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ORIGINAL RESEARCH

# Differential Associations of Cystatin C Versus Creatinine-Based Kidney Function With Risks of Cardiovascular Event and Mortality Among South Asian Individuals in the UK Biobank

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**BACKGROUND:** South Asian individuals have increased cardiovascular disease and mortality risks. Reliance on creatinine- rather than cystatin C–based estimated glomerular filtration rate (eGFR<sub>cys</sub>) may underestimate the cardiovascular disease risk associated with chronic kidney disease.

**METHODS AND RESULTS:** Among 7738 South Asian UK BioBank participants without prevalent heart failure (HF) or atherosclerotic cardiovascular disease, we investigated associations of 4 eGFR<sub>cys</sub> and creatinine-based estimated glomerular filtration rate categories (<45, 45–59, 60–89, and ≥90 mL/min per 1.73 m<sup>2</sup>) with risks of all-cause mortality, incident HF, and incident atherosclerotic cardiovascular disease. The mean age was 53±8 years; 4085 (53%) were women. Compared with creatinine, cystatin C identified triple the number of participants with estimated glomerular filtration <45 (n=35 versus n=113) and 6 times the number with estimated glomerular filtration 45 to 59 (n=80 versus n=481). After multivariable adjustment, the eGFR<sub>cys</sub> 45 to 59 category was associated with higher risks of mortality (hazard ratio [HR], 2.38 [95% CI, 1.55–3.65]) and incident HF (sub-HR [sHR], 1.87 [95% CI, 1.09–3.22]) versus the eGFR<sub>cys</sub> ≥90 category; the creatinine-based estimated glomerular filtration rate 45 to 59 category had no significant associations with outcomes. Of the 7623 participants with creatinine-based estimated glomerular filtration rate ≥60, 498 (6.5%) were reclassified into eGFR<sub>cys</sub> <60 categories. Participants who were reclassified as having eGFR<sub>cys</sub> <45 had higher risks of mortality (HR, 4.88 [95% CI, 2.56–9.31]), incident HF (sHR, 4.96 [95% CI, 2.21–11.16]), and incident atherosclerotic cardiovascular disease (sHR, 2.29 [95% CI, 1.14–4.61]) versus those with eGFR<sub>cys</sub> ≥90; those reclassified as having eGFR<sub>cys</sub> 45 to 59 had double the mortality risk (HR, 2.25 [95% CI, 1.45–3.51]).

**CONCLUSIONS:** Among South Asian individuals, cystatin C identified a high-risk chronic kidney disease population that was not detected by creatinine and enhanced estimated glomerular filtration rate–based risk stratification for mortality, incident HF, and incident atherosclerotic cardiovascular disease.

**Key Words:** cardiovascular risk ■ chronic kidney disease ■ creatinine ■ cystatin C ■ estimated glomerular filtration rate ■ South Asian

Individuals of South Asian ancestry account for nearly a quarter of the world's population.<sup>1</sup> Many South Asian people immigrated from their home countries, including Bangladesh, Bhutan, India, the Maldives, Nepal, Pakistan, and Sri Lanka to Europe and North America, where they have become one of the largest and

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## CLINICAL PERSPECTIVE

### What Is New?

- Among the South Asian population in the UK Biobank, cystatin C identified >5 times the number of participants with estimated glomerular filtration rate <60 mL/min per 1.73 m<sup>2</sup> compared with creatinine.
- Cystatin C identified a chronic kidney disease population at high risk for mortality, incident heart failure, and incident atherosclerotic cardiovascular disease that was not detected by creatinine.

### What Are the Clinical Implications?

- Among South Asian individuals, cystatin C–based estimated glomerular filtration rate improves risk prognostication for mortality, incident heart failure, and incident atherosclerotic cardiovascular disease compared with creatinine-based estimated glomerular filtration rate.

## Nonstandard Abbreviations and Acronyms

<b>eGFRcr</b>	creatinine-based estimated glomerular filtration rate
<b>eGFRcys</b>	cystatin C–based estimated glomerular filtration rate

fastest-growing ethnic groups.<sup>2,3</sup> Individuals of South Asian ancestry have an >2-fold risk of cardiovascular disease (CVD) events and mortality compared with individuals of other ethnic groups.<sup>4–8</sup> Reasons for these disparities are incompletely explained by the higher prevalence of conventional cardiovascular risk factors, such as type 2 diabetes, hypertension, and central adiposity, among the South Asian population.<sup>4,5,9,10</sup>

Chronic kidney disease (CKD) is associated with an increased risk of atherosclerotic CVD (ASCVD) events and heart failure (HF).<sup>11–13</sup> Estimated glomerular filtration rate (eGFR) thresholds that are used to define CKD stages are based on risk.<sup>14</sup> Multiple prior studies have shown that using cystatin C to calculate eGFR strengthens the associations between eGFR categories and risks of mortality and CVD events in both general and CKD populations.<sup>15–21</sup> However, none of these studies included a well-defined South Asian cohort. Because South Asian individuals are underrepresented in cohort studies and clinical trials, and are frequently aggregated with other racial and ethnic groups, limited epidemiologic data exist on kidney-based risk stratification and clinical outcomes that are specific to this high-risk population.

Comparing the prognostic strengths of cystatin C–based eGFR (eGFRcys) to creatinine-based eGFR (eGFRcr) among individuals of South Asian ancestry is an important area of investigation, because multiple factors that are unrelated to kidney function may affect creatinine levels more than cystatin C levels in this population. Individuals of South Asian ancestry have on average lower physical activity, muscle mass, and dietary protein intake than individuals of European ancestry, which may lead to overestimation of kidney function by creatinine and corresponding underestimation of risk for adverse outcomes.<sup>22–24</sup> For the 1.8 million South Asian individuals globally,<sup>1</sup> this may result in a substantial number of missed opportunities for prevention of CVD events. Furthermore, unlike creatinine, cystatin C is unaffected by race or genetic ancestry,<sup>25</sup> which is one of the reasons for the recent recommendation from the National Kidney Foundation and American Society of Nephrology to increase the use of cystatin C to estimate kidney function.<sup>26</sup>

The objectives of this study were to (1) determine whether among a South Asian population, use of eGFRcys strengthens the relationships between eGFR categories and adjusted risks of mortality, incident HF, and incident ASCVD compared with the use of eGFRcr; and (2) investigate whether using cystatin C to estimate glomerular filtration rate can identify individuals with high-risk CKD that is not detected by creatinine.

## METHODS

The data that support the findings of this study are available from the UK Biobank and can be requested at <https://www.ukbiobank.ac.uk/enable-your-research/register>.

### Study Design and Population

The UK Biobank is a prospective cohort study of 502 460 adults aged 40 to 69 years enrolled between 2006 and 2010 from 22 assessment centers across the United Kingdom.<sup>27</sup> At the baseline study visit, participants underwent nurse-led interviews and completed detailed questionnaires about medical history, medication use, sociodemographic factors, and lifestyle. Participants underwent a range of physical assessments and provided blood and urine at the baseline visit. The UK Biobank study was approved by the North West Multi-Centre Research Ethics Committee, and all participants provided written informed consent.

Among the UK Biobank cohort, 8935 participants self-reported South Asian ancestry, defined as Indian, Pakistani, or Bangladeshi ethnicity or country of birth in Nepal or Sri Lanka. After excluding 718 participants who did not have both serum cystatin C and creatinine measurements at baseline and 479 participants

with history of ASCVD or HF, our final analytic cohort included 7738 participants of South Asian ancestry. Exclusion of prevalent ASCVD or HF at enrollment was based on self-report or linked hospital admission records confirming a diagnosis of myocardial infarction, ischemic stroke, or HF before the baseline assessment date. *International Classification of Diseases, Ninth Revision and Tenth Revision (ICD-9 and ICD-10)* codes used for exclusion criteria are listed in Data S1.

This research was conducted under UK Biobank application number 69891 and approved by the University of California, San Francisco institutional review board. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline and adhered to the Declaration of Helsinki.

## Predictors

Our predictors of interest were eGFR<sub>cys</sub> and eGFR<sub>cr</sub>. Serum cystatin C and creatinine levels were measured at baseline; eGFR<sub>cys</sub> was calculated using the 2012 CKD Epidemiology Collaboration equation, and eGFR<sub>cr</sub> was calculated using the 2021 CKD Epidemiology Collaboration race-free equation.<sup>28,29</sup> Serum cystatin C levels were measured using a latex-enhanced immunoturbidimetric assay by Siemens (Erlangen, Germany) on the Siemens Advia 1800, with an interassay coefficient of variation of 1.1%.<sup>30</sup> Serum creatinine levels were measured using an enzyme-based assay by Beckman Coulter (High Wycombe, United Kingdom) on the Beckman Coulter AU5800, with a coefficient of variation of 2.0%.<sup>31</sup> Details pertaining to biomarker sampling, handling, and quality control have been previously described.<sup>31,32</sup>

## Outcomes

The primary outcome of interest was all-cause mortality. Secondary outcomes included incident HF, defined as first diagnosis of HF, and incident ASCVD, defined as first diagnosis of myocardial infarction or ischemic stroke. Outcomes were ascertained between January 1, 2006 and August 31, 2021 using *ICD-9* and *ICD-10* codes from linked hospital admissions data and the death registry (Data S1). Participants were not censored after experiencing 1 of our secondary outcomes. At recruitment, all participants were registered with a general practitioner in the National Health Service and consented to linkage of their hospital inpatient records and national death registries. All ischemic stroke events were centrally validated by UK Biobank study staff.

## Covariates

Covariates that may confound the association of kidney function with risks of mortality or CVD events

were obtained at the baseline study visit. Age, sex, ethnicity, country of origin, smoking history, and medication use were self-reported. At the baseline visit, waist circumference, weight, and height were measured, and blood and urine were collected according to study protocol.<sup>33</sup> Two sets of systolic and diastolic blood pressure measurements were obtained using an Omron 705 IT electronic blood pressure monitor and standardized technique; the average of the 2 measurements was recorded as the baseline blood pressure.<sup>34</sup> History of type 2 diabetes was determined by self-report of prior diagnosis, use of medications for diabetes, hemoglobin A1c  $\geq 6.5\%$  at enrollment, or *ICD-9* and *ICD-10* codes indicating type 2 diabetes diagnosis before baseline assessment. History of hypertension was determined from self-report of prior diagnosis, use of medications for blood pressure, average systolic blood pressure  $\geq 140$  mmHg, average diastolic blood pressure  $\geq 90$  mmHg, or *ICD-9* and *ICD-10* codes indicating hypertension diagnosis before baseline assessment. Family history of ASCVD referred to heart disease or stroke in a biological parent or sibling. The Townsend Deprivation Index score is a measure of material deprivation within a population and is a composite measure of unemployment, lack of car or home ownership, and household overcrowding.<sup>35</sup> Presence of chronic inflammatory diseases was defined as a clinical diagnosis of rheumatoid arthritis, systemic lupus erythematosus, or HIV infection by self-report or *ICD-9* and *ICD-10* codes. Thyroid disease included hypothyroidism or hyperthyroidism diagnoses by self-report or *ICD-9* and *ICD-10* codes.

## Statistical Analysis

We evaluated the distributions of eGFR<sub>cys</sub> and eGFR<sub>cr</sub> and categorized eGFR into 4 categories, with cut points that represent thresholds for CKD stages<sup>14</sup>:  $<45$ , 45 to 59, 60 to 89, and  $\geq 90$  mL/min per 1.73 m<sup>2</sup>. We summarized baseline characteristics overall and stratified by eGFR<sub>cys</sub> category. Differences across baseline eGFR<sub>cys</sub> categories were compared using  $\chi^2$ , analysis of variance, and Kruskal-Wallis tests. Hereinafter, units of eGFR categories will be assumed to be milliliters per minute per 1.73 m<sup>2</sup>.

We constructed Cox proportional hazard models to estimate associations of each eGFR measure with all-cause mortality. All models were adjusted for demographic variables, including age at study enrollment, sex, and ethnicity. Multivariable adjusted models additionally included Townsend Deprivation Index at recruitment; type 2 diabetes; hypertension; systolic blood pressure; tobacco smoking; family history of ASCVD; urine albumin-to-creatinine ratio; body mass index; waist circumference; low-density lipoprotein; high-density lipoprotein; hemoglobin A1c; lipoprotein

(a); and use of aspirin, statin, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, or  $\beta$ -blocker. Because traditional cardiovascular risk factors inadequately predict risk of CVD events and mortality among South Asian individuals,<sup>4</sup> we included additional measures of adiposity and metabolism as covariates.<sup>9,36,37</sup> Urine albumin-to-creatinine ratio, lipoprotein (a), and hemoglobin A1c were log-transformed to correct right-skewed distributions. To investigate the associations of each eGFR measure with incident HF and incident ASCVD event, we adjusted for these same covariates in Fine-Gray proportional subhazard models, accounting for death as a competing risk. Next, we limited the cohort to individuals without CKD by creatinine, defined as those with eGFRcr  $\geq 60$  mL/min per 1.73m<sup>2</sup>, and modeled associations of eGFR-cys categories with risk of our 3 clinical outcomes.

We conducted additional analyses to further explore the associations between each eGFR measure and clinical outcomes. Because thyroid disease, steroid use, and inflammation have been reported as non-glomerular filtration rate determinants of cystatin C levels,<sup>38–40</sup> we repeated our multivariable analyses after adding thyroid disease, steroid use, C-reactive protein, and history of chronic inflammatory illnesses to our multivariable models. Given the recent National Kidney Foundation and American Society of Nephrology Task Force recommendations to adopt the combined eGFRcr-cys equations to estimate kidney function,<sup>26</sup> we estimated the risks of mortality, incident HF, and incident ASCVD associated with each category of eGFRcr-cys by the 2021 Chronic Kidney Disease Epidemiology Collaboration race-free combined equation.<sup>29</sup> Next, we compared the associations of eGFRcys versus eGFRcr with clinical outcomes by including both eGFR values in the same multivariable-adjusted model.

Proportional hazard assumptions were assessed using Schoenfeld residuals. Multivariable imputation by chained equations, with 5 imputations, was used to impute missing covariates. All covariates had <5% missing data except for hemoglobin A1c (7%), high-density lipoprotein (9%), and lipoprotein (a) (12%). All tests were 2-tailed, with a statistical significance level of  $P < 0.05$ . Statistical analyses were performed using R, version 4.1.0 (R Foundation for Statistical Computing).

## RESULTS

In general, compared with the South Asian participants included in this study, the group of 671 excluded participants had a slightly higher proportion of women; the 2 groups were otherwise similar (Table S1). Among the included 7738 South Asian participants, mean age at enrollment was 53.1 years, 4085 (52.8%) were women,

and most individuals were Indian or Pakistani (Table 1). Mean (SD) of eGFRcys was 86 (18) mL/min per 1.73m<sup>2</sup>, and eGFRcr was 99 (14) mL/min per 1.73m<sup>2</sup>. Approximately 9% of participants had albuminuria. Participants with the lowest eGFRcys values were generally older and had higher prevalence of baseline comorbidities and medication use than participants with higher eGFRcys (Table 1). At baseline, 594 (7.7%) South Asian participants had an eGFRcys <60 mL/min per 1.73m<sup>2</sup> and 115 (1.0%) had eGFRcr <60 mL/min per 1.73m<sup>2</sup> (Figure 1). Compared with creatinine, cystatin C identified triple the number of participants in the eGFR <45 category (n=35 versus n=113), and 6 times the number of participants in the eGFR 45 to 59 category (n=80 versus n=481) (Table 2).

During a median follow-up time of 11.0 years (interquartile range, 10.5–11.7), 294 (3.8%) participants died, 226 (2.9%) developed incident HF, and 452 (5.8%) experienced an incident ASCVD event.

### Risk of All-Cause Mortality

In demographic adjusted models, the eGFR <45 and 45 to 59 categories by both creatinine and cystatin C were associated with higher risk of mortality compared with the eGFR  $\geq 90$  category. After additional multivariable adjustment, only the eGFRcr <45 group (n=35) had a statistically significant elevated risk of mortality compared with the eGFRcr  $\geq 90$  (Table 2), whereas the eGFRcys <45 and 45 to 59 groups had 5.2-fold and 2.4-fold risks for mortality, respectively, compared with participants with eGFRcys  $\geq 90$  (Table 2).

### Risk of Incident HF

After adjustment for demographics, eGFRcr <45 and 45 to 59 categories were associated with risk of incident HF compared with the eGFRcr  $\geq 90$  category. As was observed with the multivariable adjusted mortality models, the eGFRcr <45 category (n=35) was the only eGFRcr category that retained a statistically significant association with incident HF compared with the eGFRcr  $\geq 90$  category (Table 2). In contrast, eGFRcys categories maintained a graded association with risk of incident HF after multivariable adjustment (Table 2). Participants in the eGFRcys <45 and 45 to 59 categories had 5.7-fold and 1.9-fold risks of incident HF, respectively, compared with those in the eGFRcys  $\geq 90$  category. The eGFRcys 60 to 89 category was associated with a 52% higher risk of incident HF.

### Risk of Incident ASCVD Event

In demographic adjusted models, eGFRcr <45 and eGFRcys <45 and 45 to 59 groups were associated with risk of incident ASCVD compared with the corresponding eGFR  $\geq 90$  category. After multivariable

**Table 1. Baseline Characteristics by eGFRcys Category**

Characteristic	Category of eGFRcys, mL/min per 1.73m <sup>2</sup>				
	Overall	<45	45–59	60–89	≥90
	N=7738	N=113	N=481	N=3739	N=3405
Demographics					
Age, y, mean (SD)	53.1 (8.4)	60.8 (7.2)	61.4 (6.5)	55.8 (7.8)	48.7 (6.9)
Female sex, n (%)	4085 (52.8)	69 (61.1)	230 (47.8)	2048 (54.8)	1738 (51.0)
Country of origin					
India, n (%)	5188 (67.0)	85 (75.2)	364 (75.7)	2580 (69.0)	2159 (63.4)
Pakistan, n (%)	1548 (20.0)	11 (9.7)	82 (17.0)	730 (19.5)	725 (21.3)
Sri Lanka, n (%)	657 (8.5)	11 (9.7)	19 (4.0)	293 (7.8)	334 (9.8)
Bangladesh, n (%)	189 (2.4)	4 (3.5)	14 (2.9)	80 (2.1)	91 (2.7)
Nepal, n (%)	156 (2.0)	2 (1.8)	2 (0.4)	56 (1.5)	96 (2.8)
Townsend Deprivation Index score, median (IQR)	0.2 (–2.2 to 2.4)	0.1 (–2.2 to 1.9)	0.6 (–1.7 to 2.9)	0.2 (–2.2 to 2.4)	0.1 (–2.4 to 2.3)
Family history of ASCVD, n (%)	3827 (49.5)	49 (43.4)	242 (50.3)	1868 (50.0)	1668 (49.0)
Comorbidities					
Diabetes, n (%)	1461 (18.9)	58 (51.3)	136 (28.3)	739 (19.8)	528 (15.5)
Hypertension, n (%)	4004 (51.7)	102 (90.3)	360 (74.8)	2142 (57.3)	1400 (41.1)
Systolic blood pressure, mmHg, mean (SD)	135 (18)	141 (20)	143 (21)	137 (18)	131 (18)
Diastolic blood pressure, mmHg, mean (SD)	83 (10)	81 (10)	84 (11)	83 (10)	82 (10)
Thyroid disease, n (%)	558 (7.2)	14 (12.4)	54 (11.2)	300 (8.0)	190 (5.6)
Smoking, n (%)					
Never	6056 (78.6)	88 (77.9)	381 (79.2)	2889 (77.6)	2698 (79.7)
Previous	901 (11.7)	17 (15.0)	56 (11.6)	441 (11.8)	387 (11.4)
Current	664 (8.6)	4 (3.5)	38 (7.9)	352 (9.4)	270 (8.0)
Chronic inflammatory illness, n (%)	139 (1.8)	4 (3.5)	17 (3.5)	78 (2.1)	40 (1.2)
Body mass index, kg/m <sup>2</sup> , mean (SD)	27.2 (4.4)	30.1 (5.5)	29.3 (5.1)	27.6 (4.3)	26.3 (4.0)
Waist circumference, cm, mean (SD)	91.4 (11.7)	99.5 (12.9)	97.3 (12.0)	93.1 (11.4)	88.4 (11.2)
Medications, n (%)					
Statins	1577 (20.4)	60 (53.1)	154 (32.0)	833 (22.3)	530 (15.6)
ASA	1143 (14.8)	50 (44.2)	128 (26.6)	620 (16.6)	345 (10.1)
ACEI/ARB	1134 (14.7)	72 (63.7)	144 (29.9)	606 (16.2)	312 (9.2)
β-Blockers	392 (5.1)	25 (22.1)	56 (11.6)	223 (6.0)	88 (2.6)
Steroids	75 (1.0)	8 (7.1)	7 (1.5)	43 (1.2)	17 (0.5)
Laboratory values					
eGFRcr, mL/min per 1.73m <sup>2</sup> , mean (SD)	99 (14)	55 (22)	83 (14)	96 (11)	106 (9)
eGFRcys, mL/min per 1.73m <sup>2</sup> , mean (SD)	86 (18)	35 (10)	54 (4)	77 (8)	102 (8)
eGFRcr-cys, mL/min per 1.73m <sup>2</sup> , mean (SD)	96 (16)	43 (14)	68 (7)	89 (8)	109 (8)
UACR, n (%)					
<30mg/g	6749 (91.2)	47 (43.9)	364 (82.4)	3305 (92.0)	3033 (93.1)
30–300mg/g	565 (7.6)	34 (31.8)	64 (14.5)	259 (7.2)	208 (6.4)
>300mg/g	85 (1.1)	4 (3.5)	6 (1.2)	43 (1.2)	29 (0.9)

(Continued)

**Table 1. Continued**

Characteristic	Category of eGFRcys, mL/min per 1.73m <sup>2</sup>				
	Overall	<45	45–59	60–89	≥90
	N=7738	N=113	N=481	N=3739	N=3405
LDL cholesterol, mg/dL, mean (SD)	131 (32)	107 (29)	124 (32)	131 (32)	132 (32)
HDL cholesterol, mg/dL, mean (SD)	49 (12)	43 (12)	46 (11)	49 (12)	50 (13)
Lipoprotein (a), nmol/L, median (IQR)	32 (13 to 65)	31 (13 to 64)	33 (13 to 70)	33 (14 to 65)	29 (13 to 64)
Hemoglobin A1c, %, median (IQR)	5.6 (5.4 to 6.0)	6.1 (5.6 to 6.9)	5.9 (5.5 to 6.3)	5.7 (5.4 to 6.1)	5.5 (5.3 to 5.9)
C-reactive protein, mg/L, median (IQR)	1.6 (0.8 to 3.3)	2.6 (1.2 to 4.6)	2.7 (1.2 to 5.7)	1.8 (0.9 to 3.5)	1.3 (0.6 to 2.7)

Chronic inflammatory illness includes a prior diagnosis of systemic lupus erythematosus, rheumatoid arthritis, and human immunodeficiency virus. ACEI/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ASA, aspirin; ASCVD, atherosclerotic cardiovascular disease; eGFRcr, creatinine-based estimated glomerular filtration rate (using the 2021 CKD-EPI race-free equation); eGFRcr-cys, creatinine and cystatin C–based estimated glomerular filtration rate (using the 2021 Chronic Kidney Disease Epidemiology Collaboration race-free combined equation); eGFRcys, cystatin C–based estimated glomerular filtration rate (using the 2012 Chronic Kidney Disease Epidemiology Collaboration equation); HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; and UACR, urine albumin-to-creatinine ratio.

adjustment, participants with eGFR <45 by either cystatin C or creatinine had >2- to >3-fold the risk of incident ASCVD events compared with participants with eGFR ≥90 (Table 2). Higher eGFR categories were not significantly associated with ASCVD risk using either marker.

### CKD Reclassification

Among this South Asian cohort, eGFRcys was on average lower than eGFRcr by 13 mL/min per 1.73m<sup>2</sup> (SD of the difference was 14). Of the 7623 participants with eGFRcr ≥60, 498 (6.5%) had CKD diagnosed by eGFRcys (Table 3). When limiting the cohort to the 1487 participants with eGFRcr of 60 to 89, the prevalence of CKD by eGFRcys was 21%. Among participants with eGFRcr ≥60, 449 (5.8%) were reclassified by cystatin C into the eGFR 45 to 59 category and 49 (0.6%) were reclassified into the eGFR <45 category (Table 3). The 498 individuals who had eGFRcr ≥60 but eGFRcys <60 had higher unadjusted cumulative incidence of all 3 clinical outcomes compared with participants who had concordant eGFR values ≥60 (Figure 2). In multivariable adjusted models including only participants with eGFRcr, reclassification by cystatin C into the eGFR <45 category was associated with a nearly 5-fold risk of mortality and incident HF, and a >2-fold risk of incident ASCVD compared with participants with eGFRcys ≥90 (Table 3). Reclassification by cystatin C into the eGFR 45 to 59 group was associated with a 2.3-fold risk of mortality compared with the same reference (Table 3).

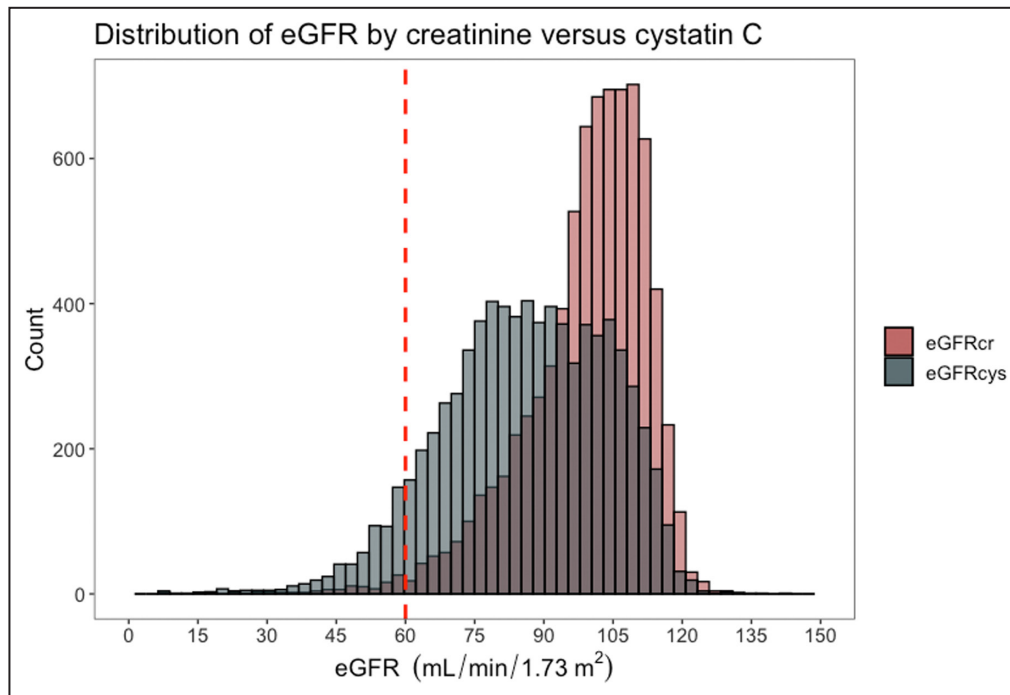
### Secondary and Sensitivity Analyses

Associations of eGFR categories with mortality, incident HF, and incident ASCVD were minimally changed

by additional adjustment for thyroid disease, steroid use, C-reactive protein, and chronic inflammatory illnesses (Table S2). Using the combined eGFRcr-cys equation to define eGFR categories led to similar estimates of associated risk of mortality, incident HF, and incident ASCVD as eGFRcys; however, the number of participants with eGFRcr-cys <60 was 179, only 30% of the proportion with CKD that were identified by cystatin C (Table S3). When both eGFRcys and eGFRcr were included in the same multivariable-adjusted model, only eGFRcys was associated with the 3 clinical outcomes (Table S4).

## DISCUSSION

In this population-based cohort study of 7738 individuals of South Asian ancestry, cystatin C strengthened the association between eGFR categories and risks of mortality, incident HF, and incident ASCVD. Cystatin C also identified a substantial portion of participants with high-risk CKD that was not detected by creatinine. Although current guidelines recommend adding cystatin C to confirm a diagnosis of CKD determined by routinely measured creatinine,<sup>14,26</sup> we found in this South Asian population that creatinine only captured 19% of the CKD population that was identified as having reduced kidney function by cystatin C. Participants who did not have CKD by creatinine but had eGFR <45 by cystatin C had a nearly 5-fold risk of mortality and incident HF, and a 2.3-fold risk of incident ASCVD compared with participants with eGFRcys ≥90; those who were reclassified into the eGFR 45 to 59 category by cystatin C had a >2-fold risk of mortality. Furthermore, when both eGFRcys and eGFRcr were included in the same multivariable-adjusted model, only eGFRcys



**Figure 1. Histogram of eGFRcr vs eGFRcys among South Asian participants in the UK Biobank (N=7738).**

eGFR indicates estimated glomerular filtration rate; eGFRcr, creatinine-based estimated glomerular filtration rate; and eGFRcys, cystatin C–based estimated glomerular filtration rate.

was associated with clinical outcomes. Individuals of South Asian ancestry carry a disproportionate burden of premature CVD and mortality compared with most other ethnicities.<sup>4–8</sup> Our study provides evidence that use of cystatin C enhances eGFR-based risk stratification among South Asian individuals, which may help alleviate the substantial health disparities affecting this population.

Differences in eGFRcys and eGFRcr values likely reflect confounding by factors that are unrelated to kidney function. Physical activity, muscle mass, and diet are known non–glomerular filtration rate factors that impact creatinine more than cystatin C levels; these variables vary widely across individuals from diverse ethnic backgrounds and are particularly relevant to the South Asian population.<sup>22–24</sup> Therefore, we hypothesized that cystatin C might better capture the risks from reduced kidney function compared with creatinine. Few prior studies have compared the prognostic values of cystatin C and creatinine among South Asian individuals. One study conducted in a community-based cohort in Canada and another in a UK-based CKD cohort confirmed that lower eGFRcr was associated with higher risk of mortality among South Asian participants, but they did not have data on eGFRcys.<sup>41,42</sup> Another study including 1104 South Asian participants recruited from primary care offices in London found that neither eGFRcr nor eGFRcys was associated with

all-cause mortality, CVD mortality, and incident CVD.<sup>43</sup> Although that study had a similar number of clinical events as our study, only 118 (11%) of their participants had eGFRcys  $\leq 60$  mL/min per 1.73 m<sup>2</sup>, and 40 (3%) had eGFRcr  $\leq 60$  mL/min per 1.73 m<sup>2</sup>. Thus, the investigators may have had insufficient power to detect associations of eGFR with clinical outcomes. In that same study, approximately one-third of individuals were discordantly classified by eGFRcr versus eGFRcys across all eGFR stages, and South Asian individuals were over twice as likely to be reclassified into lower eGFR stages by cystatin C compared with European individuals.<sup>43</sup> Our study adds evidence that South Asian participants who did not have CKD detected by creatinine but who were reclassified by cystatin C into eGFR  $< 60$  categories were at substantially higher risk of adverse clinical outcomes.

There is abundant medical literature from countries in South Asia, North America, and Europe demonstrating that South Asian individuals have higher CVD risk and a greater proportion of premature CVD deaths compared with other populations.<sup>44–50</sup> This disparity was initially attributed to a higher burden of risk factors such as diabetes, central adiposity, and hypertension among South Asian individuals<sup>44,51–53</sup>; however, more recent evidence has shown that these risk factors do not completely explain their disproportionate burden of CVD and mortality.<sup>4,5</sup> Furthermore, the American Heart



**Table 2. Association of eGFRcr and eGFRcys Categories With Risks of Mortality and CVD Events Among South Asian Participants in the UK Biobank (N=7738)**

Category	Subhazard and hazard ratios (95% CI) by eGFRcr category			
	<45	45–59	60–89	≥90
	N=35	N=80	N=1487	N=6136
All-cause mortality				
Demographic adjusted	10.34 (6.04–17.71), <i>P</i> <0.001	2.31 (1.24–4.29), <i>P</i> =0.008	1.12 (0.85–1.47), <i>P</i> =0.41	1.00
Fully adjusted	6.49 (3.62–11.64), <i>P</i> <0.001	1.49 (0.77–2.86), <i>P</i> =0.23	1.15 (0.87–1.52), <i>P</i> =0.33	1.00
Incident HF				
Demographic adjusted	9.83 (5.07–19.04), <i>P</i> <0.001	2.88 (1.49–5.58), <i>P</i> =0.002	1.05 (0.76–1.44), <i>P</i> =0.77	1.00
Fully adjusted	5.27 (2.53–10.95), <i>P</i> <0.001	1.82 (0.82–4.02), <i>P</i> =0.14	1.10 (0.79–1.53), <i>P</i> =0.57	1.00
ASCVD event				
Demographic adjusted	4.39 (2.32–8.32), <i>P</i> <0.001	1.65 (0.92–2.97), <i>P</i> =0.09	1.04 (0.83–1.30), <i>P</i> =0.74	1.00
Fully adjusted	2.92 (1.40–6.09), <i>P</i> =0.004	1.31 (0.70–2.48), <i>P</i> =0.40	1.09 (0.86–1.38), <i>P</i> =0.48	1.00
Category	Subhazard and hazard ratios (95% CI) by eGFRcys category			
	<45	45–59	60–89	≥90
	N=113	N=481	N=3739	N=3405
Mortality				
Demographic adjusted	7.90 (5.00–12.48), <i>P</i> <0.001	2.73 (1.82–4.11), <i>P</i> <0.001	1.22 (0.89–1.66), <i>P</i> =0.22	1.00
Fully adjusted	5.19 (3.13–8.59), <i>P</i> <0.001	2.38 (1.55–3.65), <i>P</i> <0.001	1.25 (0.91–1.73), <i>P</i> =0.17	1.00
Incident HF				
Demographic adjusted	11.42 (6.47–20.18), <i>P</i> <0.001	2.80 (1.67–4.70), <i>P</i> <0.001	1.70 (1.16–2.48), <i>P</i> =0.006	1.00
Fully adjusted	5.74 (3.07–10.71), <i>P</i> <0.001	1.87 (1.09–3.22), <i>P</i> =0.02	1.52 (1.03–2.24), <i>P</i> =0.04	1.00
ASCVD event				
Demographic adjusted	3.36 (2.10–5.36), <i>P</i> <0.001	1.74 (1.22–2.49), <i>P</i> =0.002	1.10 (0.88–1.38), <i>P</i> =0.42	1.00
Fully adjusted	2.31 (1.38–3.89), <i>P</i> =0.002	1.40 (0.96–2.03), <i>P</i> =0.08	1.06 (0.84–1.34), <i>P</i> =0.61	1.00

Demographic-adjusted models: age, sex, ethnicity/country of birth. Fully adjusted models: demographic-adjusted model + Townsend Deprivation Index at recruitment, type 2 diabetes, hypertension, systolic blood pressure, tobacco smoking, family history of ASCVD, urine albumin-to-creatinine ratio, body mass index, waist circumference, low-density lipoprotein, high-density lipoprotein, hemoglobin A1c, lipoprotein (a), and use of aspirin, statin, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, or  $\beta$ -blocker. Hazard ratios for mortality were obtained using Cox proportional hazard models. Subhazard ratios for incident HF and ASCVD event were obtained using Fine-Gray proportional subhazard regression, modeling mortality as a competing risk. ASCVD indicates atherosclerotic cardiovascular disease; CVD, cardiovascular events; eGFRcr, creatinine-based estimated glomerular filtration rate (using the 2021 Chronic Kidney Disease Epidemiology Collaboration race-free equation); eGFRcys, cystatin C–based estimated glomerular filtration rate (using the 2012 Chronic Kidney Disease Epidemiology Collaboration equation); and HF, heart failure.

Association/American College of Cardiology guidelines indicate that individuals of South Asian ancestry are a high-risk ethnic group for whom the pooled cohort equations<sup>54</sup> underestimate cardiovascular risk.<sup>55</sup> In Europe, the QRISK3 risk calculator<sup>56</sup> was developed to account for South Asian ancestry by using a multiplicative factor of 1.3 to 1.7 to predict CVD risk. Although the QRISK3 calculator includes CKD as a risk factor, it does not specify whether eGFRcr or eGFRcys should be used to diagnose CKD. Given the strong associations of kidney function with CVD morbidity and mortality,<sup>11,15,16</sup> cystatin C has advantages for providing kidney-based risk stratification among this high-risk South Asian population. In broad multiethnic populations, reductions of kidney function identified by cystatin C below an eGFR of 90 are associated with higher risks of mortality and CVD events, whereas this threshold is delayed until an eGFR of 60 to 70 by

creatinine.<sup>16,21</sup> Thus, use of cystatin C to detect early stages of kidney function decline may be particularly imperative among populations with high CVD risk, such as the South Asian population.

Our findings have important clinical implications. First, we provide evidence that among this South Asian population, eGFRcr fails to appropriately identify individuals at high-risk of complications associated with kidney disease, and that eGFRcys improves risk prognostication. Our results extend the findings of a previous study, which found that South Asian individuals at each eGFRcr milestone had significantly higher prevalence of hyperphosphatemia, hyperparathyroidism, and hypoalbuminemia compared with White individuals.<sup>57</sup> Given our findings, misclassification of CKD by creatinine may explain these observed differences in CKD-associated metabolic abnormalities. Second, although the National Kidney Foundation and American

**Table 3. Association of eGFR<sub>cys</sub> Categories With Risks of Mortality and CVD Events Among South Asian Participants in the UK Biobank Among Participants With eGFR<sub>cr</sub> ≥60 mL/min per 1.73 m<sup>2</sup> (N=7623)**

Category	Subhazard and hazard ratios (95% CI) by eGFR <sub>cys</sub> category			
	<45	45–59	60–89	≥90
	N=49	N=449	N=3724	N=3401
All-cause mortality				
Demographic adjusted	6.78 (3.68–12.50), <i>P</i> <0.001	2.58 (1.69–3.92), <i>P</i> <0.001	1.19 (0.86–1.63), <i>P</i> =0.29	1.00
Fully adjusted	4.88 (2.56–9.31), <i>P</i> <0.001	2.25 (1.45–3.51), <i>P</i> <0.001	1.22 (0.88–1.69), <i>P</i> =0.22	1.00
Incident HF				
Demographic adjusted	8.67 (3.97–18.93), <i>P</i> <0.001	2.46 (1.44–4.20), <i>P</i> =0.001	1.64 (1.12–2.40), <i>P</i> =0.01	1.00
Fully adjusted	4.96 (2.21–11.16), <i>P</i> <0.001	1.53 (0.87–2.69), <i>P</i> =0.14	1.45 (0.97–2.16), <i>P</i> =0.07	1.00
ASCVD event				
Demographic adjusted	2.92 (1.46–5.84), <i>P</i> =0.003	1.78 (1.23–2.56), <i>P</i> =0.002	1.09 (0.86–1.37), <i>P</i> =0.48	1.00
Fully adjusted	2.29 (1.14–4.61), <i>P</i> =0.02	1.40 (0.95–2.08), <i>P</i> =0.09	1.05 (0.83–1.32), <i>P</i> =0.70	1.00

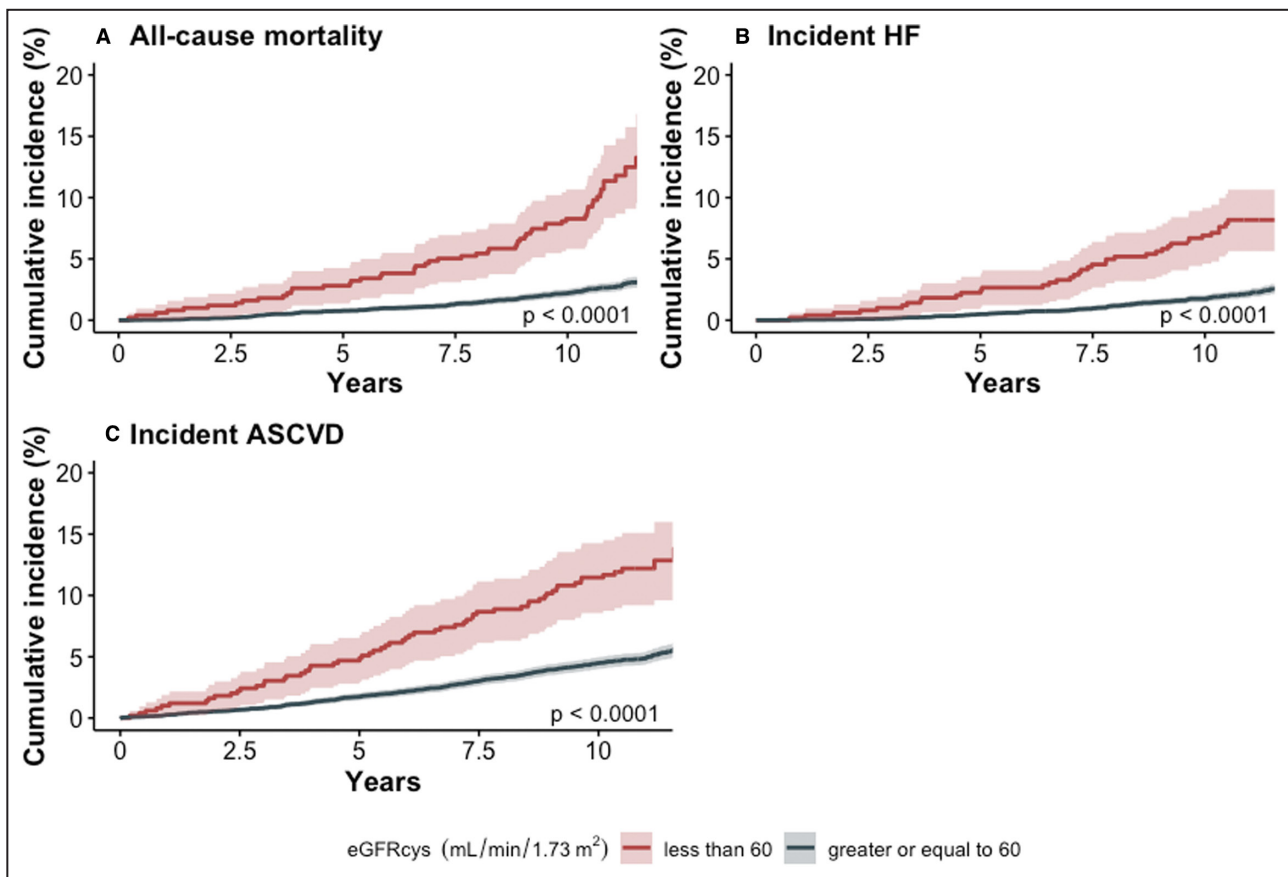
Demographic adjusted models: age, sex, ethnicity/country of birth. Fully adjusted models: demographic-adjusted model+Townsend Deprivation Index at recruitment, type 2 diabetes, hypertension, systolic blood pressure, tobacco smoking, family history of ASCVD, urine albumin-to-creatinine ratio, body mass index, waist circumference, low-density lipoprotein, high-density lipoprotein, hemoglobin A1c, lipoprotein (a), and use of aspirin, statin, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, or  $\beta$ -blocker. Hazard ratios for mortality were obtained using Cox proportional hazard models. Subhazard ratios for incident HF and ASCVD event were obtained using Fine-Gray proportional subhazard regression, modeling mortality as a competing risk. ASCVD indicates atherosclerotic cardiovascular disease; CVD, cardiovascular events; eGFR<sub>cr</sub>, creatinine-based estimated glomerular filtration rate (using the 2021 Chronic Kidney Disease Epidemiology Collaboration race-free equation); eGFR<sub>cys</sub>, cystatin C-based estimated glomerular filtration rate (using the 2012 Chronic Kidney Disease Epidemiology Collaboration equation); and HF, heart failure.

Society of Nephrology Task Force recently recommended use of the combined eGFR<sub>cr</sub>-cys equation to obtain the most accurate estimate of kidney function,<sup>26,29</sup> we provide evidence that this combined equation only identified 30% of the high-risk CKD population that were categorized as eGFR <60 by cystatin C. The combined eGFR<sub>cr</sub>-cys equation is thought to be most accurate because it averages the impact of non-glomerular filtration rate factors on creatinine and cystatin C. However, among South Asian populations, non-glomerular filtration rate factors that are known to impact creatinine levels, including physical activity, muscle mass, and vegetarianism, may be more relevant than in other populations. Although our study did not focus on assessing the performance of eGFR equations relative to measured glomerular filtration rate, we provide evidence that use of the combined eGFR<sub>cr</sub>-cys, which was developed among study cohorts with primarily Black and White participants, may not be the best eGFR equation for purposes of kidney-based risk stratification. Although non-glomerular filtration rate factors such as systemic inflammation, adiposity, thyroid disease, and steroid use have been reported to affect cystatin C levels,<sup>38–40</sup> the magnitude of these effects appeared relatively small, because additional adjustment for these factors in multivariable analyses did not impact our findings.<sup>20,58,59</sup> The non-glomerular filtration rate influences on creatinine appear to be larger in magnitude, given its weak associations with clinical outcomes in our study.

The strengths of this study include a large, well-phenotyped South Asian population with standardized

measurements of creatinine and cystatin C and outcomes that were linked with a national health registry. Our analyses included surrogate measures of adiposity, metabolism, and inflammation that have been previously shown to be associated with cardiovascular risk among South Asian individuals.<sup>9,56,60–62</sup> We investigated incident ASCVD in addition to incident HF events, which to our knowledge has not been previously studied in the context of cystatin C among the South Asian population. HF is an important clinical end point, because recent studies have forecasted a rapid increase in the prevalence of HF among South Asian populations in upcoming years.<sup>63</sup>

Our study also has several important limitations. First, because glomerular filtration rate was not measured, we cannot definitively conclude that cystatin C detects high-risk CKD earlier than creatinine. However, to our knowledge there are no diverse, population-based cohort studies that have measured glomerular filtration rate. Second, UK Biobank participants are in general healthier and have lower mortality rates than the general population, which may result in healthy-volunteer selection bias.<sup>64</sup> Analyses of prognosis are most heavily influenced by clinical outcomes, and confounding by non-glomerular filtration rate determinants of creatinine may particularly bias the eGFR among the subset of South Asian participants at highest risk for adverse outcomes. Therefore, we suspect that our findings could be stronger among a population with higher comorbidity burden. Third, few participants in this population-based cohort had eGFR <45, which explains the relatively wide confidence intervals for



**Figure 2.** Crude cumulative incidence curves of mortality (A), incident HF (B), and incident ASCVD (C) by eGFRcys category among South Asian participants in the UK Biobank with eGFRcr  $\geq 60$  mL/min per  $1.73 \text{ m}^2$ .

ASCVD indicates atherosclerotic cardiovascular disease; eGFRcr, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C–based estimated glomerular filtration rate; and HF, heart failure.

risk estimates in this lowest eGFR category. Fourth, this analysis defined CKD based on 1 baseline eGFR measurement, and relatively few participants had advanced CKD at baseline. This is a limitation, however, of most epidemiological studies that have defined the risk associations of eGFR. Fifth, this study relied on self-report, diagnosis codes from inpatient admissions, and national procedure and death registries to ascertain clinical outcomes. We separately ascertained all clinical outcomes based on *ICD-9* and *ICD-10* codes to capture additional clinical events that were not included through the UK Biobank algorithmically defined outcomes. Sixth, we adjusted for multiple potential confounders in our primary and sensitivity analyses, but cannot rule out residual confounding attributable to the observational study design. Last, our results do not generalize to South Asian individuals living outside of the United Kingdom. Furthermore, we acknowledge that heterogeneity in risk factors and health outcomes exist within the South Asian population, and these differences may not align with country borders.<sup>4,62,65,66</sup> Therefore, the relative influences of

non–glomerular filtration rate factors on creatinine and cystatin C may vary among South Asian individuals with diverse cultures, immigration patterns, diets, educational opportunities, and health care access. Future studies are needed to better delineate the impact of this heterogeneity on health outcomes in the South Asian population.

## CONCLUSIONS

In this prospective cohort study of South Asian individuals, use of cystatin C to calculate eGFR enhanced risk stratification for mortality, incident HF, and incident ASCVD. CKD detection using cystatin C affords an opportunity to apply cardiovascular prevention strategies aimed at improving health outcomes and reducing risk and health disparities among this vulnerable population.

## ARTICLE INFORMATION

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## Supplemental Material

Data S1

Tables S1–S4

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# **Supplemental Material**

## Data S1.

### Supplemental Methods

#### ICD Codes

Incident myocardial infarction and stroke were identified through UK Biobank algorithmically-defined events and supplemented with the selected ICD 9 and 10 codes above. Incident heart failure events were identified using ICD10 codes only as there was no UK Biobank algorithm for this outcome.

Diagnosis	ICD codes
Myocardial infarction	ICD9: 410, 410.0, 410.1, 410.2, 410.3, 410.4, 410.5, 410.6, 410.7, 410.8, 410.9, 411, 411.0, 411.1, 411.8 ICD10: I21,I21.0,I21.1,I21.2,I21.3,I21.4,I21.9, I21.A1, I21.A9, I22, I22.0, I22.1, I22.2, I22.8, I22.9, I23, I23.0, I23.1, I23.2, I23.3, I23.4, I23.5, I23.6, I23.8, I24, I24.0, I24.8, I24.9
Stroke	ICD9: 430.X, 431.X, 434.X, 434.0, 434.1, 434.9, 436.X ICD10: I60, I60.0, I60.1, I60.2, I60.3, I60.4, I60.5, I60.6, I60.7, I60.8, I60.9, I61, I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, I61.8, I61.9, G45, G45.0, G45.1, G45.2, G45.3, G45.4, G45.8, G45.9, G46.3, G46.4, I63, I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9, I63.X, I65, I65.0, I65.1, I65.2, I65.8, I65.9, I66, I66.0, I66.1, I66.2, I66.3, I66.8, I66.9
Heart failure	ICD10: I11.0,I13.0,I13.2,I25.5,I42.0,I42.1,I42.2,I42.5,I42.8,I42.9,I50,I50.0,I50.1,I50.2, I50.3, I50.4, I50.8, I50.9
Hypertension	ICD 9: 4010, 4011, 4019, 4039 ICD 10: I10, I15, I15.0, I15.1, I15.2, I15.8, I15.9
Type 2 diabetes mellitus	ICD 9: 2500, 25000, 25001, 25009, 25011, 25019, 2503, 2504, 2505, 25099 ICD 10: E11, E11.0, E11.1, E11.2, E11.3, E11.4, E11.5, E11.6, E11.8, E11.9 E13, E13.1, E13.2, E13.3, E13.4, E13.5, E13.6, E13.8, E13.9
Systemic lupus erythematosus	ICD 9: 6954, 7100 ICD 10: M32, M32.0, M32.1, M32.8, M32.9
Rheumatoid arthritis	ICD9: 7140, 7141, 7142, 7143, 7144, 7148, 7149 ICD 10: M05, M05.0, M05.1, M05.2, M05.3, M05.4, M05.5, M05.6, M05.7, M05.8, M05.9, M06, M06.0, M06.1, M06.2, M06.3, M06.4, M06.8, M06.9
Human immunodeficiency virus	ICD 10: B20.0, B20.1, B20.2, B20.3, B20.4, B20.6, B20.7, B20.8, Z21
Thyroid disease	ICD9: 2449, 24499, 2420, 2422, 2423, 2428, 2429 ICD10: E03.9, E05, E05.0, E05.1, E05.2, E05.3, E05.4, E05.5, E05.8, E05.9



**Table S1.** Associations of eGFRcr or eGFRcys with risks of mortality and CVD events, adding adjustment for thyroid disease, steroid use, C-reactive protein, or chronic inflammatory illness (N = 7,738)

	Subhazards and Hazard ratios (95% CI) by eGFRcr category			
	<45 N = 35	45-59 N = 80	60-89 N = 1,487	≥ 90 N = 6,136
<b>All-cause mortality</b>				
Fully-adjusted	6.49 (3.62, 11.64), p<0.001	1.49 (0.77, 2.86), p=0.23	1.15 (0.87, 1.52), p=0.33	1.00
Exploratory	6.23 (3.46, 11.22), p<0.001	1.49 (0.78, 2.86), p=0.23	1.12 (0.85, 1.49), p=0.42	1.00
<b>Incident HF</b>				
Fully-adjusted	5.27 (2.53, 10.95), p<0.001	1.82 (0.82, 4.02), p=0.14	1.10 (0.79, 1.53), p=0.57	1.00
Exploratory	5.10 (2.45, 10.62), p<0.001	1.84 (0.83, 4.08), p=0.13	1.09 (0.79, 1.51), p=0.60	1.00
<b>ASCVD event</b>				
Fully-adjusted	2.92 (1.40, 6.09), p=0.004	1.31 (0.70, 2.48), p=0.40	1.09 (0.86, 1.38), p=0.48	1.00
Exploratory	2.72 (1.33, 5.57), p=0.006	1.31 (0.70, 2.45), p=0.40	1.08 (0.85, 1.37), p=0.54	1.00
	Subhazards and Hazard ratios (95% CI) by eGFRcys category			
	<45 N = 113	45-59 N = 481	60-89 N = 3,739	≥ 90 N = 3,405
<b>All-cause mortality</b>				
Fully-adjusted	5.19 (3.13, 8.59), p<0.001	2.38 (1.55, 3.65), p<0.001	1.25 (0.91, 1.73), p=0.17	1.00
Exploratory	4.70 (2.83, 7.79), p<0.001	2.16 (1.40, 3.33), p<0.001	1.20 (0.87, 1.65), p=0.28	1.00
<b>Incident HF</b>				
Fully-adjusted	5.74 (3.07, 10.71), p<0.001	1.87 (1.09, 3.22), p=0.02	1.52 (1.03, 2.24), p=0.04	1.00
Exploratory	5.59 (2.96, 10.54), p<0.001	1.81 (1.04, 3.15), p=0.04	1.50 (1.01, 2.22), p=0.04	1.00
<b>ASCVD event</b>				
Fully-adjusted	2.31 (1.38, 3.89), p=0.002	1.40 (0.96, 2.03), p=0.08	1.06 (0.84, 1.34), p=0.61	1.00
Exploratory	2.23 (1.33, 3.73), p=0.002	1.35 (0.92, 1.97), p=0.12	1.04 (0.83, 1.31), p=0.74	1.00

Fully-adjusted models: age, sex, ethnicity/country of birth, Townsend deprivation index at recruitment, type 2 diabetes, HTN, SBP, tobacco smoking, family history of ASCVD, urine albumin/creatinine, body mass index, waist circumference, low-density lipoprotein, high-density lipoprotein, hemoglobin A1c, lipoprotein (a), and use of aspirin, statin, angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, or beta-blockers

Exploratory: fully-adjusted model + thyroid disease, steroid use, C-reactive protein, and chronic inflammatory illness (SLE, RA, HIV)

Hazard ratios for mortality were obtained using Cox proportional hazards models. Subhazard ratios for incident HF and ASCVD event were obtained using Fine and Gray proportional subhazards regression, modeling mortality as a competing risk.

**Table S2.** Association of eGFRcr-cys categories with risks of mortality and CVD events among South Asians in the UK Biobank (N = 7,738)

	Subhazards and Hazard ratios (95% CI) by eGFRcr-cys category			
	<45 N = 52	45-59 N = 127	60-89 N = 2,455	≥ 90 N = 5,104
<b>All-cause mortality</b>				
Demographic-adjusted	9.85 (6.04, 16.07), p<0.001	2.76 (1.68, 4.56), p<0.001	1.18 (0.91, 1.54), p=0.22	1.00
Fully-adjusted	5.97 (3.47, 10.26), p<0.001	1.83 (1.08, 3.09), p=0.02	1.16 (0.88, 1.52), p=0.30	1.00
<b>Incident HF</b>				
Demographic-adjusted	12.96 (7.03, 23.92), p<0.001	4.85 (2.75, 8.54), p<0.001	1.61 (1.17, 2.22), p=0.004	1.00
Fully-adjusted	6.47 (3.17, 13.20), p<0.001	3.11 (1.67, 5.78), p<0.001	1.42 (1.02, 1.98), p=0.04	1.00
<b>ASCVD event</b>				
Demographic-adjusted	5.69 (3.29, 9.84), p<0.001	1.43 (0.84, 2.44), p=0.19	1.29 (1.04, 1.59), p=0.02	1.00
Fully-adjusted	3.71 (1.99, 6.92), p<0.001	1.11 (0.63, 1.96), p=0.73	1.27 (1.02, 1.58), p=0.03	1.00

Demographic-adjusted models: age, sex, ethnicity/country of birth

Fully-adjusted models: demographic-adjusted model + Townsend deprivation index at recruitment, type 2 diabetes, hypertension, systolic blood pressure, tobacco smoking, family history of ASCVD, urine albumin-to-creatinine ratio, body mass index, waist circumference, low-density lipoprotein, high-density lipoprotein, hemoglobin A1c, lipoprotein (a), and use of aspirin, statin, angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, or beta-blockers

Hazard ratios for mortality were obtained using Cox proportional hazards models. Subhazard ratios for incident HF and ASCVD event were obtained using Fine and Gray proportional subhazards regression, modeling mortality as a competing risk.

**Table S3.** Associations of jointly-modeled eGFRcys and eGFRcr with risks of mortality and CVD events among South Asians in the UK Biobank (N = 7,738)

	Subhazards and Hazard ratios (95% CI) per 15 mL/min/1.73 m <sup>2</sup> lower eGFR	
	eGFRcys	eGFRcr
<b>All-cause mortality</b>	1.50 (1.29, 1.74), p<0.001	0.96 (0.83, 1.12), p=0.62
<b>Incident HF</b>	1.46 (1.21, 1.75), p<0.001	0.98 (0.82, 1.17), p=0.79
<b>ASCVD event</b>	1.22 (1.08, 1.38), p=0.002	0.98 (0.86, 1.13), p=0.81

**Jointly-modeled** estimates obtained after adjustment for age, sex, ethnicity/country of birth, Townsend deprivation index at recruitment, type 2 diabetes, hypertension, systolic blood pressure, tobacco smoking, family history of ASCVD, urine albumin-to-creatinine ratio, body mass index, waist circumference, low-density lipoprotein, high-density lipoprotein, hemoglobin A1c, lipoprotein (a), and use of aspirin, statin, angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, or beta-blockers

Hazard ratios for mortality were obtained using Cox proportional hazards models. Subhazard ratios for incident HF and ASCVD event were obtained using Fine and Gray proportional subhazards regression, modeling mortality as a competing risk.

**Table S4.** Baseline demographics of South Asian participants in the UK Biobank who were included versus excluded from the study cohort

<b>Baseline Characteristics</b>	<b>Included (N = 7,738)</b>	<b>Excluded (N=671)</b>	<b>P value</b>
Demographics			
Age, years, mean (SD)	53.1 (8.4)	53.4 (8.4)	0.48
Female sex, n (%)	3653 (47)	357 (53)	0.003
Ethnicity or Country of Origin			0.10
India, n (%)	5188 (67)	430 (64)	
Pakistan, n (%)	1548 (20)	149 (22)	
Sri Lanka, n (%)	657 (9)	60 (9)	
Bangladesh, n (%)	189 (2)	24 (4)	
Nepal, n (%)	156 (2)	8 (1)	
Townsend deprivation index score, median (IQR)	0.2 (-2.2, 2.4)	0.3 (-2.1, 2.5)	0.45
Family history of ASCVD, n (%)	3827 (50)	357 (53)	0.068
Comorbidities			
Diabetes, n (%)	1461 (19)	141 (21)	0.19
Hypertension, n (%)	4004 (52)	340 (51)	0.62
Systolic blood pressure, mmHg, mean (SD)	135 (19)	135 (20)	0.78
Diastolic blood pressure, mmHg, mean (SD)	83 (10)	82 (11)	0.30
Thyroid disease, n (%)	558 (7)	48 (7)	1.00
Smoking, n (%)			0.76
Never	6056 (79)	528 (79)	
Previous	901 (12)	77 (12)	
Current	664 (8.6)	55 (8.2)	
Chronic inflammatory illness, n (%)	139 (2)	13 (2)	0.91
Body mass index, kg/m <sup>2</sup> , mean (SD)	27 (4)	27 (5)	0.38
Waist circumference, cm, mean (SD)	91.4 (11.7)	90.9 (11.9)	0.36
Medications, n (%)			
Statins	1577 (20.4)	146 (21.8)	0.42

ASA	1143 (14.8)	96 (14.3)	0.79
ACEI/ARB	1134 (14.7)	100 (14.9)	0.91
Beta-blockers	392 (5.1)	32 (4.8)	0.81
Steroids	75 (1)	7 (1)	1.00
Laboratory values			
UACR, n (%)			0.84
<30 mg/g	6749 (91)	501 (91)	
30-300 mg/g	565 (8)	44 (8)	
>300 mg/g	85 (1)	5 (1)	
LDL cholesterol, mg/dL, mean (SD)	131 (32)	133 (40)	0.86
HDL cholesterol, mg/dL, mean (SD)	49 (12)	43 (15)	0.43
Lipoprotein (a), nmol/L, median (IQR)	32 (13, 65)	28 (21, 34)	0.76
Hemoglobin A1c, %, median (IQR)	5.6 (5.4, 6.0)	5.7 (5.4, 6.0)	0.70
C-reactive protein, mg/L, median (IQR)	1.6 (0.8, 3.3)	2.4 (0.8, 3.0)	0.69

Abbreviations: SD, standard deviation; IQR, interquartile range; ASCVD, atherosclerotic cardiovascular disease; ASA, aspirin; ACEI/ARB, angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker; UACR, urine albumin-to-creatinine ratio; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Chronic inflammatory illness includes a prior diagnosis of systemic lupus erythematosus, rheumatoid arthritis, and human immunodeficiency virus.