Estimated glomerular filtration rate, albuminuria and adverse outcomes

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Key Points (100 word limit)

Question: Are lower values for eGFR (based on either creatinine alone or creatinine and cystatin) and higher values for albuminuria associated with adverse kidney and cardiovascular outcomes?

Findings: In this retrospective individual-level data analysis of 27,503,140 participants from 114 cohorts, lower eGFR and higher albuminuria were each associated with higher rates of adverse kidney outcomes including kidney failure with replacement therapy and acute kidney injury. They were also associated with adverse cardiovascular outcomes including cardiovascular mortality, heart failure, and atrial fibrillation.

Meaning: Lower eGFR values and more severe albuminuria were associated with multiple adverse outcomes.

Abstract

Importance: Chronic kidney disease (low eGFR or albuminuria) affects approximately 14% of people in the United States.

Objective: To evaluate associations of lower eGFR using creatinine alone (eGRFcr), lower eGFR using creatinine combined with cystatin C (eGFRcr-cys), and higher albuminuria with adverse kidney outcomes, cardiovascular outcomes, and other health outcomes.

Design, setting, participants: Retrospective individual-level data analysis of 27,503,140 participants from 114 global cohorts (eGFRcr) and 720,736 participants from 20 cohorts (eGFRcr-cys) and 9,067,753 participants from 114 cohorts (albuminuria) from 1980 to 2021.

Exposures: CKD-EPI 2021 equations for eGFRcr and eGFRcr-cys; albuminuria estimated as urine albumin-to-creatinine ratio (ACR).

Main outcomes and measures: The risk of kidney failure with replacement therapy, all-cause mortality, cardiovascular mortality, acute kidney injury, any hospitalization, coronary heart disease, stroke, heart failure, atrial fibrillation, and peripheral artery disease. Analyses were performed within each cohort and summarized with random-effect meta-analyses.

Results: Within the eGFRcr population (mean age: 54 years, 51% women), mean eGFRcr was 90 ml/min/1.73 m^2 (SD, 22) and median ACR was 11 mg/g (interquartile range 8-16 mg/g). Within the eGFRcr-cys population (mean age: 59 years, 53% women), mean eGFRcr-cys was 88 ml/min/1.73 m^2 (SD, 22) and median ACR was 9 mg/g (interquartile range 6-18 mg/g). Lower eGFR (whether based on eGFRcr or eGFRcr-cys) and higher ACR were each associated with higher risk of all ten adverse outcomes, including in the mildest categories of CKD. For example, among people with ACR <10 mg/g, an eGFRcr 45-59 ml/min/1.73 m^2 was associated with significantly higher hospitalization rates, compared to eGFR 90-105 ml/min/1.73 m^2

(adjusted hazard ratio 1.28, 95% CI: 1.24-1.32; 101 vs. 79 events per 1000 person-years; excess absolute risk 22 events per 1000 person-years, 95% CI: 19 to 25).

Conclusions and relevance: In this retrospective analysis of 114 cohorts, lower eGFRcr, lower eGFRcr-cys, and higher ACR were each associated with increased rates of 10 adverse outcomes, including adverse kidney outcomes, cardiovascular diseases, and hospitalization.

Introduction

Chronic kidney disease (CKD), defined by albuminuria ≥30 mg per day or glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 that persists for at least three months, affects approximately 14% of adults in the US.[1] Both lower estimated GFR (eGFR) values and more severe albuminuria have been associated with higher rates of kidney failure with replacement therapy, acute kidney injury, all-cause and cardiovascular mortality.[2-6]

This study evaluated associations of albuminuria, eGFR, and the combination of albuminuria and eGFR with 10 adverse health outcomes, consisting of incident kidney failure with replacement therapy, all-cause mortality, cardiovascular mortality, acute kidney injury, hospitalization, coronary heart disease, stroke, heart failure, atrial fibrillation, and peripheral artery disease. Associations were evaluated within subgroups of age, sex, and presence of diabetes and cardiovascular disease. GFR was assessed using race-free equations incorporating creatinine alone (eGFRcr) or both creatinine and cystatin C (eGFRcr-cys),[8] and pre-specified analyses included evaluating whether eGFRcr-cys was more strongly associated with adverse outcomes compared to eGFRcr.

Methods

Study Population

Investigators in the CKD Prognosis Consortium (ckdpc.org) were invited to participate in the current meta-analysis if their represented cohorts included participants with both eGFR and albuminuria as well as ≥50 events of at least one outcome. 120 cohorts were evaluated: two did not agree to participate, and four were unable to send data or run code within the time allotted,

leaving 114 participating cohorts. Data sources included 37 observational studies or clinical trials of participants identified from the general population, 49 electronic health record databases, and 28 observational studies or clinical trials of people with CKD. Additional information on included cohorts is included in the **Supplemental Appendix 1**. For measures of prevalence and absolute incidence of adverse outcomes, we used Optum Labs Data Warehouse (OLDW), a data set with de-identified administrative claims and electronic health record (EHR) data on patients followed longitudinally. The EHR-derived data included a subset of data that was normalized and standardized into a single database.[11] The study was approved by the Institutional Review Board (IRB) at the Johns Hopkins Bloomberg School of Public Health. Data were pre-existing and de-identified, but in accordance with individual cohort policies, the study underwent expedited IRB approval. The IRB waived the requirement for informed consent.

Kidney Measures

All participants had serum creatinine measurements with eGFRcr estimated at baseline using the race-free CKD-EPI 2021 creatinine equation [overall population (eGFRcr population)].[8] A subset also had cystatin C measurements with eGFRcr-cys estimated using the CKD-EPI 2021 creatinine-cystatin C equation [population with cystatin C (eGFRcr-cys population)]. Methods for creatinine and cystatin C for each cohort are described in **Supplemental Appendix 1**.[12-14] eGFR was categorized as follows: ≥105, 90-104, 60-89, 45-59, 30-44,15-29, and <15 ml/min/1.73 m^2.

Albuminuria was measured and calculated as urine albumin-to-creatinine ratio (ACR), urine protein-to-creatinine ratio, or dipstick proteinuria. For the former two methods, both spot and 24-hour collections were accepted. For the latter two methods, values were extrapolated to ACR

using a previously published multivariable conversion equation.[7] In the categorical analyses, dipstick proteinuria was classified to ACR categories in the following manner: negative to <10 mg/g, trace to 10-29 mg/g, 1+ to 30-299 mg/g, 2+ to 300-999 mg/g, 3+ or 4+ to 1000 mg/g and higher. In sensitivity analyses without dipstick values, all dipstick measures were classified in the missing ACR category.

Outcomes

The following outcomes were requested from each cohort: all-cause mortality, cardiovascular mortality (death due to cardiovascular disease), kidney failure with replacement therapy (receipt of chronic dialysis or kidney transplantation,), all-cause hospitalization, and hospitalizations for stroke (ischemic or hemorrhagic), myocardial infarction, heart failure (any hospitalization or death with heart failure), acute kidney injury, atrial fibrillation, and peripheral artery disease. Some cohorts linked to the United States Renal Data System (USRDS)[15] in order to ascertain kidney failure with replacement therapy, some cohorts performed expert adjudication for specific outcomes, and some identified outcomes based on ICD-coding alone. Cohort-specific outcome definitions are listed in the **Supplemental Appendix 1**. Individuals with a prior history of the outcome were excluded from the analyses of incident events. Each cohort contributed between 1 and 10 analyses, depending on the outcomes available for each cohort. General population cohorts with fewer than fifty events for a specific outcome and CKD cohorts with fewer than 25 events were excluded from the meta-analysis for the corresponding outcome.

Statistical Analyses

Each analysis was performed separately within each cohort. Hazard ratios were then meta-analyzed using random-effect models. Categories of eGFR (<15, 15-29, 30-44, 45-59, 60-89,

90-104, and 105+ ml/min/1.73 m^2) and ACR (<10, 10-29, 30-299, 300-999, and 1000+ mg/g) at a single visit were used. Interaction terms included all combinations of the eGFR and ACR categories (e.g., the product terms of eGFR <15 ml/min/1.73 m^2 and ACR <10 mg/g, eGFR 15-29 ml/min/1.73 m^2 and ACR <10 mg/g, eGFR 30-44 ml/min/1.73 m^2 and ACR <10 mg/g, etc.). Because relatively few participants had data to contribute to the eGFRcr-cys analyses, less common categories of eGFR and ACR were combined to ensure adequate numbers of events. Hence, the two lowest categories of eGFR were combined (<15 and 15-29 ml/min/1.73 m^2), as were the two highest categories of ACR (ACR 300-999 and 1000+ mg/g). Model adjustment differed for different outcomes and included a subset of the following covariates: age, sex, smoking status (current, former, never), systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, body-mass index, use of anti-hypertensive medications, and a medical history of diabetes, coronary heart disease, stroke, heart failure, atrial fibrillation, peripheral artery disease, cancer, and chronic obstructive pulmonary disease, where relevant (e.g., an analysis of incident peripheral artery disease as an outcome would not include peripheral artery disease as an adjustment variable). All covariate definitions and models are detailed in **Supplemental Appendix 1**. Quantitative covariates were included in the model using a continuous scale. Missing data for albuminuria were treated as a separate category when missingness exceeded 10% in a given cohort, otherwise complete case analysis was performed. For other variables, the extent and handling of missing data are detailed in the **Table S1** and **Supplemental Appendix 1**. The statistical model used for all outcomes was Cox proportional hazards regression. For categorical analyses, hazard ratios were calculated for the general population cohorts and for the electronic health record cohorts, since the CKD cohorts lacked participants in the reference cell (eGFR 90-104 ml/min/1.73 m^2 and ACR <10 mg/g), and models were performed overall and by stratum of age (<65 years, 65+ years) and sex (female, male).

To facilitate comparison of associations across cohorts, outcomes, and by filtration marker (eGFRcr vs. eGFRcr-cys), eGFR and ACR were also modeled continuously: eGFR with linear spline terms with knots at 60 and 105 ml/min/1.73 m^2, and ACR with log-transformation. Model parameters were otherwise identical to those of the categorical analyses. Continuous analyses were performed in all cohorts, including the general population, electronic health record, and CKD cohorts. Beta coefficients from Cox proportional hazards models were then meta-analyzed with random effects, as above. Forest plots were examined to assess heterogeneity of effect sizes across cohorts and cohort characteristics, and subgroup analyses by age, sex, diabetes, and presence of cardiovascular disease were performed. In sensitivity analyses, continuous associations were also examined using other estimating equations for GFR, including previous CKD-EPI equations[16,17] but using only the non-Black race value (CKD-EPI 2009 eGFRcr and CKD-EPI 2012 eGFRcr-cys) and European Kidney Function Collaboration equations[18] (EKFC eGFRcr and eGFRcr-cys).

To determine whether associations were similar across populations or subgroups of populations, comparisons of meta-analyzed beta coefficients (log-hazard ratios) within each combined category of eGFR and ACR were performed using Wilcoxon matched pair signed rank tests, and differences between populations in beta coefficients of the combined eGFR and ACR categories were summarized using median and interquartile interval. A p-value <.05 was considered statistically different.

The largest cohort, the Optum Labs Data Warehouse, an electronic health record population in the US, was used to estimate prevalence of eGFR and ACR categories and the unadjusted

incidence rates of each adverse outcome within categories of eGFR and ACR. For these analyses, a single measure of eGFR and albuminuria were used. The incidence of adverse outcomes was estimated individually within each of the 39 health systems and summarized as median value across each health system (e.g., 19 health systems had higher incidence rates and 19 health systems had lower incidence rates) and 25^{th}-75^{th} percentile. Adjusted excess incidence (i.e., the difference in incidence comparing one combined eGFR and ACR category to the reference) was estimated by treating incidence rates in the median health system in the reference cell among OLDW cohorts as a constant and combining with the meta-analyzed hazard ratios for each cell in the categorical analysis of eGFRcr.

All analyses were conducted using Stata MP 16.1. All statistical testing was two-sided. Statistical significance was determined as $p < .05$.

Results

Study Population

Of the 120 cohorts evaluated for inclusion, 114 cohorts including 27,503,140 people had data available for eGFRcr and were included in analyses. Among these participants, mean age was 54 years (standard deviation (SD), 17), 51% were female, mean eGFRcr was 90 (SD, 22) ml/min/1.73 m^2, and 33.0% had measures of albuminuria. Of those with albuminuria measures, median ACR was 11 mg/g (interquartile range 8-16 mg/g). In the eGFRcr population, the number of cohorts contributing to each outcome ranged from 52 (acute kidney injury) to 108 (all-cause mortality). Rates of adverse outcomes were lowest for peripheral artery disease (median

of 62 cohorts, 1.4 events per 1,000 person-years) and kidney failure with replacement therapy (median of 83 cohorts, 1.3 events per 1,000 person-years) and the highest for hospitalization (median of 52 cohorts, 94 events per 1,000 person-years) (**Table S2**).

20 cohorts with 721,394 people included data for cystatin C (eGFRcr-cys population). For these participants, mean age was 59 years (SD, 12), 53% were female, mean eGFRcr was 89 (SD, 20) ml/min/1.73 m^2 and eGFRcr-cys was 88 (22) ml/min/1.73 m^2, and 44.4% had measures of albuminuria. Among those with albuminuria measures, median ACR was 9 mg/g (interquartile range 6-18 mg/g) (**Table 1**). Clinical characteristics for each cohort are shown in **Table S3** (eGFRcr population) and **Table S4** (eGFRcr-cys population). Most participants who were missing albuminuria data came from EHR cohorts (95.4% of the eGFRcr population and 99.8% of the eGFRcr-cys population).

Overall, the mean follow-up time was 4.8 years (SD, 3.2). For analyses of eGFRcr-cys, mean follow-up was 10.8 years (SD, 4.1) and the number of cohorts contributing data (ranged from 3 (for hospitalizations) to 20 (for all-cause mortality)) (**Table S5**).

Analyses According to eGFRcr and ACR

In the categorical analyses of eGFRcr, compared to the reference of eGFR of 90-105 ml/min/1.73 m^2, lower eGFR categories below eGFR 60 ml/min/1.73 m^2 were significantly associated with higher risk of each outcome. Compared to the reference of ACR <10 mg/g, higher ACR categories were associated with higher rates of each outcome (**Figure 1**). Risks among people with missing ACR were comparable to those within the ACR 10-29 mg/g

category [median (interquartile interval) difference in log-hazard ratios: -0.03 (-0.11 to 0.09), p =.39] (**Table S6**). The patterns of risk associations were similar across each age category and among men and women, although relative risks were weaker in older compared to younger age and very slightly stronger in women compared with men [median (IQI) difference in log-hazard ratios, older vs. younger age groups, -0.45 (-0.70 to -0.14), p <.001; women vs. men: 0.04 (-0.05 to 0.13), p <.001] (**Table S7**).

Compared to eGFRcr 90-105 ml/min/1.73 m^2, CKD category G3a (eGFRcr 45-59 ml/min/1.73 m^2) was significantly associated with higher adjusted hazard ratios of each outcome, even among people with ACR <10 mg/g, ACR 10 to <30 mg/g, or missing ACR (**Table 2**). When stratified by age and sex, relative risks for CKD category G3a were smaller among older adults compared to younger adults [median (IQI) difference in log-hazard ratios, older vs. younger age groups, -0.36 (-0.49 to -0.27), p < .001]; however, all remained statistically significant except for hospitalizations among older adults in people with missing data for ACR. Relative risks between men and women were not significantly different [median (IQI) difference in log-hazard ratios, women vs. men, 0.02 (-0.04 to 0.07), p =.19] (**Table S8**).

In continuous analyses, hazard ratios for the spline term for lower eGFR below 60 ml/min/1.73 m^2 and 8-fold higher ACR were highest for kidney failure with replacement therapy [hazard ratio for eGFR<60 per 15 ml/min/1.73 m^2 lower, 3.89 (95% CI: 3.73, 4.06)], with all (eGFR) or nearly all (ACR) associations statistically significant in the individual cohorts (**Table S9, Figure S1**). In sensitivity analyses excluding albuminuria measured by dipstick, ACR associations were not statistically different from those when dipstick measures were included [median (IQI) difference

in log-hazard ratios, excluding vs. including: -0.02 (-0.02 to -0.004), p =.06] (**Table S10**). Hazard ratios by subgroup of age, sex, diabetes, and cardiovascular disease are shown in **Table S11**.

Analyses According to eGFRcr-cys and ACR

In categorical analyses of eGFRcr-cys, compared to the reference of eGFR of 90-105 ml/min/1.73 m^2, lower eGFR categories below eGFR 60 ml/min/1.73 m^2 were significantly associated with higher risk of each outcome. Compared to the reference of ACR <10 mg/g, higher ACR categories were associated with higher rates of each outcome (**Figure 2, Table S12**). Associations remained statistically significant in subset analyses by age and sex, with weaker relative risks in older compared with younger adults [median (IQI) difference in log-hazard ratios, older vs. younger, -0.14 (-0.36 to 0.03), p<.001; women vs. men: -0.002 (-0.10 to 0.11), p =.53] (**Table S13**). The differences in adjusted hazard ratios for eGFRcr-cys between older and younger age groups was smaller than those seen with eGFRcr [median (IQI) difference in differences, eGFRcr-cys vs. eGFRcr -0.16 (-0.34 to -0.01), p<.001)] (**Table S13**). Risk for all outcomes was increased in CKD category G3a (eGFRcr-cys 45-59 ml/min/1.73 m^2) even among people with levels of albuminuria of <10 mg/g, and these risks remained statistically significant in analyses of subsets by age and sex (**Table 3, Table S14**). Compared to analyses with eGFRcr, risk associations with eGFRcr-cys were stronger and less U-shaped [median (IQI) difference in log-hazard ratios, 0.10 (0.02 to 0.21), p<.001] (**Figure 3**).

Associations with alternative estimating equations for GFR are shown in **Table S15**. The alternative estimating equations were highly correlated with eGFR estimated using CKD-EPI 2021 in all cohorts (range of Pearson correlations between eGFRcr estimated with CKD-EPI 2021 and EKFC, 0.98-1; between eGFRcr-cys estimated with CKD-EPI 2021 and EKFC, 0.93-

0.99; between eGFRcr estimated with CKD-EPI 2021 and CKD-EPI 2009 NB, 0.99-1; between eGFRcr-cys estimated with CKD-EPI 2021 and CKD-EPI 2012 NB 0.996-1).

Prevalence of CKD and Incidence of Adverse Outcomes

In a large, national US electronic health record database, 63% of people were missing a measure of albuminuria (including dipstick measures). The prevalence of each category of eGFRcr was similar with and without the inclusion of those missing albuminuria: for example, 9.6% and 10% of individuals had eGFRcr <60 ml/min/1.73 m^2, respectively. Among those with measures of albuminuria, the prevalence of ACR 30-299 mg/g (category A2), ACR 300-999 mg/g and ACR 1000+ mg/g was 9.9%, 3.1%, and 1.2%, respectively (**Table S16**).

The unadjusted incidence rate of each outcome was higher with more severe categories of eGFR and ACR. Hospitalizations were the most common adverse outcome. Rates per 1000 person-years in the reference group (eGFR 90-104 ml/min/1.73m^2 and ACR<10 mg/g) from most common to least common were: hospitalizations 79, all-cause mortality 11, acute kidney injury 4.5, atrial fibrillation 4.0, heart failure 3.9, cardiovascular mortality 2.7, stroke 2.1, myocardial infarction 1.7, peripheral artery disease 0.6 and kidney failure with replacement therapy 0.1 (**Table S17**). For the most severe CKD categories (eGFR<15 ml/min/1.73m^2 and ACR 1000+ mg/g), the highest rates of adverse outcomes per 1000 person-years were hospitalizations (504), mortality (187) and kidney failure with replacement therapy (175). Adjusted excess mortality is shown in **Table S18**. Unadjusted incidence rates by age and sex are shown in **Table S19-22**.

Discussion

This individual-participant data meta-analysis of more than 27 million people evaluated associations of eGFR and albuminuria with ten adverse outcomes that included kidney outcomes, all-cause mortality, cardiovascular mortality, hospitalizations, and other cardiovascular events. There were strong, graded associations with lower eGFR and adverse outcomes for the new, race-free 2021 CKD-EPI eGFRcr equation[8] and also when cystatin C was included as an additional filtration marker in eGFRcr-cys. The pattern of associations persisted irrespective of age, sex, diabetes, and cardiovascular disease and were stronger for eGFRcr-cys as compared with eGFRcr. This work supports recent recommendations to increase the use of cystatin C in clinical practice.[9,10]

Prior meta-analyses of eGFR and albuminuria with adverse outcomes evaluated only 5 adverse outcomes in 1.2 million participants and 21 cohorts from 14 countries.[2-6] These reports used eGFRcr estimated with the MDRD Study equation, which includes race, and an unvalidated equation to impute urine ACR from urine protein-to-creatinine ratios. In this study, eGFR was calculated using the race-free estimating equations for both eGFRcr and eGFRcr-cys per 2021 recommendations by the National Kidney Foundation and American Society of Nephrology.[9,10] ACR was imputed from urine protein-to-creatinine ratio and urine dipstick protein using a validated equation.[7,19] This study adds to current literature by providing strong evidence for the classification and risk stratification of CKD using the most up-to-date estimates of GFR, more categories of albuminuria, and additional cardiovascular outcomes. The use of 114 cohorts from across the world enhances generalizability of the results.

The results underscore the importance of albuminuria in risk assessment. Even mildly elevated albuminuria (A2: ACR 30-299 mg/g) was statistically significantly associated with increased risk for all outcomes. The adjusted excess risk of mortality associated with category A3 (ACR 300-999 mg/g) at normal eGFR was comparable to that of stage 1 colon cancer (17 deaths per 1000 person-years vs. 5-year survival rate of 91%).[20] Similar to previous observations, however, this study demonstrates low rates of albuminuria measurement in electronic health records.[21]

Some guidelines recommend cystatin C testing in patients with CKD, and others discourage measurement of cystatin C.[2,24] The current study provides evidence as to the potential utility of the combined eGFRcr-cys equation. With eGFRcr, there was a U-shape association of eGFR with study outcomes, with higher risk in both lower eGFRcr <60 ml/min/1.73 m^2 and higher eGFRcr >105 ml/min/1.73 m^2. This finding may indicate imprecision and systematic overestimation of GFR among people who progress to adverse events (thus contributing to the U-shaped curve). With eGFRcr-cys, there was a more linear risk relationship. Both creatinine and cystatin C values are affected by clinical characteristics independent of GFR, [25] and the most widely recognized non-GFR determinant for creatinine is muscle mass.[26] Persons with low muscle mass, on average, have higher eGFRcr than eGFRcys.[27] Differences in relative risks between eGFRcr and eGFRcr-cys were observed among older adults. suggesting that when clinically available, additional use of cystatin C could better identify high-risk individuals, particularly among older populations.

This study has several strengths. First, the sample size was large and included people from multiple countries. Second, the most recent eGFR equations were evaluated. Third, results suggested that deviations in risk associations across type, geographical location, or

characteristic of cohorts were unlikely. Fourth, subgroup analyses demonstrated the higher risk associated with lower eGFR and higher albuminuria across categories of age, sex, presence of diabetes, and history of cardiovascular disease.

Limitations

This study has several limitations. First, other estimating equations of GFR, were not comprehensively tested.[16,18] Second, the included cohorts used different study designs and protocols for outcome ascertainment. Outcomes were often based on ICD codes, which have variable sensitivity and specificity for each outcome measure. Third, cystatin C was available in only a subset of cohorts. Fourth, data were observational and causal inferences should not be made.[28] Fifth, although findings support the use of eGFRcr-cys in the detection and staging of CKD, cystatin C is not widely available and may be expensive. Sixth, some variables such as baseline heart failure were missing from several cohorts, and may have confounded the relationship between eGFR and outcomes, particularly acute kidney injury.

Conclusion

In this retrospective analysis of 114 cohorts, lower eGFRcr, lower eGFRcr-cys, and higher ACR were each associated with increased rates of 10 adverse outcomes, including adverse kidney outcomes, cardiovascular diseases, and hospitalization.

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Data Availability Statement: Under agreement with the participating cohorts, CKD-PC cannot share individual data with third parties. Inquiries regarding specific analyses should be made to ckdpc@jhmi.edu. Investigators may approach the original cohorts regarding their own policies for data sharing (e.g., https://sites.cscc.unc.edu/aric/distribution-agreements for the Atherosclerosis Risk in Communities Study).

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Table 1. Participant characteristics for the eGFRcr and eGFRcr-cys populations

	eGFRcr population	**eGFRcr-cys population**
N of Cohorts	114	20
N of participants	27,503,140	721,394
Age (SD), years	54 (17)	59 (12)
Female, %	51%	53%
Male, %	49%	47%
Mean follow-up, years	4.8 (3.3)	10.8 (4.1)
Medical History: Comorbid Conditions		
Medications for hypertension, %	17%	27%
Diabetes mellitus, %	15%	9.4%
Former smoker, %	13%	35%
Current smoker, %	11%	11%
Coronary heart disease, %	9.9%	6.3%
History of cancer, %	13%	11%
Chronic obstructive pulmonary disease, %	7.5%	2.4%
Atrial fibrillation, %	4.5%	4.7%
History of heart failure, %	3.5%	3.2%
History of stroke, %	3.2%	3.5%
Peripheral artery disease, %	1.6%	1.0%
Medical History: Vital Signs and Laboratory Studies		
Systolic blood pressure (SD), mmHg	126 (17)	138 (20)
Body-mass index (SD), kg/m^2	29 (7)	28 (5)
Total cholesterol (SD), mmol/L	4.7 (1.3)	5.0 (1.1)
High-density lipoprotein (SD), mmol/L	1.3 (0.4)	1.3 (0.4)
eGFR (SD), ml/min/1.73 m^2	90 (22)	89 (20)
eGFRcr-cys (SD), ml/min/1.73 m^2		88 (22)
Median albuminuria (IQR), mg/g	11 (8-16)	9 (6-18)

*The column N is not necessarily the denominator for each characteristic. The proportion with missing data for each characteristic is shown in Table S1. For albuminuria, available data represented <50% of the analytic population: 9,067,753 (33.0%) for eGFRcr and 320,443 (44.4%) for the eGFRcr-cys population. Detailed definitions of each of these elements are provided in Supplemental Appendix 1.

Figure 1. Categorical analysis of the associations of eGFR and albuminuria with subsequent adverse outcomes: eGFRcr population

Overall	Urine albumin-creatinine ratio, mg/g					Urine albumin-creatinine ratio,, mg/g				
eGFRcr	<10	10-29	30-299	300-999	1000+	<10	10-29	30-299	300-999	1000+
	All-cause Mortality: 82 cohorts participants=26,444,384; events=2,604,028					Myocardial Infarction: 64 cohorts participants=22,838,356; events=451,063				
105+	1.6	2.2	2.9	4.3	5.8	1.1	1.4	2.0	2.7	3.8
90-104	ref	1.3	1.8	2.6	3.1	ref	1.3	1.6	2.2	3.2
60-89	1.0	1.3	1.7	2.2	2.8	1.1	1.3	1.6	2.2	3.1
45-59	1.3	1.6	2.0	2.4	3.1	1.4	1.7	2.0	2.8	3.7
30-44	1.8	2.0	2.5	3.2	3.9	1.9	2.0	2.4	3.2	4.3
15-29	2.8	2.8	3.3	4.1	5.6	2.7	3.1	3.1	4.2	5.1
<15	4.6	5.0	5.3	6.0	7.0	4.6	5.6	4.8	6.0	6.0
	Cardiovascular Mortality: 76 cohorts participants=26,022,346; events=776,441					Stroke: 68 cohorts participants=24,746,436; events=461,785				
105+	1.4	2.0	3.0	4.1	5.4	1.2	1.6	2.2	3.1	4.3
90-104	ref	1.3	1.9	2.7	3.6	ref	1.3	1.6	2.4	3.1
60-89	1.0	1.4	1.7	2.4	3.2	1.1	1.3	1.7	2.2	3.0
45-59	1.4	1.7	2.2	2.8	3.8	1.4	1.6	1.9	2.3	2.9
30-44	2.0	2.3	2.8	3.7	4.6	1.6	1.7	2.0	2.4	3.0
15-29	3.2	3.1	3.5	5.0	6.5	1.8	2.1	2.1	2.7	3.0
<15	6.1	6.4	6.4	7.3	8.2	3.2	2.8	2.9	3.2	3.8
	Kidney Failure with Replacement Therapy: 57 cohorts; participants=25,466,956; events=158,846					Heart Failure: 61 cohorts participants=24,603,016; events=1,132,443				
105+	0.5	1.2	2.9	7.7	25	1.2	1.7	2.7	4.2	6.9
90-104	ref	1.8	4.3	12	43	ref	1.3	2.0	2.8	4.2
60-89	2.3	4.9	10	27	85	1.1	1.4	1.9	2.7	4.2
45-59	13	19	37	89	236	1.6	1.8	2.4	3.4	5.0
30-44	50	58	115	240	463	2.2	2.5	3.1	4.2	6.5
15-29	283	301	443	796	1253	3.6	3.5	4.1	5.8	8.1
<15	770	1040	1618	2297	2547	5.1	5.7	5.8	7.9	9.9
	Acute Kidney Injury: 49 cohorts participants=23,914,614; events=1,408,929					Atrial Fibrillation: 50 cohorts participants=22,886,642; events=1,068,701				
105+	1.0	1.6	2.4	3.7	5.5	1.1	1.3	1.7	2.4	3.5
90-104	ref	1.4	2.1	3.2	5.0	ref	1.2	1.5	1.9	2.3
60-89	1.6	2.2	3.1	4.3	6.7	1.0	1.2	1.4	1.7	2.2
45-59	3.5	4.0	5.1	6.9	9.0	1.2	1.3	1.5	1.8	2.4
30-44	5.6	5.9	6.8	8.6	11	1.4	1.5	1.7	2.0	2.4
15-29	8.3	8.0	8.5	9.9	10	1.9	1.8	2.0	2.6	3.0
<15	8.5	11	7.9	5.5	5.7	2.6	2.5	3.1	3.6	4.2
	Hospitalization: 49 cohorts participants=25,426,722; events=8,398,637					Peripheral Artery Disease: 54 cohorts participants=24,830,794; events=378,924				
105+	1.4	1.7	2.1	2.1	2.3	0.9	1.4	1.9	2.8	5.0
90-104	ref	1.1	1.3	1.5	1.7	ref	1.3	1.9	2.8	4.3
60-89	1.0	1.1	1.3	1.5	1.8	1.0	1.3	1.8	2.5	3.8
45-59	1.3	1.3	1.5	1.7	2.1	1.5	1.7	2.1	2.9	4.2
30-44	1.5	1.5	1.6	1.9	2.3	2.0	1.9	2.5	3.6	5.0

15-29	1.8	1.8	1.9	2.4	2.8	3.3	3.3	3.8	5.7	8.1
<15	2.7	2.8	3.0	3.2	3.8	9.1	9.0	9.6	13	14

* Ref: reference cell. Numbers reflect the adjusted hazard ratio compared with the reference cell. Adjustment variables included: age, sex, smoking status (current, former, never), systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, body-mass index, use of anti-hypertensive medications, and a medical history of diabetes, coronary heart disease, stroke, heart failure, atrial fibrillation, peripheral artery disease, cancer, and chronic obstructive pulmonary disease, where relevant. All models are shown in Supplemental Appendix 1. The cohorts used in these analyses are the general population and electronic health record cohorts (CKD cohorts do not have sufficient participants in the reference cells) and a missing albuminuria category was included. Sample sizes include participants who are missing albuminuria. Adjusted hazard ratios for participants missing albuminuria measures, as well as N/n for individual cells, are shown in Supplemental Table 6. The colors were determined for each outcome separately using the following rule: the percentile shaded the darkest green color corresponds to the proportion of cells in the grid without CKD (e.g., 6 out of 35 cells with eGFR ≥60 ml/min/1.73 m^2 and ACR <30 mg/g), and the percentile shaded the darkest red color corresponds to proportion expected to be at highest risk (e.g., 11 out of 35 cells with eGFR <15 ml/1.73 m^2 and ACR 1000+ mg/g). In this manner, the numbers of green and red cells are consistent across outcomes, but the patterns are allowed to differ.

Table 2. Adjusted hazard ratios of subsequent adverse outcomes for individuals with mild-moderate kidney disease (CKD category G3a with urine albumin-to-creatinine rate (ACR) <10 mg/g, ACR 10-29 mg/g, and missing ACR)

	eGFRcr population				**eGFRcr-cys population**		
Hazard Ratio (95% CI)	**eGFRcr 90-105 and ACR<10**	**eGFRcr 45-59 and ACR<10**	**eGFRcr 45-59 and ACR 10-29**	**eGFRcr 45-59 and ACR missing**	**eGFRcr-cys 90-105 and ACR<10**	**eGFRcr-cys 45-59 and ACR<10**	**eGFRcr-cys 45-59 and ACR 10-29**
All-cause mortality	ref	1.3 (1.2, 1.4)	1.6 (1.5, 1.7)	1.6 (1.5, 1.7)	ref	1.7 (1.5, 1.8)	2.2 (2.1, 2.3)
Cardiovascular mortality	ref	1.4 (1.3, 1.4)	1.7 (1.5, 1.9)	1.6 (1.4, 1.8)	ref	1.9 (1.6, 2.2)	2.7 (2.4, 3.0)
Kidney failure with replacement therapy	ref	12.7 (11.1, 14.6)	19.0 (15.6, 23.1)	17.7 (14.2, 22.1)	ref	5.8 (2.4, 14.2)	12.5 (5.4, 29.1)
Acute kidney injury	ref	3.5 (3.3, 3.7)	4.0 (3.7, 4.3)	3.8 (3.5, 4.2)	ref	3.9 (3.5, 4.4)	4.7 (4.2, 5.2)
Hospitalization	ref	1.3 (1.2, 1.3)	1.3 (1.3, 1.4)	1.2 (1.2, 1.3)	ref	1.3 (1.1, 1.5)	1.4 (1.1, 1.7)
Coronary heart disease	ref	1.4 (1.3, 1.5)	1.7 (1.6, 1.8)	1.6 (1.4, 1.8)	ref	1.6 (1.3, 2.0)	2.0 (1.7, 2.3)
Stroke	ref	1.4 (1.3, 1.5)	1.6 (1.5, 1.7)	1.5 (1.4, 1.7)	ref	1.6 (1.4, 1.9)	1.8 (1.5, 2.2)
Heart failure	ref	1.6 (1.5, 1.7)	1.8 (1.7, 2.0)	1.9 (1.8, 2.1)	ref	1.5 (1.1, 2.1)	2.2 (1.8, 2.8)
Atrial fibrillation	ref	1.2 (1.2, 1.3)	1.3 (1.3, 1.4)	1.4 (1.3, 1.5)	ref	1.3 (1.1, 1.5)	1.6 (1.5, 1.9)
Peripheral artery disease	ref	1.5 (1.3, 1.6)	1.8 (1.6, 2.0)	1.9 (1.6, 2.1)	ref	2.5 (1.5, 4.2)	3.7 (2.7, 4.9)

** Ref: reference cell: eGFR 90-105 ml/min/1.73 m^2 and ACR <10 mg/g. Numbers reflect the adjusted hazard ratio compared with the reference cell. Adjustment variables included: age, sex, smoking status (current, former, never), systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, body-mass index, use of anti-hypertensive medications, and a medical history of diabetes, coronary heart disease, stroke, heart failure, atrial fibrillation, peripheral artery disease, cancer, and chronic obstructive pulmonary disease, where relevant. All models are shown in Supplemental Appendix 1. The cohorts used in these analyses are the general population and electronic health record cohorts (CKD cohorts do not have sufficient participants in the reference cells) and a missing albuminuria category was included. All p-values <0.001. eGFR, estimated glomerular filtration rate. ACR, urine albumin-to-creatinine ratio. Number of cohorts are listed in Table 2 and 4, and cell-specific sample size and events are listed in Supplemental Table 6 and 12. CKD is staged into G categories and A categories, with higher categories indicating more severe disease.

Figure 2. Categorical analysis of the associations of eGFR and albuminuria with subsequent adverse outcomes in the eGFRcr-cys population

	Urine albumin-creatinine ratio, mg/g				Urine albumin-creatinine ratio, mg/g			
eGFRcr-cys	**<10**	**10-29**	**30-299**	**300+**	**<10**	**10-29**	**30-299**	**300+**
	All-cause Mortality: 11 cohorts participants=692,802; events=97,006				**Myocardial Infarction: 10 cohorts participants=649,365; events=17,926**			
105+	1.0	1.3	1.6	2.5	0.9	1.2	1.4	2.8
90-104	ref	1.3	1.5	2.0	ref	1.2	1.4	1.8
60-89	1.2	1.5	1.9	2.5	1.2	1.4	1.5	1.9
45-59	1.7	2.2	2.5	3.3	1.6	1.9	2.3	3.3
30-44	2.3	2.6	3.4	4.4	2.1	2.6	3.1	3.3
<30	3.6	4.0	5.5	7.1	5.1	3.0	4.9	5.0
	Cardiovascular Mortality: 11 cohorts participants=692,322, events=25,322				**Stroke: 9 cohorts participants=662,605; events=16,909**			
105+	1.0	1.4	1.8	4.1	1.0	1.2	1.6	2.5
90-104	ref	1.5	1.6	2.9	ref	1.2	1.5	2.3
60-89	1.2	1.7	2.3	3.4	1.2	1.4	1.8	2.5
45-59	1.9	2.7	3.2	4.6	1.6	1.7	2.1	2.7
30-44	2.5	3.5	4.5	5.9	1.7	2.0	2.3	2.6
<30	5.8	5.0	6.1	8.7	1.9	2.3	2.8	4.4
	Kidney Failure with Replacement Therapy: 5 cohorts; participants=630,370; events=4,306				**Heart Failure: 9 cohorts participants=641,298; events=27,406**			
105+	0.6	0.8	2.3	10	0.9	1.2	1.7	3.7
90-104	ref	1.5	4.5	11	ref	1.3	1.4	2.5
60-89	1.9	3.7	8.3	31	1.2	1.6	1.9	3.0
45-59	5.8	13	25	73	1.5	2.2	3.0	4.1
30-44	20	23	78	191	2.5	2.9	4.1	5.7
<30	111	261	343	580	5.3	4.8	6.5	7.7
	Acute Kidney Injury: 5 cohorts participants=630,370; events=24,062				**Atrial Fibrillation: 5 cohorts participants=607,102; events=37,278**			
105+	0.8	1.0	1.4	3.5	0.9	1.0	1.1	1.9
90-104	ref	1.3	1.7	2.8	ref	1.2	1.4	2.2
60-89	1.6	2.5	2.9	5.3	1.1	1.3	1.5	2.0
45-59	3.9	4.7	5.5	7.5	1.3	1.6	1.8	2.2
30-44	5.8	7.0	8.4	10	1.6	2.0	2.2	2.5
<30	11	12	12	21	2.0	2.0	2.7	4.4
	Hospitalization: 3 cohorts participants=630,489; events=464,894				**Peripheral Artery Disease: 6 cohorts participants=642,624; events=3,943**			
105+	1.0	1.1	1.1	1.6	0.9	1.9	1.8	2.9
90-104	ref	1.1	1.3	1.4	ref	1.5	2.0	3.2
60-89	1.1	1.2	1.3	1.6	1.3	1.8	2.1	3.9
45-59	1.3	1.4	1.5	1.7	2.5	3.7	3.3	4.0
30-44	1.5	1.5	1.6	2.1	4.0	3.7	4.5	6.9
<30	1.8	2.0	2.1	3.0	7.8	4.5	9.0	12

* Ref: reference cell. Numbers reflect the adjusted hazard ratio compared with the reference cell. Adjustment variables included: age, sex, smoking status (current, former, never), systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, body-mass index, use of anti-hypertensive medications, and a medical history of diabetes, coronary heart disease, stroke, heart failure, atrial fibrillation, peripheral artery disease, cancer, and chronic obstructive pulmonary disease, where relevant. All models are shown in Supplemental Appendix 1. The

cohorts used in these analyses are the general population and electronic health record cohorts (CKD cohorts do not have sufficient participants in the reference cells) and a missing albuminuria category was included. Sample sizes include participants who are missing albuminuria. Adjusted hazard ratios for participants missing albuminuria measures, as well as N/n for individual cells, are shown in Supplemental Table 12.The colors were determined for each outcome separately using the following rule: the percentile shaded the darkest green color corresponds to the proportion of cells in the grid without CKD (e.g., 6 out of 24 cells), and the percentile shaded the darkest red color corresponds to proportion expected to be at highest risk (e.g., 5 out of 24 cells). In this manner, the numbers of green and red cells are consistent across outcomes, but the patterns are allowed to differ.

Figure 3. Hazard ratios for adverse outcomes using a continuous model of eGFR in the population with creatinine and cystatin C, comparison of the shape of associations between eGFRcr and eGFRcr-cys with outcomes

Panel A. Associations of eGFRcr with all-cause mortality, cardiovascular mortality, all-cause hospitalizations, myocardial infarction, stroke, heart failure, atrial fibrillation, peripheral artery disease.

Panel B. Associations of eGFRcr-cys with all-cause mortality, cardiovascular mortality, all-cause hospitalizations, myocardial infarction, stroke, heart failure, atrial fibrillation, peripheral artery disease.

Panel C. Associations of eGFRcr with kidney failure with replacement therapy and acute kidney injury.

Panel D. Associations of eGFRcr-cys with kidney failure with replacement therapy and acute kidney injury.

Dots indicate that the 95% confidence interval for the hazard ratio from this spline model does not include 1.0 (which is indicated with a diamond as the reference point at eGFR 90 ml/min/1.73 m^2).