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Measured and Estimated Glomerular Filtration Rates and Risk of Adverse Health Outcomes

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Editorial

Supplemental content

IMPORTANCE Lower estimated glomerular filtration rate (eGFR) is associated with increased rates of death and kidney and cardiovascular events. Associations of measured GFR (mGFR) with outcomes remain unclear.

OBJECTIVE To quantify associations between mGFR and adverse clinical outcomes and to compare these with eGFR-based associations.

DESIGN, SETTING, AND PARTICIPANTS Retrospective observational cohort study of 6174 adults from Stockholm, Sweden, between January 1, 2011, and December 31, 2021.

EXPOSURE Measured GFR was obtained based on plasma clearance of intravenously administered iohexol (primary independent variable of interest). Estimated GFR was calculated with plasma creatinine (eGFRcr), cystatin C (eGFRcys), or both (eGFRcr-cys), using the Chronic Kidney Disease Epidemiology Collaboration 2021 and 2012 equations.

MAIN OUTCOMES AND MEASURES Primary outcomes were all-cause mortality and kidney failure with replacement therapy. Associations of each GFR measure with outcomes were evaluated using hazard ratios adjusted for age, sex, body mass index (calculated as weight in kilograms divided by height in meters squared), medical history, medications, and urine albumin to creatinine ratio.

RESULTS Of 6174 participants (median age, 59 years [IQR, 43-69]; 3686 [60%] were male and 2488 [40%] were female), 1977 (32%) died and 426 (6.9%) developed kidney failure with replacement therapy during a median follow-up of 5.9 years (IQR, 3.0-8.8 years). Compared with a baseline mGFR of 90 mL/min/1.73 m^2, an mGFR of 60 mL/min/1.73 m^2 was associated with higher rates of all-cause mortality (27.6 vs 22.4 per 1000 person-years; hazard ratio [HR], 1.21; 95% CI, 1.14-1.28) and kidney failure with replacement therapy (1.2 vs 0.4 per 1000 person-years; HR, 2.85; 95% CI, 2.06-3.94). For all-cause mortality, associations for eGFRcr-cys did not significantly differ from those for mGFR (ratio of HRs [RHRs] at 60 mL/min/1.73 m^2, 1.03; 95% CI, 0.96-1.10), whereas eGFRcr underestimated the mGFR-based association (RHR, 0.87; 95% CI, 0.79-0.95) and eGFRcys overestimated it (RHR, 1.17; 95% CI, 1.08-1.27).

CONCLUSIONS AND RELEVANCE Among adults in Sweden, mGFR values of 60 mL/min/1.73 m^2 were associated with higher rates of all-cause mortality and kidney failure compared with mGFR values of 90 mL/min/1.73 m^2, supporting the current GFR threshold of 60 mL/min/1.73 m^2 to define chronic kidney disease. Associations of mGFR with mortality were most closely represented by the association of eGFRcr-cys with mortality, whereas eGFRcr underestimated and eGFRcys overestimated mortality risk.

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Chronic kidney disease (CKD) affects 10% to 14% of the population worldwide and is associated with increased rates of death, adverse kidney outcomes, and cardiovascular events. A glomerular filtration rate (GFR) threshold of 60 mL/min/1.73 m^2 or less has been used to define CKD because it represents half of normal kidney function in young adults and is associated with adverse outcomes compared with values of 90 mL/min/1.73 m^2.[1,2] Additional thresholds of 45, 30, and 15 mL/min/1.73 m^2 are used to stage the severity of CKD. These thresholds are used worldwide for diagnosis, evaluation of prognosis, and treatment decisions in people with CKD.

Although measured GFR (mGFR) is the reference standard for assessing kidney function, empirical evidence to support current GFR thresholds is based on associations between adverse outcomes and estimated GFR (eGFR), which uses creatinine (eGFRcr), cystatin C (eGFRcys), or both (eGFRcr-cys) to estimate GFR.[3-8] Serum creatinine level is decreased by lower muscle mass, whereas serum cystatin C level is increased by obesity, inflammation, and smoking.[9,10] Consequently, eGFR is considered less accurate than mGFR for evaluating kidney function, which has raised uncertainty about whether existing thresholds using eGFR may be biased by other non-GFR factors.[11]

Associations of specific values for mGFR with clinically important outcomes remain unclear. In addition, it remains unclear whether eGFR calculated according to eGFRcr, eGFRcys, or eGFRcr-cys most accurately captures risk related to mGFR. Therefore, this study evaluated associations between major clinical outcomes and mGFR, eGFRcr, eGFRcys, and eGFRcr-cys in a large cohort of patients in Sweden.

Key Points

Question What is the association between measured glomerular filtration rate (mGFR) and adverse clinical outcomes?

Findings In this observational cohort study of 6174 adults in Sweden, compared with an mGFR of 90 mL/min/1.73 m^2, mGFR of 60 mL/min/1.73 m^2 was associated with a statistically significant higher rate of all-cause mortality (27.6 vs 22.4 per 1000 person-years) and kidney failure with replacement therapy (1.2 vs 0.4 per 1000 person-years).

Meaning Among adults in Sweden, compared with an mGFR of 90 mL/min/1.73 m^2, mGFR of 60 mL/min/1.73 m^2 was associated with higher rates of mortality and kidney failure.

Methods

This cohort study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

Data Source

The Stockholm CREAtinine Measurements (SCREAM) project contains health care data for 3.2 million Stockholm residents (2006-2021).[12] A single health care system provides universal tax-funded health care to 20% to 25% of Sweden's population. Core components of SCREAM include a central laboratory repository covering greater than 96% of all laboratory tests in the region and an administrative health data registry of the Stockholm region encompassing all primary and specialist outpatient consultations and hospitalizations since 1997.[12] We further linked these to the Swedish Prescribed Drug Registry, which records all filled prescriptions at Swedish pharmacies; the Swedish Renal Registry, which captures all patients receiving kidney replacement therapy; and the Swedish Cause of Death Registry, which provides date and cause of death.[13-15] The study was approved by the regional ethics board and the Swedish National Board of Health and Welfare, with waiver of informed consent due to the use of pseudonymized data.

Study Population

Participants were 6174 adults (≥18 years) who underwent mGFR testing in Stockholm between January 1, 2011, and December 31, 2021, at the discretion of treating specialists. In general, indications for mGFR testing include patients who require a precise GFR for drug dosing (such as in cancer chemotherapy), patients with liver cirrhosis, patients who are kidney transplant recipients or living kidney donors, and patients with discordance between eGFRcr and eGFRcys.[16] Eligible individuals had serum creatinine and cystatin C levels measured within 30 days of mGFR. We excluded patients receiving dialysis or with mGFR less than 0 mL/min/1.73 m^2 or greater than 150 mL/min/1.73 m^2 (eFigures 1 and 2 in Supplement 1). Estimated GFR was calculated with the race-free Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021 equations for eGFRcr and eGFRcr-cys and 2012 equation for eGFRcys, with each equation incorporating age, sex, and serum creatinine level, cystatin C level, or both.[17,18]

Measurement of GFR, Creatinine Level, and Cystatin C Level

Measured GFR was determined with single-sample plasma clearance of intravenously administered iohexol at the Department of Clinical Chemistry of Karolinska University Hospital.[19] Because iohexol is freely filtered at the glomerulus, is not protein bound, and is neither secreted nor reabsorbed by the tubules, its clearance from plasma closely approximates GFR.[20] Clearance was calculated from a single plasma iohexol concentration with the Jacobsson equation (detailed information in the eMethods in Supplement 1).[21] Both creatinine and cystatin C assays were standardized to isotope dilution mass spectrometry and 2010 reference standards, respectively.[22-24]

Covariates

For each individual, we extracted information on demographics, comorbid conditions, medication use, and laboratory measurements (covariate definitions provided in eTable 1 in Supplement 1). Comorbid conditions were identified from *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* diagnosis codes recorded in any diagnosis position using an infinite look-back period (defined as using the entire available history of a patient's medical records, from the earliest date of data availability up to the index date, to identify comorbid conditions) that went back to 1997, when coding started (eFigure 1 in Supplement 1). Kidney transplant recipients were identified through the Swedish Renal Registry. Medications were considered concomitant if a prescription was filled in the 183 days before the GFR measurement, as recorded in the Swedish Prescribed Drug Registry.

Study Outcomes

The primary outcomes of interest were all-cause mortality and kidney failure with replacement therapy (defined as start of dialysis or kidney transplant). Secondary outcomes were major adverse cardiovascular events (composite of cardiovascular mortality, hospitalization for myocardial infarction, and stroke), hospitalization for heart failure, and hospitalization with acute kidney injury (definitions in eTable 1 in Supplement 1). Follow-up began on the date of GFR measurement and ended on the earliest of outcome occurrence, death, emigration from the region of Stockholm, or December 31, 2021.

Statistical Analysis

Baseline characteristics were summarized across GFR categories (<30, 30-44, 45-59, 60-74, 75-89, and ≥90 mL/min/1.73 m^2). Continuous variables are reported as median with first and third quartiles (IQR); categorical variables, as counts (percentages). Pairwise relationships between mGFR and eGFR were assessed with Pearson correlation coefficients. We used Cox proportional hazards models to estimate adjusted hazard ratios (HRs) for mGFR or eGFR and outcomes. Continuous GFR was modeled using restricted cubic splines with 4 knots placed at fixed percentiles (fifth, 35th, 65th, and 95th) of the GFR distributions.[25] From this spline model, we estimated HRs for GFR levels of 15, 30, 45, 60, 75, and 120 mL/min/1.73 m^2 compared with the reference of 90 mL/min/1.73 m^2. Hazard ratios were adjusted for the following variables, based on subject matter knowledge and prior literature[4,8]: age, sex, body mass index (calculated as weight in kilograms divided by height in meters squared), medical history (myocardial infarction, hypertension, heart failure, stroke, atrial fibrillation, peripheral vascular disease, diabetes, chronic obstructive pulmonary disease, cancer, liver disease, and kidney transplant recipient status) (**Table 1**), medications (antihypertensives, glucocorticosteroids, lipid-lowering drugs, and nonsteroidal anti-inflammatory drugs) (Table 1), and log-transformed urine albumin to creatinine ratio. Consistent with previous studies[8] and to prevent index event bias,[26] we excluded individuals with a history of the outcome at baseline from each outcome-specific analysis (acute kidney injury, hospitalization for heart failure, and major adverse cardiovascular events) to restrict analyses to incident events. Individuals with a history of kidney transplant were included for the outcome of kidney failure with replacement therapy because transplant recipients have a new functioning organ and remain at risk of incident graft failure. Adjusted incidence rates were estimated using Poisson regression with a log link and an offset for person-time, with covariates fixed at their median values for continuous variables and at their modal values for categorical variables. From this Poisson model we estimated adjusted incidence rates at GFR levels of 15, 30, 45, 60, 75, 90, and 120 mL/min/1.73 m^2. To quantify the extent to which eGFR-outcome associations reproduced mGFR-outcome associations, we computed ratios of HRs, defined as the HR for the eGFR-outcome association divided by that for the mGFR-outcome association at the same GFR value. A ratio of 1 indicates concordance with the mGFR-outcome association, whereas ratios below or above 1 indicate underestimation or overestimation of the mGFR-outcome association, respectively. CIs for the ratio of HRs were obtained using bootstrapping with 500 iterations, and a ratio was considered statistically significant when the 95% CI excluded 1.

We used multiple imputation by chained equations with predictive mean matching to account for missing data for body mass index and urine albumin to creatinine ratio because these data were not missing completely at random (eTable 2 in Supplement 1), imputing 50 datasets with 10 iterations each.[27] Variables in the imputation model included all GFRs with their spline transformation, all covariates included in the Cox model, kidney donor status, event indicators, and the cumulative hazard estimated with the Nelson-Aalen estimator. When bootstrapping was performed, multiple imputation by chained equations was conducted within each bootstrap sample.[28] All analyses were performed with R version 4.4.2 (R Foundation for Statistical Computing), with analytic codes available online. Analyses were performed from January 1, 2023, through May 1, 2026.

Sensitivity Analyses

We performed the following sensitivity analyses: first, to assess potential selection bias related to indications for mGFR testing, we compared the association between eGFRcr and all-cause mortality in our cohort (N = 6174) with that observed among all individuals in Stockholm who had serum creatinine level measured between 2011 and 2021 (N = 1 584 287). Second, we recalculated incidence rates and HRs using the CKD-EPI 2009 equation (eGFRcr), currently recommended in Europe, and the 2012 CKD-EPI equation (eGFRcr-cys), without the race coefficient.[18,29,30] Third, we recalculated incidence rates and HRs using the European Kidney Function Consortium 2021 (eGFRcr) and 2023 (eGFRcys) equations, with eGFRcr-cys calculated as the mean of these 2.[31,32] Fourth, we recalculated incidence rates and HRs, excluding urine albumin to creatinine ratio values derived from urine protein to creatinine ratio or dipstick conversions.[33] These values were treated as missing and subsequently imputed using the same imputation model as the main analysis. Fifth, we excluded kidney transplant recipients because their risk profiles may differ from those of individuals with CKD who have not undergone transplant. Sixth, we conducted analyses without restricting participants to those with no history of the outcome measure.

Table 1. Baseline Characteristics of Persons Undergoing mGFR Testing Using Plasma Clearance of Iohexol With Simultaneous Creatinine and Cystatin C Testing During 2011-2021

	mGFR category, mL/min/1.73 m^2					
Baseline characteristics	<30 (n = 881)	30-44 (n = 768)	45-59 (n = 904)	60-74 (n = 1017)	75-89 (n = 1153)	≥90 (n = 1451)
Demographics and anthropometrics						
Age, median (IQR), y	68 (57-75)	68 (59-75)	65 (54-73)	60 (47-69)	53 (38-65)	43 (30-55)
Sex, No. (%)						
Male	509 (58)	417 (54)	519 (57)	596 (59)	718 (62)	927 (64)
Female	372 (42)	351 (46)	385 (43)	421 (41)	435 (38)	524 (36)
Body mass index, median (IQR)	26.2 (23.0-30.1) [n = 722]	25.7 (22.9-29.0) [n = 637]	25.2 (22.6-28.7) [n = 732]	24.8 (22.3-27.8) [n = 772]	24.7 (22.4-28.0) [n = 751]	24.9 (22.4-28.4) [n = 852]
Laboratory values, median (IQR)						
Creatinine, mg/dL	2.78 (2.00-3.86)	1.46 (1.22-1.74)	1.17 (0.98-1.35)	0.97 (0.83-1.14)	0.88 (0.74-1.03)	0.80 (0.67-0.94)
Cystatin C, mg/L	3.07 (2.52-3.72)	1.86 (1.62-2.15)	1.46 (1.30-1.66)	1.17 (1.04-1.33)	0.99 (0.89-1.11)	0.86 (0.76-0.95)
eGFRcr, mL/min/1.73 m^2	23 (15-32)	46 (39-56)	64 (53-75)	80 (69-93)	94 (83-103)	106 (96-116)
eGFRcys, mL/min/1.73 m^2	17 (13-22)	33 (27-39)	46 (38-54)	63 (53-74)	81 (69-94)	100 (87-113)
eGFRcr-cys, mL/min/1.73 m^2	19 (14-25)	39 (33-45)	53 (47-61)	71 (63-80)	88 (79-97)	104 (94-114)
mGFR, mL/min/1.73 m^2	19 (14-24)	37 (34-41)	52 (49-56)	67 (63-71)	82 (79-86)	101 (95-109)
Urine albumin to creatinine ratio, mg/g	259 (44-1216) [n = 844]	48 (19-274) [n = 638]	29 (16-184) [n = 704]	20 (10-57) [n = 758]	15 (5-29) [n = 857]	12 (4-22) [n = 1048]
Urine albumin to creatinine ratio category, No. (%), mg/g	[n = 844]	[n = 638]	[n = 704]	[n = 758]	[n = 857]	[n = 1048]
A1 (<30)	174 (21)	269 (42)	374 (53)	482 (64)	658 (77)	858 (82)
A2 (30-300)	272 (32)	226 (35)	202 (29)	181 (24)	144 (17)	142 (14)
A3 (>300)	398 (47)	143 (22)	128 (18)	95 (13)	55 (6)	48 (5)
Serum albumin, median (IQR), g/dL	3.4 (3.1-3.7) [n = 869]	3.5 (3.1-3.7) [n = 722]	3.5 (3.1-3.8) [n = 834]	3.6 (3.3-3.9) [n = 910]	3.8 (3.4-4.0) [n = 1008]	3.8 (3.5-4.1) [n = 1272]
Medical history, No. (%)						
Hypertension	743 (84)	551 (72)	542 (60)	404 (40)	293 (25)	232 (16)
Diabetes	357 (41)	238 (31)	211 (23)	165 (16)	122 (11)	151 (10)
Heart failure	241 (27)	147 (19)	121 (13)	80 (8)	38 (3)	24 (2)
Acute kidney injury	179 (20)	80 (10)	41 (5)	48 (5)	24 (2)	16 (1)
Atrial fibrillation	169 (19)	126 (16)	112 (12)	83 (8)	40 (3)	27 (2)
Cancer in previous year	131 (15)	267 (35)	380 (42)	404 (40)	380 (33)	436 (30)
Chronic obstructive pulmonary disease	126 (14)	93 (12)	79 (9)	94 (9)	68 (6)	61 (4)
Myocardial infarction	118 (13)	78 (10)	62 (7)	47 (5)	28 (2)	16 (1)
Peripheral vascular disease	110 (12)	64 (8)	48 (5)	39 (4)	27 (2)	23 (2)
Stroke	82 (9)	56 (7)	59 (7)	37 (4)	32 (3)	14 (1)
Liver disease	80 (9)	104 (14)	168 (19)	153 (15)	161 (14)	195 (13)
Kidney transplant recipient	58 (7)	34 (4)	43 (5)	27 (3)	4 (0.3)	2 (0.1)
Kidney donor	1 (0.1)	0	15 (2)	32 (3)	26 (2)	48 (3)
Medications, No. (%)						
ACEi/ARB	619 (70)	474 (62)	445 (49)	332 (33)	224 (19)	185 (13)
β-Blocker	533 (60)	373 (49)	351 (39)	233 (23)	152 (13)	130 (9)
Diuretic	568 (64)	305 (40)	274 (30)	176 (17)	125 (11)	78 (5)
Glucocorticosteroids	246 (28)	240 (31)	291 (32)	268 (26)	239 (21)	229 (16)
Calcium-channel blocker	473 (54)	275 (36)	238 (26)	170 (17)	111 (10)	72 (5)
Lipid-lowering drug	407 (46)	291 (38)	242 (27)	190 (19)	132 (11)	105 (7)
Nonsteroidal anti-inflammatory drug	49 (6)	74 (10)	116 (13)	133 (13)	164 (14)	169 (12)

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; eGFRcr, estimated glomerular filtration rate based on creatinine; eGFRcr-cys, estimated GFR based on creatinine and cystatin C; eGFRcys, estimated GFR based on cystatin C; mGFR, measured GFR. Body mass index is calculated as weight in kilograms divided by height in meters squared.

SI conversion factors: To convert creatinine to μmol/L, multiply by 88.4; to convert albumin to g/L, multiply by 10.

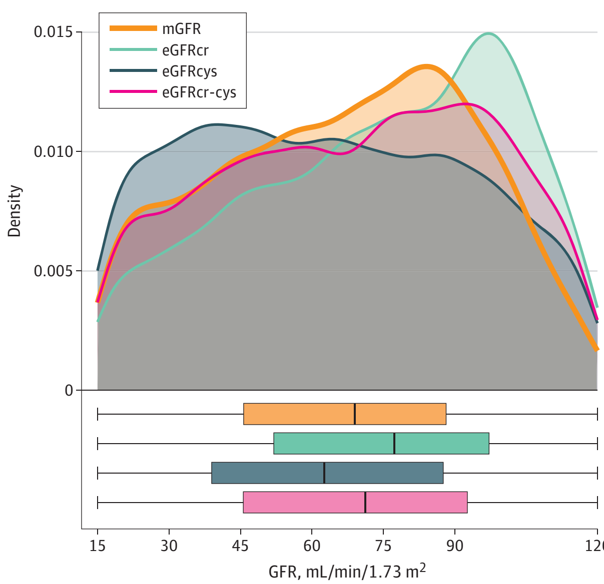
Results

Baseline Characteristics

Of 6174 individuals undergoing GFR measurement with concurrent creatinine and cystatin C testing, 4789 (78%) had these measurements on the same day (eFigure 2 in Supplement 1). Median age was 59 years (IQR, 43-69 years); 3686 (60%) were male and 2488 (40%) were female. Race was not recorded. Median mGFR was 66 mL/min/1.73 m^2 (IQR, 43-88 mL/min/1.73 m^2), and 2553 individuals (41%) had an mGFR less than 60 mL/min/1.73 m^2 (Table 1). The most common comorbid conditions were hypertension (2765 [45%]), cancer (1998 [32%]), diabetes (1244 [20%]), and heart failure (651 [11%]). Of the 2 variables with incomplete data, urine albumin to creatinine ratio was missing for 1325 patients (21%) and body mass index for 1708 patients (28%), resulting in complete data for 3467 patients (56%) in the cohort (Table 1; eTable 2 in Supplement 1). Baseline characteristics stratified by eGFRcr, eGFRcys, and eGFRcr-cys are shown in eTables 3 through 5 in Supplement 1.

Compared with the median mGFR of 68 mL/min/1.73 m^2 (IQR, 43-88 mL/min/1.73 m^2), median (IQR) eGFRcr, eGFRcys, and eGFRcr-cys values were 78 (51-99), 61 (36-88), and 71 (43-94) mL/min/1.73 m^2, respectively (**Figure 1**). Correlations with mGFR were r = 0.93 for eGFRcr-cys, r = 0.90 for eGFRcys, and r = 0.87 for eGFRcr (eFigure 3 in Supplement 1).

Figure 1. Density Plot and Box and Whisker Plot of Glomerular Filtration Rate (GFR) Distribution



Density plots and box plots represent measured GFR (mGFR; orange), estimated GFR based on plasma creatinine (eGFRcr; green), eGFR based on cystatin C (eGFRcys; blue), and eGFR based on creatinine and cystatin C (eGFRcr-cys; pink). Box plot boxes indicate the IQR with the median; whiskers extend to the most extreme values within 1.5 × IQR.

Associations of GFR With Primary Outcomes

During a median follow-up of 5.9 years (IQR, 3.0-8.8 years), 1977 individuals died (32%) and 426 (6.9%) progressed to kidney failure with replacement therapy (**Table 2**). All-cause mortality rates increased from 22.4 per 1000 person-years [PY] at an mGFR of 90 mL/min/1.73 m^2 to 27.6, 32.5, 37.4, and 42.7 per 1000 PY for mGFR levels of 60, 45, 30, and 15 mL/min/1.73 m^2, respectively. Compared with an mGFR of 90 mL/min/1.73 m^2, adjusted HRs for all-cause mortality were 1.21 (95% CI, 1.14-1.28), 1.41 (95% CI, 1.30-1.52), 1.62 (95% CI, 1.49-1.76), and 1.85 (95% CI, 1.62-2.11) for mGFR levels of 60, 45, 30, and 15 mL/min/1.73 m^2, respectively (Table 2; **Figure 2**A). There was no statistically significant association of mGFR with mortality for mGFR values between 90 and 120 mL/min/1.73 m^2 compared with the reference of 90 mL/min/1.73 m^2 (HR for a GFR level of 120 mL/min/1.73 m^2, 1.08; 95% CI, 0.86-1.36) (Figure 2A). Among people with GFR values below 90 mL/min/1.73 m^2, eGFRcr-mortality associations significantly underestimated the mGFR-mortality associations, whereas eGFRcys-mortality associations significantly overestimated the mGFR-mortality associations. For instance, at 60 mL/min/1.73 m^2, the HR for the eGFRcr-mortality association was 13% lower than that for the mGFR-mortality association (ratio of HR, 0.87; 95% CI, 0.79-0.95), whereas the HR for the eGFRcys-mortality association was 17% higher (ratio of HR, 1.17; 95% CI, 1.08-1.27). For GFR values above 90 mL/min/1.73 m^2, the direction of deviation was reversed. At 120 mL/min/1.73 m^2, the HR for the eGFRcr-mortality association was 105% higher than that for the mGFR-mortality association (ratio of HR, 2.05; 95% CI, 1.58-2.68), whereas that for the eGFRcys-mortality association was 41% lower (ratio of HR, 0.59; 95% CI, 0.44-0.79). In contrast to eGFRcr and eGFRcys, eGFRcr-cys-mortality associations were not statistically significantly different from the mGFR-mortality association at any GFR value (**Table 3**; eFigure 4 in Supplement 1).

Rates of kidney failure with replacement therapy increased from 0.4 per 1000 PY at an mGFR of 90 mL/min/1.73 m^2 to 1.2, 3.6, 14.9, and 72.2 per 1000 PY for mGFR levels of 60, 45, 30, and 15 mL/min/1.73 m^2, respectively (Figure 2B). Compared with an mGFR of 90 mL/min/1.73 m^2, the HRs for kidney failure with replacement therapy were 2.85 (95% CI, 2.06-3.94), 8.77 (95% CI, 5.81-13.24), 38.5 (95% CI, 24.69-59.90), and 200.3 (95% CI, 129.1-310.9) for mGFR levels of 60, 45, 30, and 15 mL/min/1.73 m^2, respectively (Table 2). The HRs for each eGFR-kidney failure association did not significantly differ from those for mGFR across the GFR range (Table 3). For example, the ratio of HR at 60 mL/min/1.73 m^2 was 0.56 (95% CI, 0.00-1.17) for eGFRcr, 0.82 (95% CI, 0.00-10.12) for eGFRcr-cys, and 1.41 (95% CI, 0.00->100) for eGFRcys.

Associations of GFR With Secondary Outcomes

A total of 428 of 5786 individuals (7.4%) were hospitalized with acute kidney injury, 322 of 5523 (5.8%) were hospitalized for heart failure, and 388 of 5595 (6.9%) experienced a major adverse cardiovascular event. Rates of acute kidney injury increased from 6.1 to 21.2 per 1000 PYs as mGFR declined from 90 to 15 mL/min/1.73 m^2; rates of hospitalization for heart failure increased from 3.7 to 12.7 per 1000 PYs and rates of major adverse cardiovascular events increased from 11.8 to 25.9 per

Table 2. Adjusted Incidence Rates and Hazard Ratios for the Associations of mGFR and eGFR With Health Outcomes[a]

	GFR, mL/min/1.73 m^2						
	15	30	45	60	75	90	120
All-cause mortality							
No. at risk/ No. of events	1977/6174						
mGFR							
HR (95% CI)	1.85 (1.62-2.11)	1.62 (1.49-1.76)	1.41 (1.30-1.52)	1.21 (1.14-1.28)	1.05 (0.99-1.13)	1 [Reference]	1.08 (0.86-1.36)
IR, 1000 PY	42.69	37.41	32.45	27.60	23.79	22.38	24.19
eGFRcr							
HR (95% CI)	1.34 (1.15-1.56)	1.25 (1.13-1.37)	1.15 (1.07-1.24)	1.05 (0.98-1.14)	0.97 (0.91-1.03)	1 [Reference]	2.19 (1.84-2.61)
IR, 1000 PY	32.28	30.17	28.02	25.67	23.35	24.17	56.78
eGFRcys							
HR (95% CI)	2.71 (2.39-3.07)	2.11 (1.94-2.28)	1.68 (1.55-1.82)	1.42 (1.32-1.52)	1.22 (1.11-1.33)	1 [Reference]	0.63 (0.49-0.82)
IR, 1000 PY	54.68	41.74	32.92	27.32	22.99	18.72	11.46
eGFRcr-cys							
HR (95% CI)	1.92 (1.68-2.21)	1.67 (1.53-1.81)	1.44 (1.33-1.56)	1.26 (1.17-1.34)	1.11 (1.03-1.19)	1 [Reference]	0.86 (0.70-1.07)
IR, 1000 PY	44.90	38.68	33.37	28.87	25.19	22.42	18.75
Kidney failure with replacement therapy							
No. at risk/ No. of events	426/6174						
mGFR							
HR (95% CI)	200.31 (129.07-310.85)	38.45 (24.69-59.90)	8.77 (5.81-13.24)	2.85 (2.06-3.94)	1.41 (0.88-2.25)	1 [Reference]	0.88 (0.15-5.02)
IR, 1000 PY	72.21	14.87	3.58	1.19	0.58	0.41	0.35
eGFRcr							
HR (95% CI)	133.35 (89.55-198.57)	25.18 (17.27-36.70)	5.41 (3.70-7.93)	1.81 (1.31-2.52)	1.15 (0.82-1.60)	1 [Reference]	0.43 (0.16-1.14)
IR, 1000 PY	92.18	18.23	4.32	1.52	0.94	0.78	0.35
eGFRcys							
HR (95% CI)	286.15 (121.54-673.70)	47.09 (20.63-107.47)	11.46 (4.80-27.35)	5.82 (2.10-16.18)	3.38 (1.34-8.56)	1 [Reference]	0.02 (0.00-1.68)
IR, 1000 PY	69.84	11.27	2.90	1.53	0.89	0.27	0.01
eGFRcr-cys							
HR (95% CI)	204.17 (105.60-394.74)	32.19 (17.08-60.67)	6.60 (3.45-12.61)	2.67 (1.31-5.45)	1.89 (0.83-4.32)	1 [Reference]	0.05 (0.00-1.09)
IR, 1000 PY	89.88	14.52	3.23	1.37	0.95	0.50	0.03
Acute kidney injury							
No. at risk/ No. of events	428/5786						
mGFR							
HR (95% CI)	3.48 (2.62-4.62)	3.32 (2.73-4.02)	2.87 (2.39-3.44)	2.00 (1.76-2.28)	1.22 (1.06-1.41)	1 [Reference]	1.60 (1.00-2.56)
IR, 1000 PY	21.16	20.49	17.91	12.45	7.48	6.05	9.80
eGFRcr							
HR (95% CI)	2.25 (1.66-3.05)	2.18 (1.78-2.67)	2.03 (1.71-2.42)	1.74 (1.48-2.04)	1.31 (1.17-1.46)	1 [Reference]	1.39 (1.01-1.90)
IR, 1000 PY	18.13	17.76	16.71	14.28	10.63	8.15	11.60
eGFRcys							
HR (95% CI)	5.00 (3.81-6.55)	4.04 (3.34-4.88)	3.04 (2.53-3.65)	2.04 (1.77-2.36)	1.34 (1.10-1.64)	1 [Reference]	0.79 (0.45-1.38)
IR, 1000 PY	26.90	21.84	16.48	10.94	7.09	5.28	4.17
eGFRcr-cys							
HR (95% CI)	3.67 (2.75-4.89)	3.28 (2.69-3.99)	2.77 (2.31-3.32)	2.08 (1.78-2.42)	1.39 (1.20-1.62)	1 [Reference]	0.86 (0.54-1.37)
IR, 1000 PY	23.62	21.35	18.15	13.53	8.94	6.41	5.51

(continued)

Table 2. Adjusted Incidence Rates and Hazard Ratios for the Associations of mGFR and eGFR With Health Outcomes[a] (continued)

	GFR, mL/min/1.73 m^2						
	15	30	45	60	75	90	120
Hospitalization for heart failure							
No. at risk/ No. of events	322/5523						
mGFR							
HR (95% CI)	3.44 (2.48-4.75)	2.62 (2.05-3.34)	2.02 (1.59-2.56)	1.60 (1.31-1.94)	1.29 (1.03-1.62)	1 [Reference]	0.52 (0.20-1.37)
IR, 1000 PY	12.66	9.78	7.62	6.04	4.84	3.73	1.97
eGFRcr							
HR (95% CI)	1.93 (1.38-2.70)	1.67 (1.31-2.14)	1.44 (1.16-1.80)	1.25 (1.01-1.55)	1.10 (0.90-1.34)	1 [Reference]	1.06 (0.58-1.93)
IR, 1000 PY	8.55	7.40	6.42	5.59	4.90	4.45	4.61
eGFRcys							
HR (95% CI)	4.25 (3.08-5.85)	2.96 (2.32-3.76)	2.10 (1.66-2.66)	1.60 (1.29-1.98)	1.27 (0.96-1.70)	1 [Reference]	0.59 (0.25-1.41)
IR, 1000 PY	14.55	10.21	7.37	5.63	4.46	3.51	2.09
eGFRcr-cys							
HR (95% CI)	3.11 (2.25-4.31)	2.48 (1.95-3.16)	1.97 (1.56-2.48)	1.55 (1.26-1.90)	1.22 (0.98-1.53)	1 [Reference]	0.78 (0.38-1.60)
IR, 1000 PY	11.96	9.60	7.67	6.06	4.77	3.91	3.08
Major adverse cardiovascular events							
No. at risk/ No. of events	388/5595						
mGFR							
HR (95% CI)	2.18 (1.65-2.87)	1.68 (1.37-2.06)	1.33 (1.10-1.62)	1.13 (0.98-1.30)	1.03 (0.88-1.21)	1 [Reference]	1.03 (0.56-1.89)
IR, 1000 PY	25.90	20.04	15.93	13.42	12.20	11.83	12.30
eGFRcr							
HR (95% CI)	1.74 (1.29-2.34)	1.47 (1.19-1.81)	1.25 (1.03-1.51)	1.09 (0.92-1.31)	1.01 (0.87-1.16)	1 [Reference]	1.30 (0.85-1.99)
IR, 1000 PY	22.05	18.56	15.83	13.89	12.77	12.67	16.69
eGFRcys							
HR (95% CI)	2.53 (1.92-3.33)	1.77 (1.45-2.16)	1.32 (1.08-1.61)	1.15 (0.98-1.36)	1.10 (0.88-1.37)	1 [Reference]	0.69 (0.37-1.31)
IR, 1000 PY	29.23	20.29	15.29	13.36	12.66	11.49	7.99
eGFRcr-cys							
HR (95% CI)	2.18 (1.63-2.90)	1.68 (1.36-2.06)	1.33 (1.09-1.62)	1.14 (0.96-1.34)	1.06 (0.89-1.27)	1 [Reference]	0.78 (0.44-1.37)
IR, 1000 PY	26.77	20.55	16.34	14.01	13.04	12.24	9.59

Abbreviations: eGFRcr, estimated glomerular filtration rate based on creatinine; eGFRcr-cys, eGFR based on creatinine and cystatin C; eGFRcys, eGFR based on cystatin C; HR, hazard ratio; IR, incidence rate; mGFR, measured GFR; PY, person-years.

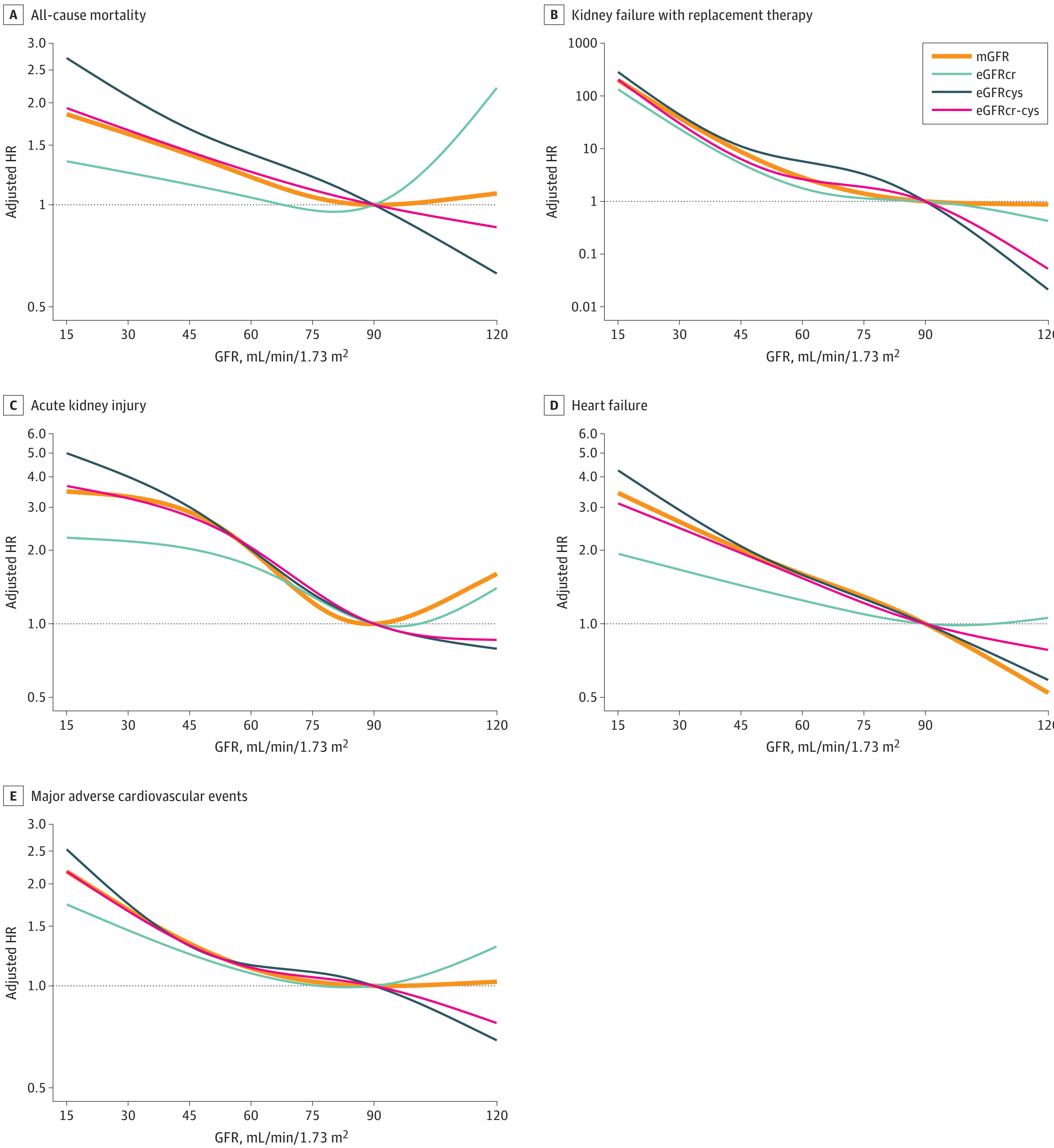
[a] Glomerular filtration rate was modeled as a continuous variable; column headers therefore present select point estimates rather than categorical ranges. Hazard ratios across the full GFR range are shown in Figure 2. Kidney failure with replacement therapy was defined as a composite of dialysis or kidney transplant. Acute kidney injury was defined as a hospitalization with acute kidney injury. Major adverse cardiovascular events were defined as a composite of cardiovascular death, hospitalization for ischemic stroke, or hospitalization for myocardial infarction. To demonstrate absolute rates of adverse outcomes, conditional incidence rates were estimated at typical covariate profiles, using the median for continuous variables and the mode for categorical variables.

1000 PYs, respectively. Correspondingly, hazard ratios of acute kidney injury, hospitalization for heart failure, and major adverse cardiovascular events were inversely associated with mGFR (Figure 2C-E). Hazard ratios for eGFR estimates did not significantly differ from those for mGFR, except for acute kidney injury and hospitalization for heart failure, for which eGFRcr underestimated the association at GFR values below 45 mL/min/1.73 m^2 (Table 3; eFigure 4 in Supplement 1). For example, the ratio of HR was 0.70 (95% CI, 0.53-0.89) for acute kidney injury and 0.71 (95% CI, 0.49-0.97) for hospitalization for heart failure at a GFR value of 45 mL/min/1.73 m^2.

Sensitivity Analyses

Hazard ratios for eGFRcr at GFR thresholds of 15, 30, 45, and 60 mL/min/1.73 m^2 compared with 90 mL/min/1.73 m^2 were comparable in the cohort of 6174 patients with mGFR to those of the cohort of all 1 584 287 individuals who underwent creatinine testing in Stockholm during 2011-2021 (eTable 6 and eFigure 5 in Supplement 1). For example, the HR for all-cause mortality at 15 mL/min/1.73 m^2 compared with the reference of 90 mL/min/1.73 m^2 was 1.70 (95% CI, 1.47-1.97; incidence rate, 41.6 vs 24.3 per 1000 PYs) in the mGFR cohort and 1.71 (95% CI, 1.67-1.75; incidence rate, 3.6 vs 2.1 per 1000 PYs) in

Figure 2. Line Graph Showing Association of Measured Glomerular Filtration Rate (mGFR) and Estimated GFR (eGFR) With the Primary and Secondary Outcomes



Adjusted hazard ratios (HRs) for all-cause mortality (A) and kidney failure with replacement therapy (B) according to mGFR (orange), estimated GFR based on plasma creatinine (eGFRcr; green), eGFR based on cystatin C (eGFRcys; blue), or eGFR based on creatinine and cystatin C (eGFRcr-cys; pink). Associations were modeled with Cox proportional hazards regression with restricted cubic splines with 4 knots, using a GFR reference value of 90 mL/min/1.73 m^2. Missing data for body mass index (calculated as weight in kilograms divided by height in meters squared) and log-transformed urine albumin to creatinine ratio were imputed with multiple imputation by chained equations. The dotted horizontal line represents an HR of 1.

the full cohort. However, HRs at 120 mL/min/1.73 m^2 compared with the reference of 90 mL/min/1.73 m^2 were 2.10 (95% CI, 1.76-2.50; incidence rate, 54.1 vs 24.3 per 1000 PYs) and 4.43 (95% CI, 4.34-4.52; incidence rate, 10.1 vs 2.1 per 1000 PYs), respectively. Associations between GFR and outcomes were consistent when alternative CKD-EPI or European Kidney Function Consortium equations were used (eTables 7 and 8 and eFigures 6 and 7 in Supplement 1), when urine albumin

Table 3. Ratio of Hazard Ratios for eGFRcr, eGFRcys, and eGFRcr-cys Compared With mGFR for Health Outcomes[a]

RHR (95% CI)	GFR, mL/min/1.73 m² 15	30	45	60	75	90	120
All-cause mortality							
eGFRcr/mGFR	0.72 (0.65-0.80)	0.76 (0.68-0.85)	0.82 (0.72-0.91)	0.87 (0.79-0.95)	0.91 (0.86-0.97)	1 [Reference]	2.05 (1.58-2.68)
eGFRcr-cys/mGFR	1.04 (0.96-1.12)	1.02 (0.94-1.10)	1.02 (0.93-1.11)	1.03 (0.96-1.10)	1.05 (1.00-1.09)	1 [Reference]	0.79 (0.62-1.03)
eGFRcys/mGFR	1.45 (1.32-1.61)	1.29 (1.16-1.43)	1.19 (1.07-1.32)	1.17 (1.08-1.27)	1.15 (1.08-1.22)	1 [Reference]	0.59 (0.44-0.79)
Kidney failure with replacement therapy							
eGFRcr/mGFR	0.58 (0.00-1.23)	0.54 (0.00-1.30)	0.50 (0.00-1.27)	0.56 (0.00-1.17)	0.76 (0.00-1.21)	1 [Reference]	0.57 (0.20->100)
eGFRcr-cys/mGFR	0.89 (0.00-7.60)	0.72 (0.00-5.95)	0.65 (0.00-5.56)	0.82 (0.00-10.12)	1.21 (0.00-13.05)	1 [Reference]	0.11 (0.00->100)
eGFRcys/mGFR	1.04 (0.00->100)	0.91 (0.00->100)	0.96 (0.00->100)	1.41 (0.00->100)	1.76 (0.00->100)	1 [Reference]	0.07 (0.00->100)
Acute kidney injury							
eGFRcr/mGFR	0.64 (0.51-0.81)	0.65 (0.50-0.82)	0.70 (0.53-0.89)	0.86 (0.68-1.05)	1.06 (0.91-1.20)	1 [Reference]	0.88 (0.54-1.57)
eGFRcr-cys/mGFR	1.05 (0.89-1.24)	0.98 (0.82-1.17)	0.96 (0.79-1.16)	1.02 (0.88-1.19)	1.13 (1.02-1.22)	1 [Reference]	0.55 (0.30-0.98)
eGFRcys/mGFR	1.43 (1.16-1.83)	1.22 (0.95-1.57)	1.06 (0.80-1.37)	1.01 (0.83-1.21)	1.09 (0.95-1.24)	1 [Reference]	0.49 (0.25-1.05)
Hospitalization for heart failure							
eGFRcr/mGFR	0.56 (0.40-0.73)	0.64 (0.45-0.86)	0.71 (0.49-0.97)	0.77 (0.56-1.03)	0.84 (0.65-1.03)	1 [Reference]	2.07 (0.93-5.55)
eGFRcr-cys/mGFR	0.90 (0.71-1.12)	0.95 (0.74-1.19)	0.97 (0.75-1.25)	0.96 (0.78-1.18)	0.94 (0.79-1.06)	1 [Reference]	1.54 (0.63-3.96)
eGFRcys/mGFR	1.23 (0.96-1.59)	1.11 (0.85-1.47)	1.03 (0.79-1.40)	0.99 (0.80-1.26)	0.97 (0.82-1.19)	1 [Reference]	1.17 (0.48-3.17)
Major adverse cardiovascular events							
eGFRcr/mGFR	0.79 (0.62-1.03)	0.87 (0.66-1.17)	0.92 (0.69-1.28)	0.96 (0.75-1.26)	0.97 (0.82-1.12)	1 [Reference]	1.31 (0.62-2.98)
eGFRcr-cys/mGFR	1.00 (0.81-1.22)	1.00 (0.79-1.25)	1.00 (0.76-1.28)	1.01 (0.82-1.23)	1.02 (0.92-1.15)	1 [Reference]	0.78 (0.41-1.52)
eGFRcys/mGFR	1.17 (0.89-1.50)	1.05 (0.78-1.41)	1.00 (0.74-1.38)	1.03 (0.81-1.33)	1.07 (0.95-1.21)	1 [Reference]	0.70 (0.39-1.19)

Abbreviations: eGFRcr, estimated glomerular filtration rate based on creatinine; eGFRcr-cys, eGFRcr and cystatin C; eGFRcys, eGFR based on cystatin C; mGFR, measured GFR; RHR, ratio of hazard ratios.

[a] Glomerular filtration rate was modeled as a continuous variable; column headers therefore present select point estimates rather than categorical ranges. Ratios of HRs across the full GFR range are shown in eFigure 4 in Supplement 1. Kidney failure with replacement therapy was defined as a composite of dialysis or kidney transplant. Acute kidney injury was defined as a hospitalization with acute kidney injury. Major adverse cardiovascular events were defined as a composite of cardiovascular death, hospitalization for ischemic stroke, or hospitalization for myocardial infarction.

to creatinine ratio results did not include converted protein to creatinine ratio and dipstick results (eTable 9 and eFigure 8 in Supplement 1), and after exclusion of kidney transplant recipients (eTable 10 and eFigure 9 in Supplement 1). Results were similar for acute kidney injury and major adverse cardiovascular events when individuals with a history of the outcome were included (eTable 11 and eFigure 10 in Supplement 1). However, for hospitalization for heart failure, HRs for eGFRcr-cys and eGFRcys were smaller when individuals with a history of heart failure were included than when excluded. For instance, at 15 mL/min/1.73 m², the HR for eGFRcys was 2.96 (95% CI, 2.39-3.66) vs 4.25 (95% CI, 3.08-5.85), respectively.

Discussion

Among 6174 adults from Sweden who underwent mGFR testing, lower mGFR values were associated with progressively higher rates of mortality, kidney failure with replacement therapy, acute kidney injury, hospitalization for heart failure, and major adverse cardiovascular events. The associations between eGFRcr-cys and all-cause mortality did not significantly differ from those for mGFR, whereas eGFRcr underestimated and eGFRcys overestimated risk associations. Hazard ratios for the outcomes of kidney failure with replacement therapy, acute kidney injury, hospitalization for heart failure, and major adverse cardiovascular events were not statistically significantly different between mGFR and any of the eGFR equations.

These findings support the current GFR thresholds by showing that, compared with an mGFR of 90 mL/min/1.73 m², adverse outcomes were increased at mGFR levels of 60 mL/min/1.73 m² and rose progressively at lower levels of 45, 30, and 15 mL/min/1.73 m². Adverse outcomes were not consistently increased for mGFR values of 75 mL/min/1.73 m².

In this study, mortality risks associated with mGFR were underestimated by eGFRcr and overestimated by eGFRcys.

Lower serum creatinine level due to reduced muscle mass raises eGFRcr and is associated with poor health status, possibly contributing to the underestimation of mortality risks for eGFRcr thresholds less than 90 mL/min/1.73 m^2.[11] In contrast, inflammation, obesity, smoking, and corticosteroid medications increase serum cystatin C level and lower eGFRcys, which may contribute to the overestimation of risk for GFR thresholds less than 90 mL/min/1.73 m^2.[9,10,34,35] Combining creatinine and cystatin C in eGFRcr-cys may offset measurement error by the factors that affect eGFRcr and eGFRcys, which may explain its greater accuracy in approximating mGFR in prior studies[16,29,30,32,33] and its greater consistency with mGFR-related risk relationships in this study compared with eGFRcr and eGFRcys. Hazard ratios for the outcomes of kidney failure with replacement therapy, acute kidney injury, hospitalization for heart failure, and major adverse cardiovascular events were not statistically significantly different between mGFR and any of the eGFR associations. However, wide CIs suggest limited statistical power, and further studies are warranted to evaluate these relationships.

The findings in this study are consistent with those of prior studies showing increased rates of mortality for lower compared with higher mGFR. These prior studies had small sample sizes and focused on specific subpopulations, such as kidney transplant recipients,[36] individuals with moderate to advanced CKD,[37,38] or those with GFR greater than 60 mL/min/1.73 m^2.[39]

Limitations

This study has several limitations. First, mGFR assessment has limitations. Results of mGFR may differ, depending on the filtration markers used to measure GFR (eg, iohexol, iothalamate, inulin) and methods used to measure clearance (plasma or urinary). Measured GFR may be associated with test-retest variability and potential imprecision.[20,40] Second, included patients had mGFR obtained at the discretion of treating specialists and results may not be generalizable to people who did not undergo mGFR testing.[10,16] Third, data represent Stockholm's health care, and information on race was not available because it cannot be recorded in Sweden. Therefore, results reported here may not be generalizable to other regions or ethnic groups. Fourth, this study did not have adequate statistical power to evaluate mGFR-related risks across categories of albuminuria. Fifth, patients with a history of each outcome were excluded from analyses for the corresponding outcome measure. Sensitivity analyses showed consistent results for acute kidney injury and major adverse cardiovascular events, but results for hospitalization for heart failure may not be generalizable to individuals with a history of this condition.

Conclusions

Among adults in Sweden, lower mGFR values were associated with higher rates of all-cause mortality, kidney failure with replacement therapy, hospitalization for heart failure, acute kidney injury, and major adverse cardiovascular events. Associations of mGFR with mortality were most closely represented by the association of eGFRcr-cys with mortality, whereas eGFRcr underestimated risk of mortality and eGFRcys overestimated it.

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