally, we also estimated standardized incidence rates instead of conditional incidence rates (additional details are provided in the **Supplement Methods**). Stata/MP 16 (StataCorp) was used for analyses.

Role of the Funding Source

The funder had no role in the design, conduct, or analysis of the study or the decision to submit the manuscript for publication.

RESULTS

Study Population

In the Stockholm region, 19% of older adults with outpatient creatinine testing had a same-day cystatin C measurement (**Supplement Figure 1**, available at Annals.org). Compared with the total population tested for creatinine, those with both a creatinine test and a cystatin C test were older and had a higher prevalence of diabetes and cardiovascular disease (**Table 1**). In the cohort with creatinine and cystatin C tests (n = 82 154), the mean age was 77 years, 50% were female, 41% had a history of cardiovascular disease, and 25% had diabetes (**Table 1**). Mean eGFRs were 67 mL/min/1.73 m^2 for $eGFR_{cr}$, 61 mL/min/1.73 m^2 for $eGFR_{cr\text{-}cys}$, and 54 mL/min/1.73 m^2 for $eGFR_{cys}$ (distributions are shown in **Supplement Figure 2**, available at Annals.org).

Association Between eGFR and Outcomes

The median follow-up was 3.9 years (IQR, 2.0 to 6.2 years). During follow-up, 31 219 persons died (9654 due to cardiovascular causes) and 841 progressed to KFRT (**Supplement Table 2**, available at Annals.org). Furthermore, counting first events only, there were 51 096 hospitalizations, of which 26 754 involved infections, 16 074 involved heart failure, 8549 involved myocardial infarction or stroke, and 5014 involved AKI.

Figure 1 shows adjusted associations between $eGFR_{cr}$, $eGFR_{cr\text{-}cys}$, $eGFR_{cys}$, and outcomes. Lower $eGFR_{cr}$ and $eGFR_{cr\text{-}cys}$ were associated with higher hazard and incidence rate ratios for all outcomes. We observed U-shaped associations for $eGFR_{cr}$, with higher hazard and incidence rate ratios at values above 90 mL/min/1.73 m^2 for all outcomes except KFRT and AKI. In contrast, associations of $eGFR_{cr\text{-}cys}$ and $eGFR_{cys}$ with outcomes were approximately linear. $eGFR_{cr\text{-}cys}$ and $eGFR_{cys}$ were more strongly associated with outcomes than $eGFR_{cr}$. For example, adjusted hazard ratios and incidence rate ratios for 60 vs. 80 mL/min/1.73 m^2 for $eGFR_{cr}$, $eGFR_{cr\text{-}cys}$, and $eGFR_{cys}$ were 1.0 (95% CI, 0.9 to 1.0), 1.2 (CI, 1.1 to 1.3), and 1.3 (CI, 1.2 to 1.4) for all-cause mortality; 1.0 (CI, 0.9 to 1.1), 1.3 (CI, 1.2 to 1.4), and 1.4 (CI, 1.2 to 1.6) for cardiovascular mortality; 1.4 (CI, 0.7 to 2.8),

Table 1. Baseline Characteristics of Persons Aged 65 Years or Older With Creatinine Testing and the Subset With Same-Day Creatinine and Cystatin C Testing in Stockholm During 2010–2019

Characteristic	Population With Creatinine Testing	Subset With Creatinine and Cystatin C Testing				
		Overall	Aged 65–74 y	Aged ≥75 y	UACR <30 mg/g*	UACR ≥30 mg/g*
Persons, *n*	432 198	82 154	39 562	42 592	29 998	11 214
Mean age (SD), *y*	73 (8)	77 (8)	70 (3)	83 (6)	76 (8)	76 (8)
Mean $eGFR_{cr}$ (SD), *mL/min/1.73 m²*	78 (18)	67 (22)	74 (21)	61 (21)	69 (21)	54 (25)
Mean $eGFR_{cr\text{-}cys}$ (SD), *mL/min/1.73 m²*	–	61 (24)	70 (23)	53 (21)	63 (23)	47 (24)
Mean $eGFR_{cys}$ (SD), *mL/min/1.73 m²*	–	54 (24)	64 (24)	45 (20)	56 (23)	40 (22)
Female, %	55.0	49.9	43.6	55.9	51.3	36.0
Hypertension, %	35.4	80.3	74.9	85.5	81.9	92.4
Antihypertensive medication use, %	19.9	75.9	71.1	80.6	77.8	88.3
Diabetes, %	10.4	24.6	26.3	23.2	31.2	52.1
History of cardiovascular disease, %	23.5	40.5	30.0	50.5	38.2	50.8
Mean total cholesterol level (SD)†						
mmol/L	5.1 (1.2)	5.1 (1.2)	5.1 (1.2)	5.0 (1.2)	5.0 (1.2)	4.7 (1.2)
mg/dL	196 (46)	195 (46)	197 (47)	192 (46)	193 (46)	183 (48)
Mean HDL cholesterol level (SD)†						
mmol/L	1.4 (0.5)	1.4 (0.5)	1.4 (0.5)	1.5 (0.5)	1.5 (0.5)	1.3 (0.4)
mg/dL	55 (18)	55 (18)	55 (18)	56 (18)	56 (18)	49 (17)
Median UACR (IQR), *mg/g*†	16 (6–58)	17 (6–68)	13 (5–58)	22 (8–79)	8.0 (4.4–14.2)	113 (52–362)

$eGFR_{cr}$ = estimated glomerular filtration rate using creatinine level; $eGFR_{cr\text{-}cys}$ = estimated glomerular filtration rate using creatinine and cystatin C levels; $eGFR_{cys}$ = estimated glomerular filtration rate using cystatin C level; HDL = high-density lipoprotein; UACR = urinary albumin–creatinine ratio.
* Converted using dipstick values when UACR was missing.
† In the population tested for creatinine, data on total cholesterol level, HDL cholesterol level, and UACR were missing in 29.4%, 44.3%, and 64.8% of persons, respectively. In the subset of persons tested for creatinine and cystatin C, the respective proportions of missing data were 24.5%, 32.7%, and 49.8% overall; 16.5%, 23.0%, and 46.3% among persons aged 65 to 74 years; 32.0%, 41.7%, and 53.1% among those aged ≥75 years; 15.2%, 21.4%, and 0% among those with UACR <30 mg/g; and 13.4%, 19.8%, and 0% among those with UACR ≥30 mg/g. To convert UACR from mg/g to mg/mmol, multiply by 0.113. The numbers shown are before multiple imputation.

2.6 (CI, 1.2 to 5.8), and 1.5 (CI, 0.6 to 3.9) for KFRT; 1.2 (CI, 1.1 to 1.4), 1.5 (CI, 1.4 to 1.7), and 1.7 (CI, 1.6 to 1.9) for heart failure; and 1.6 (CI, 1.4 to 1.9), 2.3 (CI, 2.0 to 2.6), and 2.3 (CI, 1.9 to 2.7) for AKI (**Supplement Table 3**, available at Annals.org). Differences between $eGFR_{cr}$, $eGFR_{cr\text{-}cys}$, and $eGFR_{cys}$ were also observed when eGFR levels of 30 or 45 vs. 80 mL/min/1.73 m^2 were compared (**Supplement Table 3**).

Absolute incidence rates for all events except KFRT and AKI were higher at older age (**Figure 2** and **Table 2**). For example, adjusted incidence rates per 100 person-years for all-cause mortality at $eGFR_{cr\text{-}cys}$ of 30, 60, and 80 mL/min/1.73 m^2 were 6.6 (CI, 6.1 to 7.2), 3.3 (CI, 3.1 to 3.6), and 2.7 (CI, 2.6 to 2.8), respectively, for patients aged 70 years and 12 (CI, 11 to 12), 7.4 (CI, 7.0 to 7.9), and 6.7 (CI, 6.4 to 6.9) for patients aged 80 years. Furthermore, absolute incidence rates for all outcomes were higher with lower $eGFR_{cr\text{-}cys}$. For example, incidence rates for recurrent hospitalizations at age 70 years for $eGFR_{cr\text{-}cys}$ levels of 30, 60, and 80 mL/min/1.73 m^2 were 65 (CI, 61 to 70), 44 (CI, 43 to 46), and 39 (CI, 38 to 41) per 100 person-years, respectively, despite small adjusted hazard ratios (**Figure 2** and **Table 2**).

Use of $eGFR_{cr\text{-}cys}$ versus $eGFR_{cr}$ resulted in reclassification of 31.2% of older persons, predominantly to a more severe GFR category (**Table 3**). For example, 24.0% of persons with $eGFR_{cr}$ between 60 and 89 mL/min/1.73 m^2 were reclassified to 45 to 59 mL/min/1.73 m^2 with $eGFR_{cr\text{-}cys}$, and 33.4% of those with $eGFR_{cr}$ between 30 and 44 mL/min/1.73 m^2 were reclassified to 15 to 29 mL/min/1.73 m^2 with $eGFR_{cr\text{-}cys}$. Reclassification to more severe GFR categories was greater for persons aged 75 years or older than for those aged 65 to 74 years (**Supplement Table 4**, available at Annals.org).

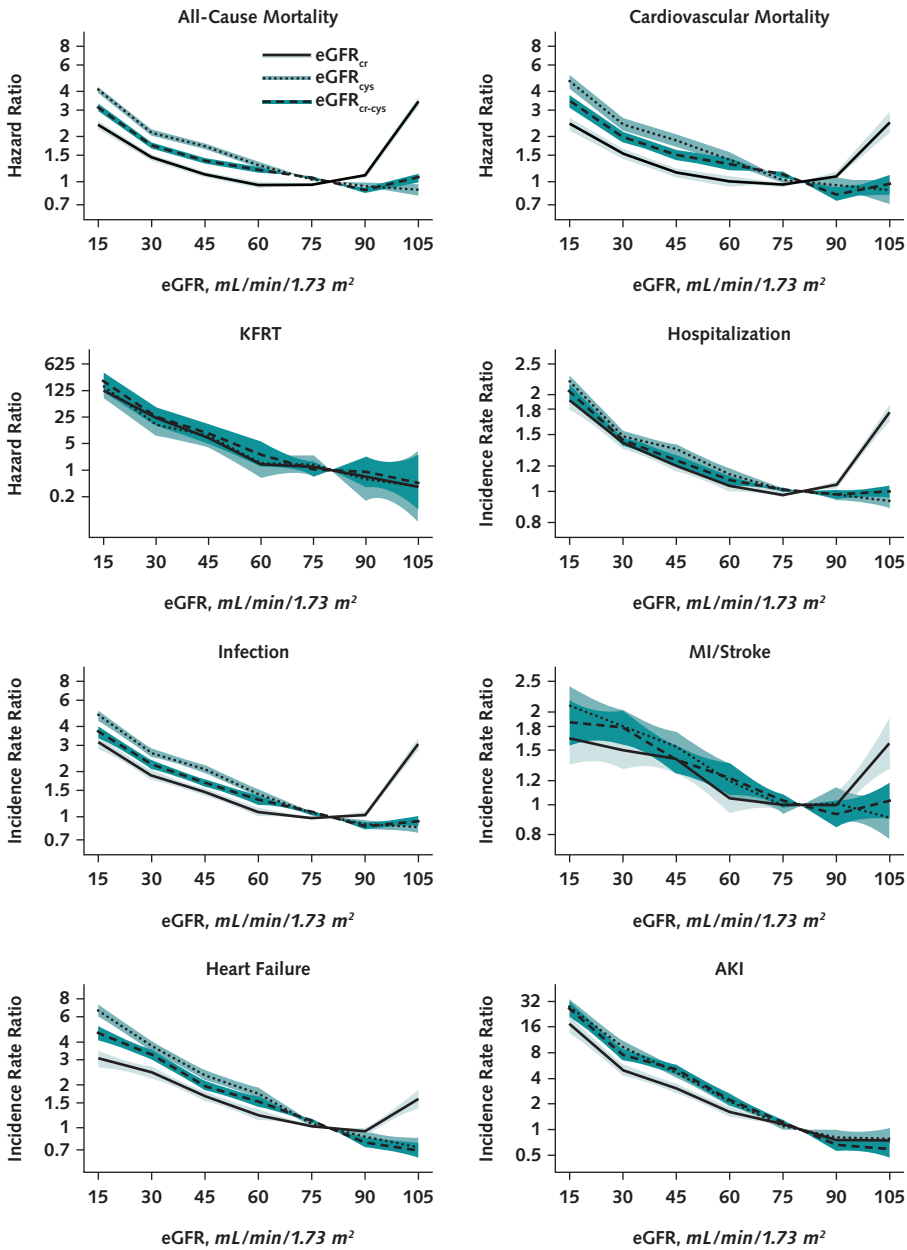
Supporting Analyses

$eGFR_{cr\text{-}cys}$ and $eGFR_{cys}$ were also more strongly associated with outcomes than $eGFR_{cr}$ within subgroups of age (65 to 74 and ≥75 years), although the magnitude of hazard and incidence rate ratios for all 3 GFR estimates was lower among those aged 75 years or older than among those aged 65 to 74 years (**Supplement Figure 3**, available at Annals.org). Similar findings were observed for subgroups of sex, cardiovascular disease, and diabetes (**Supplement Figures 4** to **6**, available at Annals.org). Among persons with UACR below 30 mg/g, $eGFR_{cr\text{-}cys}$ and $eGFR_{cys}$ were also more strongly associated with outcomes than $eGFR_{cr}$ (**Supplement Table 3** and **Supplement Figure 7**, available at Annals.org). For example, adjusted hazard and incidence rate ratios for 60 versus 80 mL/min/1.73 m^2 for $eGFR_{cr}$, $eGFR_{cr\text{-}cys}$, and $eGFR_{cys}$ were 1.0 (CI, 0.9 to 1.1), 1.2 (CI, 1.1 to 1.4), and 1.3 (CI, 1.2 to 1.5) for all-cause mortality and 2.2 (CI, 0.5 to 9.0), 7.3 (CI, 1.4 to 39.7), and 2.2 (CI, 0.3 to 14.2) for KFRT, respectively.

Similar findings were observed when the EKFC equations were used to calculate eGFR (**Supplement Tables 5** and **6** and **Supplement Figures 8** to **10**, available at Annals.org). There were substantial differences in hazard and incidence rate ratios between $eGFR_{cr}$ and $eGFR_{cr\text{-}cys}$ for 60 versus 80 mL/min/1.73 m^2: 0.8 (CI, 0.8 to 0.9) for $eGFR_{cr}$ versus 1.3 (CI, 1.3 to 1.4) for

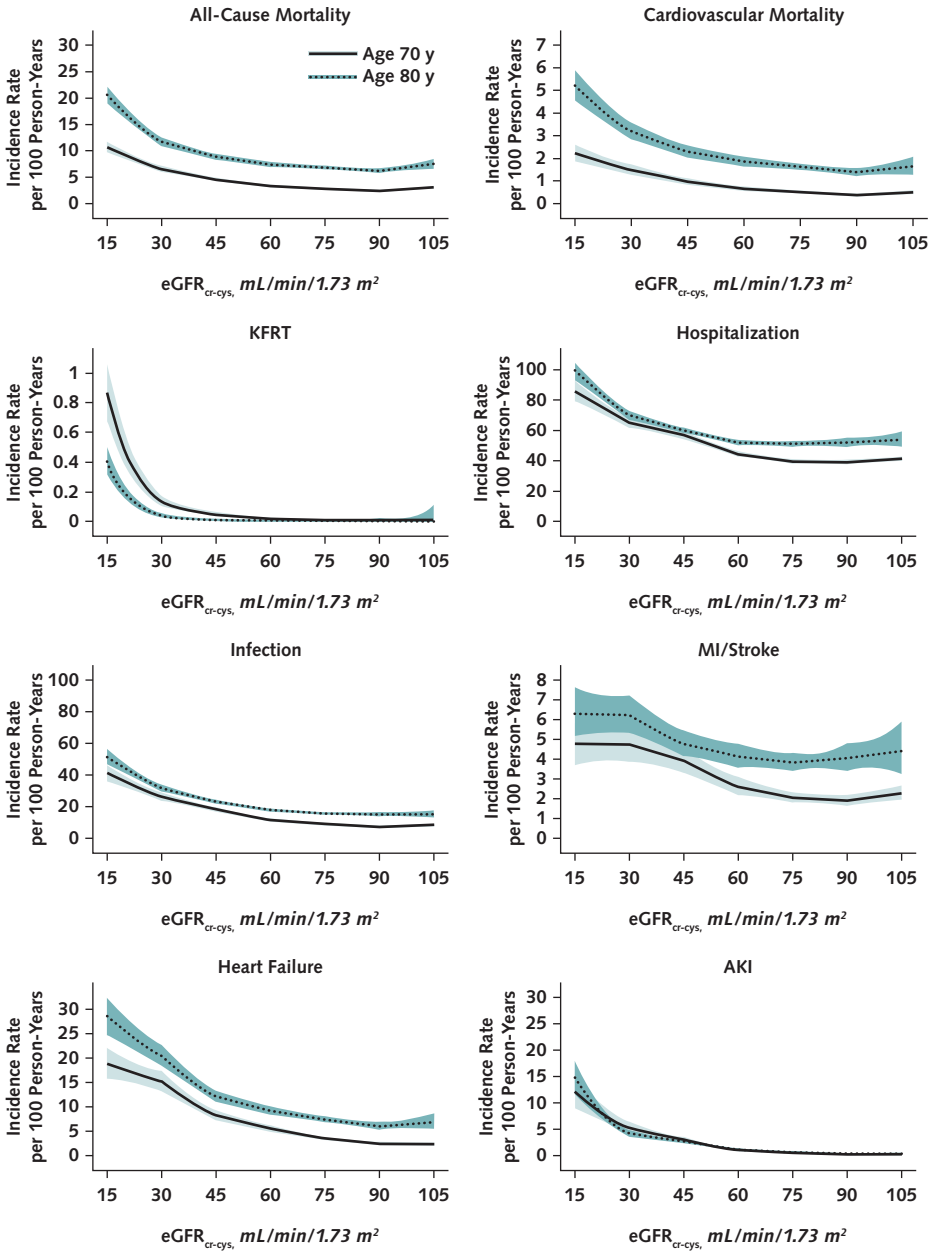
$eGFR_{cr\text{-}cys}$ for all-cause mortality; 1.0 (CI, 0.9 to 1.0) versus 1.7 (CI, 1.5 to 1.8) for cardiovascular mortality; 1.8 (CI, 1.0 to 3.3) versus 3.4 (CI, 1.6 to 7.2) for KFRT; and 2.0 (CI, 1.8 to 2.3) vs. 3.5 (CI, 3.1 to 4.1) for AKI. Results were also consistent when the CKD-EPI 2009 and 2012 equations were used (**Supplement Tables 7** and **8** and **Supplement Figures 11** and **12**, available at Annals.org). Similar results were obtained when incidence rates standardized to the study population were used, with higher absolute incidence rates of all events except KFRT and AKI at older age (**Supplement Table 9** and **Supplement Figure 13**, available at Annals.org).

Figure 1. Adjusted hazard ratios and incidence rate ratios and 95% CIs for $eGFR_{cr}$ vs. $eGFR_{cr\text{-}cys}$ vs. $eGFR_{cys}$ (per 1–mL/min/1.73 m^2 increase) and outcomes.



eGFR was modeled using a linear spline with knots at 30, 45, 60, 75, and 90 mL/min/1.73 m^2. The reference value was 80 mL/min/1.73 m^2. Adjusted hazard ratios for all-cause mortality, cardiovascular mortality, and KFRT were estimated using Cox regression, and adjusted incidence rate ratios for recurrent all-cause hospitalizations and hospitalizations with infection, MI or stroke, heart failure, and AKI were estimated using negative binomial regression. AKI = acute kidney injury; eGFR = estimated glomerular filtration rate; $eGFR_{cr}$ = estimated glomerular filtration rate using creatinine level; $eGFR_{cr\text{-}cys}$ = estimated glomerular filtration rate using creatinine and cystatin C levels; $eGFR_{cys}$ = estimated glomerular filtration rate using cystatin C level; KFRT = kidney failure with replacement therapy; MI = myocardial infarction.

Figure 2. Adjusted incidence rate per 100 person-years and 95% CIs for $eGFR_{cr\text{-}cys}$ for outcomes among persons aged 70 and 80 years.



eGFR was modeled using a linear spline with knots at 30, 45, 60, 75, and 90 mL/min/1.73 m^2. Adjusted incidence rates were estimated using Poisson regression for mortality and KFRT, and negative binomial regression was used for all other outcomes. AKI = acute kidney injury; eGFR = estimated glomerular filtration rate; $eGFR_{cr}$ = estimated glomerular filtration rate using creatinine level; $eGFR_{cr\text{-}cys}$ = estimated glomerular filtration rate using creatinine and cystatin C levels; $eGFR_{cys}$ = estimated glomerular filtration rate using cystatin C level; KFRT = kidney failure with replacement therapy; MI = myocardial infarction.

DISCUSSION

In this study, we examined 82 154 older adults from routine clinical practice with same-day outpatient measurements for creatinine and cystatin C. We found that $eGFR_{cr\text{-}cys}$ below 60 mL/min/1.73 m^2 had stronger associations with clinical outcomes than $eGFR_{cr}$. For $eGFR_{cr}$, U-shaped associations were observed for most outcomes, whereas $eGFR_{cr\text{-}cys}$ and $eGFR_{cys}$ showed more linear associations. Findings were consistent across subgroups and when alternative eGFR equations (EKFC, CKD-EPI 2009, or CKD-EPI 2012 with non-Black race coefficient) were used.

These findings inform the discussion on the definition of CKD in older adults (6, 11–16). Age-adapted

definitions for CKD have been proposed, with a GFR threshold of 45 mL/min/1.73 m^2 for persons aged 65 years or older with albuminuria below 30 mg/g, due to inconsistent associations between $eGFR_{cr}$ levels of 45 to 60 mL/min/1.73 m^2 and all-cause mortality (6). Our results show that the absence of associations is likely explained by the use of creatinine as a filtration marker rather than the GFR threshold per se, given that hazard ratios were increased for $eGFR_{cr\text{-}cys}$ of 60 mL/min/1.73 m^2 compared with the reference of 80 mL/min/1.73 m^2. Furthermore, we studied a wider range of outcomes than previous studies, which focused solely on kidney failure and mortality (8, 10). Indeed, we observed strong associations between eGFR and hospitalization with AKI or heart failure at the GFR threshold of less than 60 mL/min/1.73 m^2. These data indicate that CKD stage G3+ (GFR <60 mL/min/1.73 m^2) at older age is associated with a wider range of outcomes than previously recognized, even in the absence of albuminuria.

Our study found U-shaped associations between $eGFR_{cr}$ and outcomes, with higher risks with $eGFR_{cr}$ above 90 mL/min/1.73 m^2, which is similar to findings from previous epidemiologic studies (9, 46). In contrast, associations for $eGFR_{cr\text{-}cys}$ and $eGFR_{cys}$ were more linear (47–49), which is more biologically plausible. These differences are due to non-GFR determinants that influence creatinine and cystatin C levels (17, 18, 25, 50). Besides GFR, creatinine is also influenced by muscle mass, diet, and physical activity, whereas cystatin C is influenced by inflammation, obesity, smoking, thyroid diseases, and glucocorticoid use (17, 18, 25, 51). The higher risk with $eGFR_{cr}$ above 90 mL/min/1.73 m^2 is likely attributable to persons with low muscle mass and poorer health status. These persons have low creatinine levels leading to high $eGFR_{cr}$ that is an overestimate of their true GFR, and they are also at high risk for adverse outcomes. This also explains the weaker associations for $eGFR_{cr}$ below 60 mL/min/1.73 m^2 compared with $eGFR_{cr\text{-}cys}$. Even though the same reference value for eGFR (80 mL/min/1.73 m^2) is applied for each eGFR measure, the characteristics of the persons who are included in the reference value differ. Thus, $eGFR_{cr}$ of 80 mL/min/1.73 m^2

Table 2. Adjusted Incidence Rates per 100 Person-Years and 95% CIs for $eGFR_{cr}$ vs. $eGFR_{cr\text{-}cys}$ Among Persons Aged 70 and 80 Years at eGFR Levels of 30, 45, 60, and 80 mL/min/1.73 m^2

Outcome	Age	Adjusted Incidence Rate per 100 Person-Years (95% CI), by eGFR Level			
		30 mL/min/1.73 m^2	45 mL/min/1.73 m^2	60 mL/min/1.73 m^2	80 mL/min/1.73 m^2
$eGFR_{cr}$					
All-cause mortality	70 y	5.9 (5.4–6.5)	4.1 (3.8–4.5)	2.6 (2.4–2.8)	2.4 (2.3–2.5)
	80 y	11 (10–12)	8.1 (7.7–8.7)	6.4 (6.0–6.9)	6.7 (6.4–7.0)
Cardiovascular mortality	70 y	1.3 (1.1–1.6)	0.93 (0.80–1.1)	0.55 (0.47–0.65)	0.47 (0.44–0.51)
	80 y	3.0 (2.6–3.4)	2.2 (1.9–2.4)	1.7 (1.5–1.9)	1.6 (1.5–1.8)
KFRT	70 y	0.20 (0.15–0.26)	0.063 (0.047–0.086)	0.0130 (0.0082–0.021)	0.0077 (0.0050–0.012)
	80 y	0.070 (0.052–0.096)	0.012 (0.0070–0.021)	0.0055 (0.0025–0.012)	0.0031 (0.0014–0.0070)
Hospitalization	70 y	61 (57–66)	53 (50–56)	39 (37–41)	38 (37–39)
	80 y	70 (67–73)	58 (56–60)	51 (49–53)	49 (48–51)
Infection	70 y	23 (20–26)	17 (16–19)	8.9 (8.3–9.6)	8.0 (7.6–8.4)
	80 y	29 (27–32)	22 (21–23)	16 (15–17)	16 (15–16)
MI/stroke	70 y	3.7 (3.0–4.7)	3.9 (3.2–4.7)	2.3 (1.9–2.8)	2.1 (1.9–2.3)
	80 y	5.6 (4.7–6.6)	5.1 (4.4–6.0)	3.8 (3.3–4.4)	3.8 (3.4–4.1)
Heart failure	70 y	12 (10–14)	8.3 (7.2–9.4)	4.5 (4.0–5.1)	3.6 (3.4–3.9)
	80 y	18 (16–21)	12 (11–14)	9.2 (8.3–10.3)	7.6 (7.1–8.1)
AKI	70 y	5.2 (4.1–6.7)	2.8 (2.3–3.4)	1.1 (0.96–1.3)	0.68 (0.61–0.77)
	80 y	4.5 (3.8–5.4)	2.7 (2.3–3.1)	1.5 (1.3–1.7)	0.93 (0.83–1.0)
$eGFR_{cr\text{-}cys}$					
All-cause mortality	70 y	6.6 (6.1–7.2)	4.6 (4.2–4.9)	3.3 (3.1–3.6)	2.7 (2.6–2.8)
	80 y	12 (11–12)	8.9 (8.3–9.4)	7.4 (7.0–7.9)	6.7 (6.4–6.9)
Cardiovascular mortality	70 y	1.5 (1.3–1.7)	0.98 (0.85–1.1)	0.66 (0.56–0.78)	0.47 (0.43–0.51)
	80 y	3.2 (2.8–3.6)	2.3 (2.1–2.6)	1.9 (1.6–2.1)	1.5 (1.4–1.7)
KFRT	70 y	0.13 (0.10–0.17)	0.046 (0.033–0.064)	0.015 (0.0091–0.024)	0.0040 (0.0022–0.0073)
	80 y	0.038 (0.028–0.053)	0.0087 (0.0047–0.016)	0.0041 (0.0016–0.011)	0.0037 (0.0014–0.0095)
Hospitalization	70 y	65 (61–70)	57 (54–59)	44 (43–46)	39 (38–41)
	80 y	70 (67–73)	60 (58–62)	52 (50–54)	51 (50–53)
Infection	70 y	27 (24–29)	18 (17–20)	12 (11–13)	8.7 (8.3–9.1)
	80 y	32 (30–34)	23 (22–25)	18 (17–19)	16 (15–17)
MI/stroke	70 y	4.8 (3.9–5.9)	3.9 (3.3–4.7)	2.6 (2.2–3.1)	2.0 (1.8–2.3)
	80 y	6.2 (5.3–7.3)	4.8 (4.1–5.5)	4.1 (3.6–4.8)	3.9 (3.6–4.3)
Heart failure	70 y	15 (13–18)	8.3 (7.3–9.5)	5.6 (4.9–6.4)	3.2 (3.0–3.5)
	80 y	20 (18–23)	12 (11–13.5)	9.3 (8.4–10)	7.1 (6.6–7.6)
AKI	70 y	5.3 (4.3–6.5)	3.1 (2.6–3.7)	1.2 (0.98–1.3)	0.51 (0.45–0.57)
	80 y	4.3 (3.7–4.9)	2.8 (2.4–3.1)	1.3 (1.1–1.4)	0.62 (0.54–0.72)

AKI = acute kidney injury; eGFR = estimated glomerular filtration rate; $eGFR_{cr}$ = estimated glomerular filtration rate using creatinine level; $eGFR_{cr\text{-}cys}$ = estimated glomerular filtration rate using creatinine and cystatin C levels; KFRT = kidney failure with replacement therapy; MI = myocardial infarction.

Table 3. Reclassification Across eGFR Categories for $eGFR_{cr}$ vs. $eGFR_{cr\text{-}cys}$

$eGFR_{cr}$ Category	Patients Reclassified Into Different $eGFR_{cr\text{-}cys}$ Category, *n* (%)*						Total, *n*
	≥90 mL/min/1.73 m^2	60–89 mL/min/1.73 m^2	45–59 mL/min/1.73 m^2	30–44 mL/min/1.73 m^2	15–29 mL/min/1.73 m^2	<15 mL/min/1.73 m^2	
≥90 mL/min/1.73 m^2	7588 (50.5)	7123 (47.4)	291 (1.9)	21 (0.1)	1 (0.01)	–	15 024
60–89 mL/min/1.73 m^2	2559 (7.0)	24 137 (65.9)	8796 (24.0)	1141 (3.1)	14 (0.04)	–	36 647
45–59 mL/min/1.73 m^2	5 (0.0)	1383 (9.0)	7683 (50.0)	6050 (39.4)	249 (1.6)	1 (0.01)	15 371
30–44 mL/min/1.73 m^2	–	17 (0.2)	519 (5.3)	6049 (61.2)	3302 (33.4)	5 (0.1)	9892
15–29 mL/min/1.73 m^2	–	1 (0.0)	8 (0.2)	182 (4.2)	3673 (84.7)	473 (10.9)	4337
<15 mL/min/1.73 m^2	–	–	–	3 (0.3)	71 (8.0)	809 (91.6)	883
Total, *n*	10 152	32 661	17 297	13 446	7310	1288	82 154

eGFR = estimated glomerular filtration rate; $eGFR_{cr}$ = estimated glomerular filtration rate using creatinine level; $eGFR_{cr\text{-}cys}$ = estimated glomerular filtration rate using creatinine and cystatin C levels.
* Row percentages are shown.

likely includes more people with low muscle mass and poor health status than $eGFR_{cr\text{-}cys}$ of 80 mL/min/1.73 m^2. Similarly, the stronger associations observed with $eGFR_{cys}$ compared with $eGFR_{cr\text{-}cys}$ may not reflect GFR per se but rather the non-GFR determinants of cystatin C. Combining both markers in $eGFR_{cr\text{-}cys}$ improves precision by reducing errors that are due to variation in the non-GFR determinants of each marker (25).

Although the 2012 KDIGO guideline for the evaluation and management of CKD recommends measuring cystatin C when $eGFR_{cr}$ may be less accurate due to low muscle mass (5), this practice remains limited in most countries, including the United States (52), and also among older adults. Sweden is unique in this regard because cystatin C is widely used as a supportive test in routine clinical practice (at a cost of about $3 per test), as evidenced by the fact that one fifth of older adults in our cohort who had an outpatient creatinine measurement also had a same-day cystatin C measurement. The National Kidney Foundation and the American Society of Nephrology recently recommended increased use of cystatin C to estimate GFR in the United States (24), based on the demonstration that $eGFR_{cr\text{-}cys}$ more accurately approximates measured GFR than $eGFR_{cr}$ or $eGFR_{cys}$ (18, 22, 53). We showed that more than 30% of older adults would be reclassified to a different GFR category if $eGFR_{cr}$ were to be replaced by $eGFR_{cr\text{-}cys}$, predominantly to more severe GFR categories. Given that many treatment recommendations are based on GFR thresholds, implementation of cystatin C testing would have a significant effect on clinical practice. Future studies should investigate whether implementing cystatin C testing improves outcomes, such as through better drug dosing or more timely nephrologist referral.

Strengths of our study include its large sample size and contemporary data (2010 to 2019) involving more than 80 000 patients from routine care in a country with a long-standing history of cystatin C testing. We also restricted the study to the periods when measurements of creatinine and cystatin C were standardized and calibrated to traceable international standards. We investigated a wide range of clinically meaningful outcomes and analyzed recurrent events for outcomes that could occur more than once, which is especially relevant in older patients, who may have multiple hospitalizations.

Our study also has several limitations. First, we lacked GFR measurements, and future research should investigate associations between measured GFR and outcomes. Our analyses adjusted for cardiovascular risk factors but did not adjust for all non-GFR determinants that may influence creatinine and cystatin C levels. For example, muscle mass, diet, obesity status or body mass index, smoking, and inflammation were not available in our data sources. eGFR based on cystatin C alone may therefore overestimate risk associations with adverse outcomes compared with measured GFR. Second, only a subset of older adults with a creatinine test had a same-day cystatin C test (19%), and these persons were older and had a higher prevalence of diabetes and cardiovascular disease. It is reassuring to note that results were similar across subgroups based on age and comorbidities. Third, outcomes were based on diagnosis codes, which have high specificity but low sensitivity, particularly for AKI. Fourth, we investigated associations based on 1 eGFR measurement rather than 2 measurements more than 90 days apart, which is used in KDIGO guidelines to define CKD. However, selecting only persons with at least 2 measurements of creatinine and cystatin C would lead to highly selected samples in routinely collected health care data and would preclude studying eGFR as a continuous exposure (38, 54). Fifth, the measurement of cystatin C may have led to a change in subsequent treatment decisions. However, this would similarly affect the associations for $eGFR_{cr}$, $eGFR_{cys}$, and $eGFR_{cr\text{-}cys}$ and outcomes. Finally, we lacked information on race. According to Swedish government annual statistics, our study population consisted of predominantly White participants. Future studies should generalize our findings to populations with different racial or ethnic composition. For example, previous studies in the general population have indicated that differences between hazard ratios for $eGFR_{cr}$ vs. $eGFR_{cr\text{-}cys}$ may be even larger among Black persons (55).

In conclusion, low $eGFR_{cr\text{-}cys}$ was more strongly associated with a broad range of outcomes than low $eGFR_{cr}$ among older patients, including all-cause and

cardiovascular mortality and many specific types of hospitalizations. $eGFR_{cr}$ above 90 mL/min/1.73 m^2 was associated with higher risk, but not $eGFR_{cr\text{-}cys}$ or $eGFR_{cys}$, suggesting the risk may be driven by low creatinine generation and low muscle mass rather than high GFR itself. The broad range of risks associated with CKD at older age is better appreciated when cystatin C is included in GFR estimation.

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