Kidney Medicine

# Cystatin C- and Creatinine-based Estimated GFR Differences: Prevalence and Predictors in the UK Biobank

*Debbie C. Chen, Kaiwei Lu, Rebecca Scherzer, Jennifer S. Lees, Elaine Rutherford, Patrick B. Mark, O. Alison Potok, Dena E. Rifkin, Joachim H. Ix, Michael G. Shlipak,* and Michelle M. Estrella**

**Rationale & Objective:** Large differences between estimated glomerular filtration rate (eGFR) based on cystatin C (eGFRcys) and creatinine (eGFRcr) occur commonly. A comprehensive evaluation of factors that contribute to these differences is needed to guide the interpretation of discrepant eGFR values.

**Study Design:** Cohort study.

**Setting & Participants:** 468,969 participants in the UK Biobank.

**Exposures:** Candidate sociodemographic, lifestyle factors, comorbidities, medication usage, and physical and laboratory predictors.

**Outcomes:** eGFRdiff, defined as eGFRcys minus eGFRcr, categorized into 3 levels: lower eGFRcys (eGFRdiff, less than −15 mL/min/1.73 $m^2$), concordant eGFRcys and eGFRcr (eGFRdiff, −15 to < 15 mL/min/1.73 $m^2$), and lower eGFRcr (eGFRdiff, ≥15 mL/min/1.73 $m^2$).

**Analytical Approach:** Multinomial logistic regression models were constructed to identify predictors of lower eGFRcys or lower eGFRcr. We developed 2 prediction models comprising 375,175 participants: (1) a clinical model using clinically available variables and (2) an enriched model additionally including lifestyle variables. The models were internally validated in an additional 93,794 participants.

**Results:** Mean ± standard deviation of eGFRcys was 88 ± 16 mL/min/1.73 $m^2$, and eGFRcr was 95 ± 13 mL/min/1.73 $m^2$; 25% and 5% of participants were in the lower eGFRcys and lower eGFRcr groups, respectively. In the multivariable enriched model, strong predictors of lower eGFRcys were older age, male sex, South Asian ethnicity, current smoker (vs never smoker), history of thyroid dysfunction, chronic inflammatory disease, steroid use, higher waist circumference and body fat, and urinary albumin-creatinine ratio >300 mg/g. Odds ratio estimates for these predictors were largely inverse of those in the lower eGFRcr group. The model's area under the curve was 0.75 in the validation set, with good calibration (1.00).

**Limitations:** Limited generalizability.

**Conclusions:** This study highlights the multitude of demographic, lifestyle, and health characteristics that are associated with large eGFRdiff. The clinical model may identify individuals who are likely to have discrepant eGFR values and thus should be prioritized for cystatin C testing.

*Complete author and article information provided before references.*

*Correspondence to M.M. Estrella (michelle.estrella@ucsf.edu)*

**M.G.S. and M.M.E. contributed equally to this work and are cosenior authors.*

*Kidney Med. 6(4):100796. Published online February 16, 2024.*

*doi: 10.1016/j.xkme.2024.100796*



Recent national efforts to eliminate the use of race in assessing kidney function have galvanized the increased use of cystatin C.[1] As clinicians begin to incorporate cystatin C into their practice, there is growing recognition that estimated glomerular filtration rate (eGFR) by cystatin C (eGFRcys) frequently differs substantially from eGFR by creatinine (eGFRcr) when measured at the same time in the same individual.

Prior studies investigating populations with and without chronic kidney disease (CKD) have found that approximately 30% of individuals have eGFRcys and eGFRcr values that differ substantially.[2-5] Large eGFR differences (eGFRdiff), defined by eGFRcys and eGFRcr values that are discrepant by more than 15 mL/min/1.73 $m^2$, have strong prognostic implications.[2-5] Individuals in whom eGFRcys was substantially lower than eGFRcr (eGFRdiff < −15 mL/min/1.73 $m^2$) have higher risks of adverse outcomes, including mortality, end-stage kidney disease, hospitalizations, and cardiovascular disease (CVD) events compared to those with concordant eGFR values.[2-5] These findings were evident across baseline eGFR values. Conversely, those in whom eGFRcys was much higher than eGFRcr (eGFRdiff ≥ 15 mL/min/1.73 $m^2$) had substantially lower risks of these outcomes.

Large intraindividual differences between eGFRcys and eGFRcr likely occur when factors unrelated to kidney function differentially influence cystatin C or creatinine levels. Muscle mass, physical activity, meat consumption, chronic illness, and medications inhibiting tubular creatinine secretion are non–glomerular filtration rate (non-GFR) factors that affect serum creatinine levels, whereas obesity, hypothyroidism, cigarette smoking, and steroid use have been cited as non-GFR determinants of cystatin C.[6-11] Because eGFR-based CKD identification and prognostication are integral to its management, a comprehensive evaluation of the non-GFR factors that differentially influence creatinine and cystatin C levels may inform the clinical interpretation of discrepant eGFR values. Because health systems

**PLAIN-LANGUAGE SUMMARY**

Estimated glomerular filtration rate (eGFR) based on cystatin C and creatinine may differ substantially within an individual. Although most clinicians are aware that creatinine is influenced by muscle mass, there are additional numerous lifestyle and health characteristics that may affect serum concentrations of either biomarker. Our analyses of 468,969 individuals in the UK Biobank identified independent predictors of large differences between eGFR based on cystatin C and eGFR based on creatinine, which may inform the interpretation of discrepant eGFR values within an individual. We developed models that may be implemented at a population level to help health systems identify individuals who are likely to have large differences between eGFR based on cystatin C and eGFR based on creatinine and thus should be prioritized for cystatin C testing.

seek to contain costs related to cystatin C testing, understanding these non-GFR factors could also identify patients for whom cystatin C testing would more likely yield clinically actionable decisions (ie, those with large eGFRdiff) and thus be prioritized for cystatin C testing.

To address this knowledge and clinical gap, we leveraged comprehensive demographic, lifestyle, and clinical data in the large, population-based UK Biobank cohort both to identify characteristics that are independently associated with large eGFRdiff, thus indicating the presence of non-GFR determinants of creatinine and/or cystatin C, and to determine whether a clinically available subset of these characteristics could discriminate the likelihood of a large eGFRdiff for an individual.

## METHODS

### Study Design and Population

The UK Biobank is a prospective cohort study of 502,460 adults aged 40-69 years enrolled between 2006 and 2010 from 22 assessment centers across the United Kingdom.[12] At the baseline study visit, participants underwent nurse-led interviews and completed detailed questionnaires about their medical history, medication use, sociodemographic factors, and lifestyle. Participants underwent a range of physical assessments and provided blood and urine samples at the baseline visit. The present study included 468,969 participants who had both serum cystatin C and creatinine measurements at baseline.

At recruitment, all participants were registered with a general practitioner in the National Health Service and consented to linkage of their medical records. The UK Biobank study was approved by the North West Multicentre Research Ethics Committee, and all participants provided written informed consent. This research was conducted under UK Biobank Application No. 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.

### Outcomes

The outcome was eGFRdiff, defined as eGFRcys minus eGFRcr, categorized into 3 levels: lower eGFRcys (eGFRdiff $< -15$ mL/min/1.73 $m^2$), concordant eGFRcys and eGFRcr (eGFRdiff $-15$ to $< 15$ mL/min/1.73 $m^2$), and lower eGFRcr (eGFRdiff $\geq 15$ mL/min/1.73 $m^2$). We chose to investigate predictors of absolute differences between eGFRcys and eGFRcr rather than relative differences because absolute differences are more clinically intuitive. Serum cystatin C and creatinine levels were measured at baseline and applied to the 2012 CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation to calculate eGFRcys and to the 2021 CKD-EPI race-free equation to calculate eGFRcr.[13,14] Serum cystatin C levels were measured using a latex-enhanced immunoturbidimetric assay by Siemens on the Siemens Advia 1800 with an interassay coefficient of variation of 1.1%.[15] Serum creatinine levels were measured using an enzyme-based assay by Beckman Coulter on the Beckman Coulter AU5800 with a coefficient of variation of 2.0%.[16] Details pertaining to biomarker sampling, handling, and quality control have been previously described.[16,17]

### Candidate Predictor Variables

Based on clinical experience and prior literature, we considered candidate variables for these analyses that could plausibly be related to large discrepancies between eGFRcys and eGFRcr.[4-11] Candidate variables at the baseline study visit were considered across a set of prespecified domains: sociodemographic, lifestyle factors, comorbidities, medication usage, and physical and laboratory measures. Age, sex, race or ethnicity, meat intake, physical activity, smoking history, average household income, and medication use were self-reported. Medical history was obtained via self-report and *International Classification of Diseases Ninth Revision* (ICD-9) and *International Classification of Diseases, Tenth Revision* (ICD-10) codes. Blood and urine specimens were collected according to study protocol.[18] Candidate laboratory predictors included: hemoglobin $A_{1c}$ ($HbA_{1c}$), serum albumin, blood urea nitrogen (BUN), calcium, high-density lipoprotein (HDL), low-density lipoprotein, triglycerides, C-reactive protein, phosphate, vitamin D, hemoglobin, and urinary albumin-creatinine ratio.

Body composition, waist circumference, and grip strength were measured by trained study personnel.[18] Two sets of systolic blood pressure (SBP) 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.[19] History of hypertension was determined from self-report of prior diagnosis, use of antihypertensive, average SBP ≥ 140 mm Hg, average diastolic blood pressure ≥ 90 mm Hg, or ICD-9 or ICD-10 codes indicating hypertension diagnosis prior to baseline assessment. History of diabetes was determined by self-report of prior diagnosis, use of medications for diabetes, $HbA_{1c}$ ≥ 6.5% at enrollment, or ICD-9 or ICD-10 codes indicating diabetes diagnosis prior to baseline assessment. CVD was defined by history of atherosclerotic CVD, stroke, heart failure, or peripheral artery disease. Presence of chronic inflammatory disease was defined as a clinical diagnosis of rheumatoid arthritis, systemic lupus erythematosus, or human immunodeficiency virus infection by self-report or ICD-9 or ICD-10 codes. Thyroid disease included hypothyroidism or hyperthyroidism diagnoses by self-report or ICD-9 or ICD-10 codes.

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.[20] Meat intake was defined by self-reported consumption of beef, lamb, mutton, poultry, pork, fish, and processed meat. Physical activity was assessed using adapted questions from the validated International Physical Activity Questionnaire.[21] Time spent walking or performing moderate or vigorous physical activity was weighted by the energy expenditure for these categories of activity to produce metabolic equivalent min/week of physical activity.

## Statistical Analysis

Baseline characteristics were summarized by 3 eGFRdiff categories: lower eGFRcys (eGFRdiff < −15 mL/min/1.73 $m^2$), concordant eGFRcys and eGFRcr (eGFRdiff −15 to < 15 mL/min/1.73 $m^2$), and lower eGFRcr (eGFRdiff ≥ 15 mL/min/1.73 $m^2$). These eGFRdiff cutoffs were chosen because 15 mL/min/1.73 $m^2$ corresponds to approximately 1-standard deviation of baseline eGFRdiff, represents a clinically meaningful difference in eGFR that distinguishes CKD stages, and has been used in prior studies to categorize eGFRdiff.[2-5]

## Model Development

We selected 34 candidate variables a priori. Each continuous predictor was standardized to the same scale (mean 0, SD 1). Thresholds for categorical variables were chosen based on clinical relevance and distributions. All candidate variables had <10% missingness except for physical activity (20%), phosphate (15%), HDL (15%), calcium (14%), serum albumin (14%), and vitamin D (11%). Multiple imputation with the Markov chain Monte Carlo method for arbitrary missing multivariate normal data was used to impute missing covariates with 10 imputations. The study population was partitioned into 2 nonoverlapping cohorts, with 375,175 (80%) participants for model training and 93,794 (20%) for model testing. We used Bayesian model averaging to identify parsimonious sets of risk factors that were independently associated with eGFRdiff, using logistic regression models applied to the training data. The Bayesian model averaging procedure was run separately for the lower eGFRcys and lower eGFRcr outcomes, each time with the referent category of concordant eGFRdiff. We combined estimates by averaging posterior probabilities across the 10 imputed datasets and retained predictors with posterior probabilities >35% for either lower eGFRcys and lower eGFRcr.[22]

Using the training cohort, we incorporated the independent predictors that were identified using the Bayesian model averaging procedure into a multinomial logistic regression model to estimate the odds of an individual having lower eGFRcys and lower eGFRcr compared to the concordant reference group. The enriched model included age, sex, race or ethnicity, meat intake, physical activity, smoking, grip strength, Townsend deprivation index, average household income, diabetes, hypertension, history of cancer, thyroid dysfunction, chronic inflammatory disease, recent bone fracture, waist circumference, percentage body fat, SBP, $HbA_{1c}$, serum albumin, BUN, calcium, HDL, low-density lipoprotein, triglycerides, C-reactive protein, phosphate, vitamin D, hemoglobin, urinary albumin-creatinine ratio, steroid use, and trimethoprim use. $HbA_{1c}$, C-reactive protein, and Townsend deprivation index were log-transformed to correct right skewed distributions. We then performed a sensitivity analysis using the 2009 CKD-EPI eGFRcr equation to calculate eGFRdiff.

In addition to the enriched model described above, we developed a nested, simplified clinical model that was restricted to characteristics that are routinely available in clinical practice: age, sex, race or ethnicity, smoking, diabetes, hypertension, history of cancer, SBP, $HbA_{1c}$, BUN, calcium, HDL, low-density lipoprotein, triglycerides, hemoglobin, and urinary albumin-creatinine ratio. These predictors were also incorporated into a multinomial logistic regression model to estimate the odds of having a lower eGFRcys and lower eGFRcr, relative to the concordant eGFRcys and eGFRcr group. Finally, we repeated this model after excluding race or ethnicity as a predictor variable.

## Performance Metrics

In our testing cohort, we evaluated the performance of our 3 multivariable models: (1) clinical model; (2) clinical model without race or ethnicity; and (3) enriched model. We assessed model discrimination using C-statistics. Model calibration was evaluated by calibration slopes and visual inspection of calibration plots, comparing predicted and observed probabilities of lower eGFRcys and lower eGFRcr.

All tests were 2-tailed with a statistical significance level of $P < 0.05$. Bayesian model averaging was performed using the BMA package for R, version 4.2.1 (R Foundation

for Statistical Computing). All other analyses were conducted using the SAS system, version 9.4 (SAS Institute, Inc.).

## RESULTS

### Baseline Characteristics

Among 468,969 participants in the UK Biobank, the mean age at enrollment was 56.5 years, and 46% (214,677) were men. The race and ethnicity categories were distributed as follows: 94.3% (442,005) White, 1.6% (7,294) Black, 0.4% (1,699) East Asian or Southeast Asian, 1.7% (8,022) South Asian, and 2.1% (9,949) Other, which includes participants who self-identified as 'Mixed', 'Unknown', or 'Other'. At baseline, mean (standard deviation) of eGFRcys was 88 (16), eGFRcr was 95 (13), and eGFRdiff was −6 (13) mL/min/1.73 $m^2$. Approximately 70% of participants had concordant eGFRcys and eGFRcr; 25% (118,549) had lower eGFRcys, and 5% (23,758) had lower eGFRcr (Table 1). Participants within the lower eGFRcys group were older and had a more than 2-fold prevalence of urinary albumin-creatinine ratio ≥ 30 mg/g compared with the lower eGFRcr eGFRdiff group. The lower eGFRcys group also had a more than 3-fold prevalence of diabetes and current smoking and 2-fold prevalence of CVD compared with the lower eGFRcr group (Table 1).

The proportion of participants with lower eGFRcys or lower eGFRcr varied by self-identified race and ethnicity (Fig 1). The prevalence of lower eGFRcys was 8% among Blacks, 14% among East and Southeast Asians, 25% among Whites, and 46% among South Asians; conversely, the prevalences of lower eGFRcr among these respective racial ethnic groups were 25%, 6%, 5%, and 2% (Fig 1, Table S1).

### Predictors of Lower eGFRcys

Demographic predictors of lower eGFRcys included older age, male sex, and South Asian ethnicity. Participants who were the least physically active were more likely to have lower eGFRcys than the most physically active. Compared with participants who never smoked, current smokers were more likely to have lower eGFRcys. Lower socioeconomic status, estimated by higher Townsend deprivation indices and by average household income, was associated with lower eGFRcys (Table 2).

All comorbidities evaluated in our study were associated with higher likelihood of lower eGFRcys. Steroid use was associated with a nearly 2-fold likelihood of having a lower eGFRcys, although fewer than 1% of the population reported steroid use.

Anthropometric and physical examination predictors of lower eGFRcys included larger waist circumference, higher percentage body fat, and higher SBP. Laboratory predictors of lower eGFRcys included higher low-density lipoprotein cholesterol, triglycerides, calcium, phosphate, hemoglobin, and C-reactive protein; lower HDL cholesterol and vitamin D; and worse categories of albuminuria.

### Predictors of Lower eGFRcr

Notably, Black participants had 7.3-fold odds relative to Whites participants of having a lower eGFRcr. Higher quantities of dietary meat intake and stronger grip strength were predictors of lower eGFRcr. Trimethoprim use was also strongly associated with lower eGFRcr, but only 0.1% of the overall population reported use of trimethoprim-containing medications. Laboratory predictors of lower eGFRcr included higher HDL, BUN, and vitamin D levels and better categories of albuminuria (Table 2).

### Secondary Analyses

Associations of participant characteristics with eGFRdiff category were generally similar between the clinical and enriched models (Table 3). However, in the clinical model, men were less likely than women to have lower eGFRcys. Notably, men were more likely to have lower eGFRcys in a model adjusted for demographic characteristics (odds ratio, 1.14; 95% confidence interval, 1.13-1.16) (Table S2), but the addition of HDL and smoking in the clinical model resulted in a lower likelihood of being in the lower eGFRcys group (Table 3). Removal of race or ethnicity from our clinical model minimally affected the associations of baseline characteristics with eGFRdiff category (Table S3).

In the sensitivity analyses using the 2009 CKD-EPI eGFRcr equation, all predictors in the enriched model retained similar associations with lower eGFRcys and lower eGFRcr categories, except for Black race. Among Black participants, using the 2009 CKD-EPI equation, which includes a race coefficient, to calculate eGFRdiff resulted in nearly 3 times the prevalence of lower eGFRcys (23% vs 8%) and half the prevalence of lower eGFRcr (12% vs 25%) than when the 2021 CKD-EPI equation was used.

### Model Performance

All 3 models—clinical model, clinical model without race or ethnicity, and the enriched model—were well-calibrated (Table 4, Fig S1). The enriched model provided the best discrimination among the 3 models, achieving a C-statistic of 0.752 for predicting both lower eGFRcys and lower eGFRcr. The clinical model achieved fair discrimination for lower eGFRcys (C-statistic 0.699) and good discrimination for lower eGFRcr (C-statistic 0.723). The removal of race or ethnicity from the clinical model minimally affected the discrimination for predicting lower eGFRcys (difference in C-statistic of 0.005) but decreased the C-statistic from 0.723 to 0.705 for predicting lower eGFRcr.

## DISCUSSION

In this large community-based population of 468,969 individuals, 30% had eGFRcys and eGFRcr values that differed by at least 15 mL/min/1.73 $m^2$. We identified

**Table 1.** Baseline Characteristics by Category of Baseline eGFRdiff in the UK Biobank

| Variable | Overall | Baseline eGFRdiff (mL/min/1.73 m²)[a,b] | | |
|---|---|---|---|---|
| | | <−15 (Lower eGFRcys) | −15 to <15 (Concordant) | ≥15 (Lower eGFRcr) |
| N | 468,969 | 118,549 (25.3) | 326,662 (69.7) | 23,758 (5.1) |
| Age (y) | 56.5 (8.1) | 58.4 (7.6) | 56.1 (8.1) | 53.1 (8.0) |
| Male sex (%) | 214,677 (46) | 57,966 (48.9) | 146,840 (45.0) | 9,871 (41.5) |
| Race/ethnicity (%) | | | | |
| White | 442,005 (94.3) | 111,614 (94.2) | 309,397 (94.7) | 20,994 (88.4) |
| Black | 7,294 (1.6) | 611 (0.5) | 4,835 (1.5) | 1,848 (7.8) |
| East Asian/Southeast Asian | 1,699 (0.4) | 232 (0.2) | 1,374 (0.4) | 93 (0.4) |
| South Asian | 8,022 (1.7) | 3,652 (3.1) | 4,194 (1.3) | 176 (0.7) |
| Other | 9,949 (2.1) | 2,440 (2.1) | 6,862 (2.1) | 647 (2.7) |
| Meat intake (%) | | | | |
| <1× per week | 16,960 (3.6) | 6,985 (5.9) | 9,694 (3.0) | 281 (1.2) |
| 1 to 4× per week | 416,356 (88.9) | 102,650 (86.7) | 292,597 (89.7) | 21,109 (89.0) |
| ≥5× per week | 34,925 (7.5) | 8,651 (7.3) | 23,947 (7.3) | 2,327 (9.8) |
| Physical activity, MET-min/week (%) | | | | |
| Low (<600) | 9,706 (2.6) | 3,797 (4.1) | 5,558 (2.1) | 351 (1.8) |
| Moderate (600 to 3,000) | 252,417 (66.6) | 61,566 (67) | 177,904 (66.6) | 12,947 (65.1) |
| High (≥3,000) | 116,704 (30.8) | 26,590 (28.9) | 83,539 (31.3) | 6,575 (33.1) |
| Grip strength (kg) | 30.7 (11.0) | 29.2 (11.1) | 31.1 (10.9) | 33.0 (11.2) |
| Smoking (%) | | | | |
| Never | 255,367 (54.5) | 55,233 (46.7) | 185,282 (56.8) | 14,852 (62.6) |
| Previous | 161,998 (34.6) | 40,118 (33.9) | 114,311 (35.0) | 7,569 (31.9) |
| Current | 49,227 (10.5) | 22,370 (18.9) | 25,618 (7.8) | 1,239 (5.2) |
| Townsend deprivation index (IQR) | −2.2 (−3.7 to 0.5) | −1.7 (−3.4 to 1.4) | −2.3 (−3.7 to 0.2) | −2.3 (−3.7 to 0.4) |
| Average household income (%) | | | | |
| <18,000 | 91,092 (19.5) | 31,955 (27.1) | 56,139 (17.2) | 2,998 (12.7) |
| 18,000 to 30,999 | 101,876 (21.8) | 27,410 (23.3) | 69,826 (21.4) | 4,640 (19.6) |
| 31,000 to 51,999 | 104,416 (22.4) | 22,404 (19.0) | 76,092 (23.4) | 5,920 (25.0) |
| 52,000 to 100,000 | 81,520 (17.4) | 13,937 (11.8) | 62,105 (19.1) | 5,478 (23.1) |
| >100,000 | 21,696 (4.6) | 2,801 (2.4) | 17,122 (5.3) | 1,773 (7.5) |
| Diabetes (%) | 28,129 (6.0) | 11,199 (9.4) | 16,195 (5.0) | 735 (3.1) |
| Hypertension (%) | 250,193 (53.3) | 74,441 (62.8) | 165,829 (50.8) | 9,923 (41.8) |
| Cardiovascular disease (%)[c] | 19,643 (4.2) | 7,145 (6.0) | 11,861 (3.6) | 637 (2.7) |
| Cancer (%) | 35,565 (7.6) | 10,659 (9.0) | 23,550 (7.2) | 1,356 (5.7) |
| Thyroid dysfunction (%) | 26,929 (5.7) | 8,885 (7.5) | 16,896 (5.2) | 1,148 (4.8) |
| Chronic inflammatory disease (%) | 7,110 (1.5) | 3,225 (2.7) | 3,741 (1.1) | 144 (0.6) |
| Fractured bone in last 5 y (%) | 44,351 (9.5) | 12,526 (10.6) | 29,879 (9.2) | 1,946 (8.2) |
| Steroid use (%) | 4,842 (1.0) | 2,193 (1.8) | 2,529 (0.8) | 120 (0.5) |
| Trimethoprim use (%) | 468 (0.1) | 77 (0.1) | 323 (0.1) | 68 (0.3) |
| Waist circumference (cm) | 90.3 (13.5) | 95.7 (14.4) | 88.7 (12.7) | 85.8 (11.6) |
| Body fat (%) | 31.4 (8.5) | 33.7 (9.0) | 30.7 (8.2) | 29.3 (7.9) |
| Systolic blood pressure (mm Hg) | 138 (19) | 140 (19) | 137 (19) | 134 (18) |
| Diastolic blood pressure (mm Hg) | 82 (10) | 83 (10) | 82 (10) | 80 (10) |
| Hemoglobin A1c (%) | 5.4 (5.2 to 5.6) | 5.5 (5.2 to 5.7) | 5.4 (5.1 to 5.6) | 5.3 (5.1 to 5.5) |
| Albumin (g/dL) | 4.5 (0.3) | 4.5 (0.3) | 4.5 (0.3) | 4.6 (0.3) |
| Blood urea nitrogen (mg/dL) | 32 (8) | 32 (8) | 32 (9) | 34 (8) |
| Calcium (mg/dL) | 9.5 (0.4) | 9.5 (0.4) | 9.5 (0.4) | 9.5 (0.4) |
| High-density lipoprotein (mg/dL) | 56 (15) | 52 (14) | 57 (15) | 60 (15) |
| Low-density lipoprotein (mg/dL) | 138 (34) | 139 (35) | 137 (33) | 133 (32) |
| Triglycerides (mg/dL) | 68 (40) | 78 (43) | 64 (38) | 59 (35) |
| C-reactive protein (mg/L) (IQR) | 1.3 (0.7 to 2.8) | 2.1 (1.0 to 4.2) | 1.2 (0.6 to 2.4) | 0.9 (0.5 to 1.8) |
| Phosphate (mg/dL) | 3.6 (0.5) | 3.6 (0.5) | 3.6 (0.5) | 3.6 (0.5) |

*(Continued)*

**Table 1 (Cont'd).** Baseline Characteristics by Category of Baseline eGFRdiff in the UK Biobank

| Variable | Overall | Baseline eGFRdiff (mL/min/1.73 m²)[a,b] | | |
|---|---|---|---|---|
| | | <−15 (Lower eGFRcys) | −15 to <15 (Concordant) | ≥15 (Lower eGFRcr) |
| Vitamin D (ng/mL) | 19 (8) | 18 (8) | 20 (8) | 20 (9) |
| Hemoglobin (g/dL) | 14.2 (1.3) | 14.3 (1.3) | 14.1 (1.2) | 13.9 (1.2) |
| UACR, (mg/g) (%) | | | | |
| <30 | 434,640 (95.4) | 107,182 (93.6) | 304,873 (95.9) | 22,585 (97.6) |
| 30 to 300 | 19,094 (4.2) | 6,627 (5.8) | 11,940 (3.8) | 527 (2.3) |
| >300 | 1,865 (0.4) | 725 (0.6) | 1,103 (0.3) | 37 (0.2) |
| eGFRcr (mL/min/1.73 m²) | 94.7 (13.2) | 97.2 (10.4) | 94.8 (13.5) | 79.8 (11.7) |
| eGFRcys (mL/min/1.73 m²) | 88.25 (16.21) | 73.9 (11.7) | 92. 5 (14.6) | 102.1 (11.0) |
| eGFRdiff (mL/min/1.73 m²) | −6.40 (13.36) | −23.3 (7.0) | −2.3 (7.4) | 22.3 (6.9) |

Abbreviations: eGFRcr, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C-based estimated glomerular filtration rate; eGFRdiff, estimated glomerular filtration rate difference; IQR, interquartile range; MET, metabolic equivalent; UACR, urinary albumin-creatinine ratio.
[a]Continuous variables are summarized as mean ± SD and categorical variables as count and percentage.
[b]The lower eGFRcys category comprised individuals with eGFRcys lower than eGFRcr. The lower eGFRcr category comprised individuals eGFRcr lower than eGFRcys.
[c]Atherosclerotic cardiovascular disease or heart failure.

multiple predictors of large eGFRdiff pertaining to demographics, lifestyle, socioeconomic status, comorbidities, medication usage, and physical and laboratory measures. Notable predictors of lower eGFRcys (ie, eGFRcys lower than eGFRcr by at least 15 mL/min/1.73 m²) included older age, male sex, South Asian ethnicity, lower meat intake and physical activity, current smoking, higher comorbidity burden, steroid use, larger waist circumference and percentage body fat, and higher degrees of albuminuria. Predictors of lower eGFRcr (ie, eGFRcr lower than eGFRcys by at least 15 mL/min/1.73 m²) included Black race, more frequent meat intake, stronger grip strength, trimethoprim use, and higher BUN. As the use of cystatin C increases, identification of these epidemiologic predictors may help clinicians interpret wide discrepancies between eGFRcys and eGFRcr within an individual patient. Moreover, predicting which patients are likely to have large eGFRdiff will help cost-conscious health systems determine which individuals could benefit from more

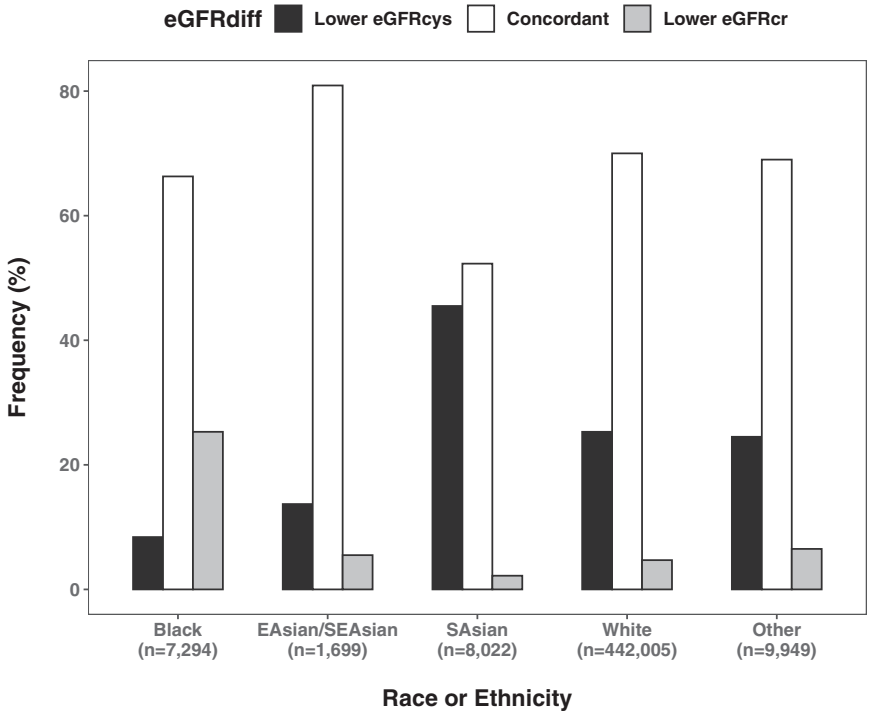


**Figure 1.** Prevalence of eGFRdiff category by race or ethnicity. Abbreviations: EAsian, East Asian; eGFRcr, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C-based estimated glomerular filtration rate; eGFRdiff, estimated glomerular filtration rate difference; SEAsian, Southeast Asian.

**Table 2.** Multivariable-Adjusted Associations of Sociodemographic, Lifestyle, and Clinical Characteristics With eGFRdiff Category in the UK Biobank (Enriched Model)

| Predictor[a] | Prevalence N (%) | Multivariable-adjusted Model[b] | | | |
|---|---|---|---|---|---|
| | | Lower eGFRcys vs Concordant Category | | Lower eGFRcr vs Concordant Category | |
| | | OR (95% CI) | *P* Value | OR (95% CI) | *P* Value |
| Demographics | | | | | |
| Age | | 1.26 (1.25-1.27) | <0.001 | 0.73 (0.72-0.75) | <0.001 |
| Sex | | | | | |
| Female | 254,292 (54.2) | Ref | | Ref | |
| Male | 214,677 (45.7) | 1.75 (1.67-1.84) | <0.001 | 0.37 (0.34-0.40) | <0.001 |
| Race/ethnicity | | | | | |
| White | 442,005 (94.3) | Ref | | Ref | |
| Black | 7,294 (1.6) | 0.24 (0.22-0.26) | <0.001 | 7.32 (6.80-7.89) | <0.001 |
| East Asian/Southeast Asian | 1,699 (0.4) | 0.70 (0.59-0.83) | <0.001 | 0.85 (0.67-1.08) | 0.18 |
| South Asian | 8,022 (1.7) | 1.59 (1.50-1.68) | <0.001 | 0.86 (0.72-1.03) | 0.10 |
| Other | 9,949 (2.1) | 0.81 (0.76-0.85) | <0.001 | 1.53 (1.39-1.68) | <0.001 |
| Lifestyle/socioeconomic | | | | | |
| Meat intake, per week | | | | | |
| <1 time | 16,960 (3.6) | Ref | | Ref | |
| 1-4 times | 416,356 (88.9) | 0.38 (0.36-0.39) | <0.001 | 2.69 (2.34-3.09) | <0.001 |
| ≥5 times | 34,925 (7.5) | 0.35 (0.33-0.37) | <0.001 | 3.22 (2.78-3.73) | <0.001 |
| Physical activity, MET-min/week | | | | | |
| Low (<600) | 9,706 (2.6) | 1.13 (1.07-1.19) | <0.001 | 1.00 (0.88-1.13) | 0.99 |
| Moderate (600-3,000) | 252,417 (66.6) | 0.96 (0.94-0.98) | <0.001 | 1.01 (0.98-1.05) | 0.53 |
| High (≥3,000) | 116,704 (30.8) | Ref | | Ref | |
| Smoking | | | | | |
| Never | 255,367 (54.5) | Ref | | Ref | |
| Previous | 161,998 (34.6) | 0.97 (0.95-0.99) | 0.001 | 0.96 (0.93-0.99) | 0.02 |
| Current | 49,227 (10.5) | 2.79 (2.72-2.87) | <0.001 | 0.58 (0.54-0.63) | <0.001 |
| Grip strength | | 0.74 (0.73-0.75) | <0.001 | 1.46 (1.42-1.50) | <0.001 |
| Townsend deprivation index | | 1.10 (1.09-1.11) | <0.001 | 0.98 (0.97-1.00) | 0.06 |
| Average household income, pounds | | | | | <0.001 |
| <18,000 | 91,092 (19.5) | 1.14 (1.11-1.17) | <0.001 | 0.88 (0.83-0.93) | 0.56 |
| 18,000-30,999 | 101,876 (21.8) | 1.04 (1.01-1.06) | 0.005 | 0.99 (0.94-1.04) | 0.97 |
| 31,000-51,999 | 104,416 (22.4) | 0.95 (0.92-0.97) | <0.001 | 1.00 (0.95-1.05) | 0.32 |
| 52,000-100,000 | 81,520 (17.4) | 0.84 (0.82-0.87) | <0.001 | 1.02 (0.98-1.07) | 0.063 |
| >100,000 | 21,696 (4.6) | Ref | | Ref | |
| Comorbidities/medications | | | | | |
| Diabetes | 28,129 (6.0) | 1.09 (1.05-1.14) | <0.001 | 0.76 (0.67-0.85) | <0.001 |
| Hypertension | 250,193 (53.3) | 1.08 (1.06-1.11) | <0.001 | 0.95 (0.91-0.99) | 0.024 |
| Cancer | 35,565 (7.6) | 1.12 (1.09-1.16) | <0.001 | 0.93 (0.87-0.99) | 0.021 |
| Thyroid dysfunction | 26,929 (5.7) | 1.22 (1.18-1.26) | <0.001 | 1.05 (0.98-1.13) | 0.19 |
| Chronic inflammatory disease | 7,110 (1.5) | 1.56 (1.47-1.66) | <0.001 | 0.60 (0.49-0.73) | <0.001 |
| Fractured bone in last 5 y | 44,351 (9.5) | 1.10 (1.07-1.13) | <0.001 | 0.92 (0.87-0.97) | 0.003 |
| Steroid use | 4,842 (1.0) | 1.93 (1.80-2.08) | <0.001 | 0.62 (0.50-0.77) | <0.001 |
| Trimethoprim use | 468 (0.1) | 0.43 (0.32-0.59) | <0.001 | 3.70 (2.72-5.04) | <0.001 |
| Physical/laboratory measures | | | | | |
| Waist circumference | | 1.31 (1.29-1.33) | <0.001 | 0.97 (0.94-1.00) | 0.070 |
| Body fat % | | 1.33 (1.31-1.36) | <0.001 | 0.77 (0.74-0.79) | <0.001 |
| SBP | | 1.02 (1.01-1.03) | 0.001 | 0.98 (0.96-1.00) | 0.10 |
| $HbA_{1c}$ | | 0.95 (0.94-0.97) | <0.001 | 0.98 (0.96-1.01) | 0.18 |
| Albumin | | 0.85 (0.84-0.86) | <0.001 | 1.00 (0.98-1.02) | 0.92 |
| BUN | | 0.91 (0.91-0.92) | <0.001 | 1.43 (1.41-1.45) | <0.001 |
| Calcium | | 1.11 (1.10-1.12) | <0.001 | 1.01 (0.99-1.03) | 0.26 |

*(Continued)*

**Table 2 (Cont'd).** Multivariable-Adjusted Associations of Sociodemographic, Lifestyle, and Clinical Characteristics With eGFRdiff Category in the UK Biobank (Enriched Model)

| Predictor[a] | Prevalence N (%) | Multivariable-adjusted Model[b] | | | |
|---|---|---|---|---|---|
| | | Lower eGFRcys vs Concordant Category | | Lower eGFRcr vs Concordant Category | |
| | | OR (95% CI) | *P* Value | OR (95% CI) | *P* Value |
| HDL | | 0.80 (0.79-0.80) | <0.001 | 1.12 (1.10-1.15) | <0.001 |
| LDL | | 1.06 (1.05-1.07) | <0.001 | 0.91 (0.90-0.93) | <0.001 |
| Triglycerides | | 1.05 (1.04-1.06) | <0.001 | 1.06 (1.04-1.08) | <0.001 |
| C-reactive protein | | 1.15 (1.14-1.16) | <0.001 | 0.91 (0.89-0.94) | <0.001 |
| Phosphate | | 1.10 (1.10-1.11) | <0.001 | 1.01 (0.99-1.03) | 0.35 |
| Vitamin D | | 0.93 (0.92-0.94) | <0.001 | 1.07 (1.05-1.09) | <0.001 |
| Hemoglobin | | 1.13 (1.12-1.14) | <0.001 | 0.95 (0.93-0.97) | <0.001 |
| UACR | | | | | |
| <30 | 434,640 (95.4) | Ref | | Ref | |
| 30-300 | 19,094 (4.2) | 1.13 (1.08-1.17) | <0.001 | 0.59 (0.53-0.66) | <0.001 |
| >300 | 1,865 (0.4) | 1.20 (1.07-1.35) | 0.002 | 0.12 (0.07-0.19) | <0.001 |

Abbreviations: BUN, blood urea nitrogen; CI, confidence interval; eGFRcr, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C-based estimated glomerular filtration rate; $HbA_{1c}$, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MET, metabolic equivalent; OR, odds ratio; Ref, reference; SBP, systolic blood pressure; UACR, urinary albumin-creatinine ratio.
[a]Continuous variables, which are listed in Table 1, are scaled per standard deviation.
[b]Multinomial logistic regression model adjusted for all predictors listed in Table 2. The lower eGFRcys category comprised individuals with eGFRdiff < −15, the concordant category served as the reference and comprised individuals with eGFRdiff between −15 and 15, and the lower eGFRcr category comprised individuals with eGFRdiff ≥ 15.

comprehensive evaluation of eGFR through cystatin C testing.

Prior studies have identified non-GFR factors, such as muscle mass or adiposity, that impact serum levels of cystatin C or creatinine independent of measured GFR.[6-9] However, these studies reported the associations of single non-GFR factors with creatinine or cystatin C after minimal multivariable adjustment. Because numerous, potentially inter-correlated non-GFR determinants may impact an individual's eGFR values, simultaneous evaluation of multiple non-GFR factors through multivariable adjustment is imperative for identifying independent epidemiologic associations. As cystatin C use increases and measured GFR remains unobtainable in routine clinical practice, large eGFRdiff will become a common clinical sign indicating the presence of non-GFR determinants that deserve clinical consideration. For patients with large eGFRdiff, providers should consider the specific non-GFR determinants in that individual patient that may explain the observed eGFRdiff and may thus inform which eGFR value is more likely to reflect true GFR. To our knowledge, this is the first study to identify predictors of large eGFRdiff in a sizable population, including individuals from diverse racial and ethnic backgrounds.

The profound differences in distribution of eGFRdiff by self-identified race and ethnicity in our study highlight the complexities inherent to using creatinine to estimate GFR among diverse populations. Prior studies have shown independent associations between Black race or African ancestry and serum creatinine levels, even after accounting for other non-GFR determinants of creatinine that correlate with race or genetic ancestry.[23] In contrast, estimation of kidney function with cystatin C was not altered or improved by including information regarding race.[23] Although prior eGFR studies have identified Black race as a non-GFR determinant of serum creatinine, our study highlights that issues pertaining to race and creatinine also apply to other non-White populations. We found that mean eGFRdiff in the UK Biobank population ranged widely across racial and ethnic groups from −13 mL/min/1.73 $m^2$ among South Asian participants to 5 mL/min/1.73 $m^2$ among Black participants. Compared with self-identified White participants, South Asian participants had nearly double the prevalence of lower eGFRcys, and Black participants had 5 times the prevalence of lower eGFRcr. Taken together with prior evidence of the incompletely understood associations between race and serum creatinine, our findings underscore the necessity of using cystatin C to assess kidney function among diverse populations. Additionally, these findings have strong implications for the diagnosis of CKD among traditionally understudied and high-risk groups, such as the South Asian population.[24,25]

Large eGFRdiff conveys important prognostic information regarding risk for adverse clinical outcomes.[2-5,26,27] Compared with individuals with concordant eGFRcys and eGFRcr, persons with lower eGFRcys have higher risks of mortality, kidney failure, hospitalizations, and CVD events; persons with lower eGFRcr have lower risks of these outcomes.[2-5,26] Given the high prevalence and prognostic importance of large eGFRdiff, both cystatin C and creatinine should be measured when providers seek to evaluate eGFR. Although health systems increasingly recognize that measuring cystatin C can inform CKD staging and prognostication, medication dosing, and kidney replacement therapy planning for individual patients, the higher cost of cystatin C relative to creatinine remains a challenge on a

**Table 3.** Multivariable-Adjusted Associations of Demographic and Clinical Characteristics that are Available in Routine Clinical Practice With eGFRdiff Category in the UK Biobank (Clinical Model)

| | Multivariable-adjusted Model[a] | | | |
|---|---|---|---|---|
| | Lower eGFRcys vs Concordant Category | | Lower eGFRcr vs Concordant Category | |
| Predictor | OR (95% CI) | *P* Value | OR (95% CI) | *P* Value |
| Demographics | | | | |
| Age | 1.40 (1.39-1.41) | <0.001 | 0.67 (0.66-0.68) | <0.001 |
| Sex | | | | |
| Female | Ref | | Ref | |
| Male | 0.70 (0.68-0.71) | <0.001 | 1.02 (0.98-1.06) | 0.33 |
| Race/ethnicity | | | | |
| White | Ref | | Ref | |
| Black | 0.36 (0.33-0.40) | <0.001 | 5.88 (5.50-6.29) | <0.001 |
| East Asian/Southeast Asian | 0.53 (0.45-0.62) | <0.001 | 0.88 (0.69-1.11) | 0.27 |
| South Asian | 2.44 (2.31-2.57) | <0.001 | 0.60 (0.50-0.71) | <0.001 |
| Other | 1.00 (0.94-1.05) | 0.91 | 1.32 (1.20-1.45) | <0.001 |
| Lifestyle | | | | |
| Smoking | | | | |
| Never | Ref | | Ref | |
| Previous | 1.07 (1.05-1.08) | <0.001 | 0.94 (0.91-0.97) | <0.001 |
| Current | 2.95 (2.88-3.02) | <0.001 | 0.60 (0.56-0.64) | <0.001 |
| Comorbidities | | | | |
| Diabetes | 1.23 (1.18-1.28) | <0.001 | 0.68 (0.61-0.76) | <0.001 |
| Hypertension | 1.32 (1.29-1.35) | <0.001 | 0.87 (0.84-0.91) | <0.001 |
| Cancer | 1.14 (1.11-1.18) | <0.001 | 0.91 (0.85-0.97) | 0.005 |
| Physical/laboratory measures | | | | |
| SBP | 0.98 (0.97-0.99) | 0.001 | 0.99 (0.97-1.01) | 0.314 |
| $HbA_{1c}$ | 1.04 (1.03-1.05) | <0.001 | 0.95 (0.93-0.97) | <0.001 |
| BUN | 0.92 (0.91-0.93) | <0.001 | 1.42 (1.40-1.44) | <0.001 |
| Calcium | 1.01 (1.01-1.02) | 0.001 | 1.02 (1.01-1.04) | 0.005 |
| HDL | 0.68 (0.67-0.68) | <0.001 | 1.19 (1.17-1.21) | <0.001 |
| LDL | 1.06 (1.05-1.07) | <0.001 | 0.89 (0.88-0.91) | <0.001 |
| Triglycerides | 1.12 (1.11-1.13) | <0.001 | 1.00 (0.98-1.02) | 0.91 |
| Hemoglobin | 1.09 (1.08-1.10) | <0.001 | 0.96 (0.94-0.98) | <0.001 |
| UACR, mg/g | | | | |
| <30 | Ref | | Ref | |
| 30-300 | 1.24 (1.19-1.28) | <0.001 | 0.56 (0.50-0.62) | <0.001 |
| >300 | 1.53 (1.36-1.71) | <0.001 | 0.10 (0.07-0.16) | <0.001 |

Abbreviations: BUN, blood urea nitrogen; CI, confidence interval; eGFRcr, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C-based estimated glomerular filtration rate; $HbA_{1c}$, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OR, odds ratio; Ref, reference; SBP, systolic blood pressure; UACR, urinary albumin-creatinine ratio.

[a]Multinomial logistic regression model adjusted for all predictors listed in Table 2. The lower eGFRcys category comprised individuals with eGFRdiff < −15, the concordant category served as the reference and comprised individuals with eGFRdiff between −15 and 15, and the lower eGFRcr category comprised individuals with eGFRdiff ≥ 15.

population level. To address this, we developed and internally validated a clinical prediction model incorporating variables that are readily available in routine clinical practice in addition to an enriched prediction model including a more comprehensive set of variables. Our prediction models achieved good discrimination and excellent calibration; they may eventually be implemented by health systems to automate the systematic identification of individuals who may have large eGFRdiff and for whom eGFR assessment by creatinine alone may be inadequate.

Among the relatively healthy ambulatory cohorts comprising the CKD-EPI Consortium, the combined eGFR equation (eGFRcr-cys) provided the most accurate estimate of GFR,[1,14] even among subgroups with large eGFRdiff characterized by either lower eGFRcys or lower eGFRcr.[28] The superior accuracy of eGFRcr-cys stems from incorporation of both creatinine and cystatin C, which at the population level, balances out the effect of non-GFR determinants on each of these biomarkers. However, large eGFRdiff at an individual level indicates a pronounced imbalance in the non-GFR determinants of creatinine and cystatin C that are informative for that individual patient's prognosis. Moreover, indiscriminate use of eGFRcr-cys among persons with large eGFRdiff

**Table 4.** Performance Characteristics of eGFRdiff Prediction Models Developed in the UK Biobank

| | Clinical Model[a] | Clinical Model Without Race or Ethnicity[b] | Enriched Model[c] |
|---|---|---|---|
| Lower eGFRcys category | | | |
| Training dataset | | | |
| C-statistic (95% CI) | 0.697 (0.695-0.699) | 0.691 (0.689-0.693) | 0.753 (0.751-0.755) |
| *P* value[d] | <0.0001 | <0.0001 | Ref |
| Calibration slope (95% CI) | 1.005 (0.980-1.030) | 1.003 (0.972-1.035) | 1.005 (0.979-1.032) |
| *P* value[e] | 0.99 | 0.91 | Ref |
| Testing dataset | | | |
| C-statistic (95% CI) | 0.699 (0.695-0.703) | 0.694 (0.690-0.697) | 0.752 (0.749-0.756) |
| *P* value[d] | <0.0001 | <0.0001 | Ref |
| Calibration slope (95% CI) | 1.011 (0.988-1.035) | 1.005 (0.974-1.035) | 0.994 (0.968-1.020) |
| *P* value[e] | 0.29 | 0.55 | Ref |
| Lower eGFRcr category | | | |
| Training dataset | | | |
| C-statistic (95% CI) | 0.717 (0.713-0.721) | 0.698 (0.694-0.702) | 0.748 (0.745-0.752) |
| *P* value[d] | <0.0001 | <0.0001 | Ref |
| Calibration slope (95% CI) | 1.043 (1.018-1.067) | 1.040 (1.014-1.066) | 1.029 (1.003-1.055) |
| *P* value[e] | 0.41 | 0.52 | Ref |
| Testing dataset | | | |
| C-statistic (95% CI) | 0.723 (0.716-0.731) | 0.705 (0.697-0.712) | 0.752 (0.746-0.759) |
| *P* value[d] | <0.0001 | <0.0001 | Ref |
| Calibration slope (95% CI) | 1.092 (1.045-1.140) | 1.076 (1.013-1.140) | 1.040 (1.004-1.076) |
| *P* value[e] | 0.057 | 0.25 | Ref |

Abbreviations: CI, confidence interval; eGFRcr, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C-based estimated glomerular filtration rate; Ref, reference.
[a]Model included age, sex, race or ethnicity, smoking, diabetes, hypertension, cancer, systolic blood pressure, hemoglobin A1c, blood urea nitrogen, calcium, high-density lipoprotein, low-density lipoprotein, triglycerides, hemoglobin, and urinary albumin-creatinine ratio.
[b]Model included age, sex, smoking, diabetes, hypertension, cancer, systolic blood pressure, hemoglobin A1c, blood urea nitrogen, calcium, high-density lipoprotein, low-density lipoprotein, triglycerides, hemoglobin, and urinary albumin-creatinine ratio.
[c]Model included age, sex, race or ethnicity, meat intake, physical activity, grip strength, smoking, Townsend deprivation index, average household income, diabetes, hypertension, cancer, thyroid dysfunction, chronic inflammatory disease, fractured bone in last 5 years, steroid use, and trimethoprim use, waist circumference, body fat, systolic blood pressure, hemoglobin A1c, albumin, blood urea nitrogen, calcium, high-density lipoprotein, low-density lipoprotein, triglycerides, C-reactive protein, phosphate, vitamin D, hemoglobin, urinary albumin-creatinine ratio.
[d]*P* value comparing C-statistics of clinical models to the enriched model.
[e]*P* value comparing calibration slopes of clinical models to that of the enriched model.

may not always provide the most accurate estimate of kidney function among patients who are elderly or those with the most severe comorbidities.[29] Future investigations with gold standard GFR measurements are needed to evaluate the performance of the GFR estimating equations among sicker patient populations who were not well-represented in the populations used to derive the eGFR equations.

Our study has several strengths. We included nearly half a million individuals with comprehensive assessment of medical history, medication usage, physical and laboratory measurements, lifestyle, and socioeconomic status. Our study included sizable South Asian and East Asian/Southeast Asian subpopulations, who are underrepresented in prior CKD epidemiological studies. All study participants had standardized measurements of creatinine and cystatin C. We also acknowledge important limitations. First, because GFR was not measured, we cannot determine whether creatinine or cystatin C was the source of bias in the setting of large eGFRdiff. Similarly, providers encountering individuals with large eGFRdiff values in the clinical setting will seek to understand the reasons for these observed differences and will unlikely have access to measured GFR. Thus, we chose to focus on identifying factors that may explain large intraindividual discrepancies between eGFRcys and eGFRcr. On the health systems level, the key is to identify individuals who are likely to have a large eGFRdiff and thus should be prioritized for cystatin C testing. Once cystatin C testing is completed, all eGFR equations would be available for clinical use, and measured GFR could also be pursued in the settings where it is available. Second, UK Biobank participants are generally younger, healthier, and have lower mortality rates than the general population, which may result in "healthy volunteer" selection bias and thus limit generalizability of our results.[30] We anticipate that the predictors of lower eGFRcys identified in our study may play a more prominent role among older individuals with higher comorbidity burden. Third, although our prediction models achieved good discrimination and calibration, external validation is required. Fourth, we highlight the wide variability in prevalence of large eGFRdiff by race or ethnicity, but we also acknowledge that our results may not generalize to all racial and ethnic groups.

In this large, population-based cohort, a multitude of predictors pertaining to demographics, lifestyle, and clinical measures and characteristics were associated with large intraindividual differences between eGFRcys and eGFRcr. Knowledge of these predictors may facilitate interpretation of discrepant eGFR values on the individual level. A prediction model based on clinically available data was derived and validated to predict likelihood of large eGFRdiff and may be implemented in the future by health systems in need of a systematic approach to prioritize patients for cystatin C testing. Future research is needed to understand how best to use knowledge of non-GFR determinants to tailor GFR estimation to individual patients.

## SUPPLEMENTARY MATERIAL

### Supplementary File (PDF)

**Figure S1:** Calibration plots for the clinical model and enriched model using the testing dataset.

**Table S1.** Distribution of Continuous and Categorical eGFRdiff by Baseline Demographic Subgroups.

**Table S2.** Multivariable-Adjusted Associations of Demographic Factors with eGFRdiff Category.

**Table S3.** Multivariable-Adjusted Associations of Demographic and Clinical Characteristics that are Available in Routine Clinical Practice with eGFRdiff Category, Without Race or Ethnicity (Clinical Model Without Race or Ethnicity).

**Table S4:** Calibration by Subgroup Using the Testing Dataset.

## ARTICLE INFORMATION

**Authors' Full Names and Academic Degrees:** Debbie C. Chen, MD, MAS, Kaiwei Lu, MS, Rebecca Scherzer, PhD, Jennifer S, Lees, MBChB, PhD, Elaine Rutherford, MBChB, PhD, Patrick B. Mark, MBChB, PhD, O. Alison Potok, MD, Dena E. Rifkin, MD, MS, Joachim H. Ix, MD, MAS, Michael G. Shlipak, MD, MPH, and Michelle M. Estrella, MD, MHS.

**Authors' Affiliations:** Division of Nephrology, Department of Medicine, University of California, San Francisco, San Francisco, CA (DCC, MME); Kidney Health Research Collaborative, San Francisco VA Health Care System & University of California, San Francisco, San Francisco, CA (DCC, KL, RS, MGS, MME); Genentech, Inc., South San Francisco, CA (DCC); Department of Medicine, San Francisco VA Health Care System, San Francisco, CA (KL, RS, MGS, MME); School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, UK (JSL, ER, PBM); Glasgow Renal and Transplant Unit, Queen Elizabeth University Hospital, Glasgow, UK (JSL, PBM); Renal Unit, Mountainhall Treatment Centre, NHS Dumfries and Galloway, Dumfries, UK (ER); Division of Nephrology and Hypertension, Department of Medicine, University of California, San Diego, San Diego, CA (OAP, DER, JHI); Nephrology Section, Veterans Affairs San Diego Healthcare System, San Diego, CA (OAP, DER, JHI); Department Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA (MGS); Division of Nephrology, Department of Medicine, San Francisco VA Health Care System, San Francisco, CA (MME).

**Address for Correspondence:** Michelle M. Estrella, MD, MHS, San Francisco VA Medical Center, 4150 Clement Street, Building 2, Room 145, San Francisco, CA 94121. Email: michelle.estrella@ucsf.edu

**Authors' Contributions:** Research idea and study design: DCC, MGS, MME; data acquisition: DCC, JSL, ER; data analysis/interpretation: DCC, KL, RS, JSL, ER, PBM, OAP, DER, JHI, MGS, MME; statistical analysis: KL, RS; supervision or mentorship: RS, JHI, MGS, MME. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

**Support:** Dr Chen was supported by National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases grant F32DK130543. Drs Shlipak and Estrella are supported by SD-20-387 from the Department of Veterans Affairs. Dr Potok is supported by American Kidney Fund Clinical Scientist in Nephrology Fellow program; Akebia Therapeutics, Inc; and National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases grant K23DK128604. Dr Rifkin is supported by VA Merit Award HSR&D IIR 15-369. The funders had no role in study design, data collection, analysis, reporting, or the decision to submit for publication.

**Financial Disclosure:** Dr Chen is an employee at Genentech, a member of the Roche Group. Drs Estrella and Shlipak receive research funding from Bayer, Inc. Dr Estrella has received an honorarium from Boehringer Ingelheim, Inc. Dr Shlipak reports honoraria from Bayer, Inc., Boehringer Ingelheim, and AstraZeneca and served as a consultant to Cricket Health and Intercept Pharmaceuticals. Dr Shlipak previously served as an advisor to and held stock in TAI Diagnostics. Dr Mark reports research funding from Boehringer Ingelheim; paid advisory boards and or lecture fees from AstraZeneca, Astellas, Napp, Vifor-Fresenius, Novartis, and Pharmacosmos; and travel support from Pharmacosmos, Napp and Vifor. Dr Ix receives research funding from Baxter International and is a member of the Data Safety Monitoring Board for Sanifit International and the Advisory Board for Jnana Pharmaceuticals, Ardelyx Inc., and AstraZeneca. The remaining authors have no disclosures.

**Peer Review:** Received September 1, 2023, as a submission to the expedited consideration track with 2 external peer reviews. Direct editorial input from the Statistical Editor and the Editor-in-Chief. Accepted in revised form December 6, 2023.

## REFERENCES

1. Delgado C, Baweja M, Crews DC, et al. A unifying approach for GFR estimation: recommendations of the NKF-ASN Task Force on reassessing the inclusion of race in diagnosing kidney disease. *Am J Kidney Dis*. 2022;79:268-288.e1.
2. Potok OA, Ix JH, Shlipak MG, et al. The difference between cystatin C- and creatinine-based estimated GFR and associations with frailty and adverse outcomes: a cohort analysis of the Systolic Blood Pressure Intervention Trial (SPRINT). *Am J Kidney Dis*. 2020;76:765-774.
3. Potok OA, Katz R, Bansal N, et al. The difference between cystatin C- and creatinine-based estimated GFR and incident frailty: an analysis of the Cardiovascular Health Study (CHS). *Am J Kidney Dis*. 2020;76:896-898.
4. Chen DC, Shlipak MG, Scherzer R, et al. Association of intraindividual difference in estimated glomerular filtration rate by creatinine vs cystatin C and end-stage kidney disease and mortality. *JAMA Netw Open*. 2022;5:e2148940.
5. Chen DC, Shlipak MG, Scherzer R, et al. Association of intraindividual differences in estimated GFR by creatinine versus cystatin C with incident heart failure. *Am J Kidney Dis*. 2022;80:762-772.e1.

6. Foster MC, Levey AS, Inker LA, et al. Non-GFR determinants of low-molecular-weight serum protein filtration markers in the elderly: AGES-Kidney and MESA-Kidney. *Am J Kidney Dis*. 2017;70:406-414.
7. Liu X, Foster MC, Tighiouart H, et al. Non-GFR determinants of low-molecular-weight serum protein filtration markers in CKD. *Am J Kidney Dis*. 2016;68:892-900.
8. Stevens LA, Schmid CH, Greene T, et al. Factors other than glomerular filtration rate affect serum cystatin C levels. *Kidney Int*. 2009;75:652-660.
9. Knight EL, Verhave JC, Spiegelman D, et al. Factors influencing serum cystatin C levels other than renal function and the impact on renal function measurement. *Kidney Int*. 2004;65:1416-1421.
10. Inker LA, Titan S. Measurement and estimation of GFR for use in clinical practice: core curriculum 2021. *Am J Kidney Dis*. 2021;78:736-749.
11. Levey AS, Inker LA, Coresh J. GFR estimation: from physiology to public health. *Am J Kidney Dis*. 2014;63:820-834.
12. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12:e1001779.
13. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med*. 2012;367:20-29.
14. Inker LA, Eneanya ND, Coresh J, et al. New creatinine- and cystatin C–based equations to estimate GFR without race. *N Engl J Med*. 2021;385:1737-1749.
15. Fry D, Almond R, Moffat S, Gordon M, Singh P. UK Biobank biomarker project. Companion document to accompany serum biomarker data. UK Biobank Organisation. March 11, 2019. Accessed December 9, 2021. https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/serum_biochemistry.pdf
16. Fry D, Almond R, Gordon M, Moffat S. *UK Biobank biomarker project. Details of assays and quality control information for the urinary biomarker data*. UK Biobank Organisation; 2016. Accessed December 9, 2021. https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/urine_assay.pdf
17. Biomarker assay quality procedures. UK Biobank Organisation. April 2, 2019. Accessed December 9, 2021. http://biobank.ctsu.ox.ac.uk/showcase/refer.cgi?id=5636
18. Protocol for a large-scale prospective epidemiological resource. UK Biobank 2007. Accessed December 9, 2021. https://www.ukbiobank.ac.uk/media/gnkeyh2q/study-rationale.pdf
19. Blood pressure. UK Biobank. April 15, 2011. Accessed December 9, 2021. https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/Bloodpressure.pdf
20. Townsend PPP, Beattie A. *Health and Deprivation: Inequality and the North*. Croom Helm; 1988.
21. IPAQ scoring protocol - International Physical Activity Questionnaire. The IPAQ Group. Accessed October 9, 2022. https://www.physio-pedia.com/images/c/c7/Quidelines_for_interpreting_the_IPAQ.pdf
22. Hoeting JA, Madigan D, Raftery AE, Volinsky CT. Bayesian model averaging: a tutorial. *Statist Sci*. 1999;14:382-401.
23. Hsu CY, Yang W, Parikh RV, et al. Race, genetic ancestry, and estimating kidney function in CKD. *N Engl J Med*. 2021;385:1750-1760.
24. Patel AP, Wang MX, Kartoun U, Ng K, Khera AV. Quantifying and understanding the higher risk of atherosclerotic cardiovascular disease among South Asian individuals: results from the UK Biobank Prospective Cohort Study. *Circulation*. 2021;144:410-422.
25. Chen DC, Lees JS, Lu K, et al. 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. *J Am Heart Assoc*. 2023;12:e027079.
26. Kim H, Park JT, Lee J, et al. The difference between cystatin C- and creatinine-based eGFR is associated with adverse cardiovascular outcome in patients with chronic kidney disease. *Atherosclerosis*. 2021;335:53-61.
27. Carrero JJ, Fu EL, Sang Y, et al. Discordances between creatinine- and cystatin C-based estimated GFR and adverse clinical outcomes in routine clinical practice. *Am J Kidney Dis*. 2023;82:534-542.
28. Wang Y, Adingwupu OM, Shlipak MG, et al. Discordance between creatinine-based and cystatin C-based estimated GFR: interpretation according to performance compared to measured GFR. *Kidney Med*. 2023;5:100710.
29. Potok OA, Rifkin DE, Ix JH, et al. Estimated GFR accuracy when cystatin C- and creatinine-based estimates are discrepant in older adults. *Kidney Med*. 2023;5:100628.
30. Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. *Am J Epidemiol*. 2017;186:1026-1034.