Population-based estimated Glomerular Filtration Rate distributions and associated health outcomes provide opportunities for early identification of and primary prevention of chronic kidney disease

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Abstract

Introduction: There are currently no established strategies for early identification and primary prevention of chronic kidney disease (CKD). Automatic reporting of estimated glomerular filtration rate (eGFR) allows opportunistic CKD screening. Here, we hypothesized that comparison with population-based eGFR distributions may further help identify individuals at elevated risk.

Methods: A population-based observational cohort study including adults aged 40 to 100 years with routine serum/plasma creatinine tests (Stockholm CREAtinine Measurements project) between 2006 and 2021 was conducted. The cohort captured 1,179,501 unique individuals (80% of the population in the region) with 6,914,993 repeated annual eGFR measurements. After computing eGFR distributions by age and sex, cause-specific Cox regressions evaluated the associations between eGFR percentiles and risks of kidney failure with replacement therapy (KFRT) and death.

Results: Median eGFR (2009 CKD-EPI) was lower at higher age, from 104–106 ml/min per 1.73 m^2 (men–women) at age 40 to 45–50 ml/min per 1.73 m^2 at age 100. Exclusion of individuals with selected comorbid conditions or adjustment for the non-tested population had minimal impact on eGFR distributions. Compared to the central percentiles (47.5–52.5th), eGFR percentiles below the 25th were significantly associated with increased risk of KFRT, and both low and high eGFR percentiles were associated with increased mortality. Associations were consistent across age groups. Among 421,547 individuals with eGFR 60 ml/min per 1.73 m^2 or more who were below the 25th percentile, only 24% underwent albuminuria/proteinuria testing in the adjacent year and could have benefited from additional diagnostic work-up.

Conclusions: Our study shows that eGFR values below the 25th percentile of the population distribution are associated with increased risks of kidney failure and death. Population-based eGFR charts may complement current automatic reporting systems and provide opportunities for early identification and primary prevention of CKD.

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Lay Summary

There are no optimal strategies for primary prevention of chronic kidney disease (CKD). This study tried to elucidate the distribution of estimated glomerular filtration rate (eGFR) in the general population and explore the hypothesis that deviations from the median distribution, even within the normal range, were associated with an increased risk of kidney failure requiring replacement therapy (KFRT) or death. In a large cohort covering 80% of the adult population of the Stockholm region aged 40–100 years, we observed that median eGFR was progressively lower at a higher age. Also, eGFR values below the 25th percentile were found to be significantly associated with increased risks of KFRT, whereas both low and high eGFR percentiles were linked to elevated mortality rates. This has implications in clinical practice. Population-based eGFR distributions may serve as a complementary tool to current automatic eGFR reporting and provide opportunities to improve early identification of people with CKD or at increased risk of CKD, thus assisting in primary prevention strategies.

Chronic kidney disease (CKD) affects 850 million people worldwide and is on track to become the fifth leading cause of years of life lost by 2040.[1,2] Individuals with CKD face increased risk of progression to kidney failure requiring dialysis or transplantation, as well as cardiovascular disease (CVD), cancer, severe infections, and premature death.[3,4] CKD significantly reduces quality of life and life expectancy, and imposes a substantial economic burden on society.[1]

Early identification of CKD enables timely interventions to treat the cause of kidney disease and delay disease progression. However, there are currently no established primary prevention strategies for CKD. One proposed approach is systematic population screening using estimated glomerular filtration rate (eGFR) and albuminuria; however, the cost-effectiveness and practicality of such screening remain debated.[5] In practice, CKD detection relies largely on opportunistic screening from routine serum creatinine measurement and automatic eGFR reporting. Introduced in the early 2000s, automatic eGFR reporting has improved CKD awareness and increased referrals to nephrology.[6] However, screening using an eGFR threshold of <60 ml/min per 1.73 m^2 means diagnosis and intervention often occur at later stages of CKD, after approximately 50% of kidney function has already been lost.[7] Earlier detection and prediction of risk of developing CKD could be achieved through albuminuria testing,[5] but despite longstanding guideline recommendations,[7–10] many clinicians do not routinely evaluate albuminuria in high-risk patients, such as those with diabetes, hypertension, or CVD.[11,12] Primary prevention relies on treatment of CKD risk factors but is not focused specifically on people with loss of kidney function before the onset of CKD, who may benefit from more intensive intervention. There is a clear need for innovative strategies for early identification and primary prevention of CKD.

Most adults (>94%) have an eGFR above 60 ml/min per 1.73 m^2.[13] Although such values are not considered decreased and may not trigger clinical intervention, they can still be higher or lower than the median for a person's age and sex. We hypothesized that analogous to pediatric growth charts or spirometry reference values,[14,15] population-based eGFR distributions could help identify individuals at risk of adverse outcomes of CKD. Previous attempts to define population-based eGFR distributions have been limited by small or unrepresentative sample sizes, narrow age ranges, selection biases, or heterogeneous data sources.[16–23] Importantly, it remains unclear whether deviations in eGFR distribution are associated with adverse outcomes.[23] Demonstrating such an association would support the use of eGFR distributions as complementary tools for identifying individuals who may benefit from further evaluation—such as albuminuria testing—and potentially preventive interventions.

In this study, we used health care data from a large, representative Swedish region to construct age- and sex-specific eGFR distributions in adults 40 years and older. We then evaluated whether individuals whose eGFR deviated from the median distribution were at increased risk of kidney failure requiring replacement therapy (KFRT) or death.

METHODS

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[24] The study protocol was approved by the Regional Ethical Review Board in Stockholm (2017/793-31). Because all data were deidentified by the Swedish Board of Health and Welfare, informed consent was not deemed necessary.

Data source

We used data from the Stockholm CREAtinine Measurements (SCREAM) project,[25] a health care utilization database of residents in Stockholm, Sweden, which captures the complete health care use of all the citizens in the region. The Stockholm region is the most populated metropolitan area in Sweden, capturing approximately 25% of the total Swedish population. Linkage with a variety of government-run databases, using the unique personal identification number of each inhabitant in Sweden, allowed precise ascertainment of the arrival/departure from the census of the region (both migration and death), and extraction of all laboratory tests, issued clinical diagnoses, and dispensed medications. The regional ethical review board in Stockholm approved the study and waived the need for informed consent because the data made available to researchers deidentified.

Part I: Generating eGFR distributions

Study design. We extracted information on health data from all citizens of the Stockholm region during 2006–2021 and identified all plasma or serum creatinine measurements conducted in any form of outpatient encounter (specialist care, primary care, or private-subsidized care). To generate population distributions representative of the region's population at risk for adverse outcomes of CKD, we restricted our analyses to individuals 40 years or older at the time of testing. We selected this age because routine creatinine testing is more common at older age and leads to higher population coverage.[26] Tests performed after an individual reached KFRT were excluded. If more than 1 creatinine test was available per chronological age (e.g., a person underwent 3 tests of creatinine while he/she was 72 years old), we calculated the median value, which may better represent the GFR during that year of age. In this way, we created a series of observations of individuals with an annual creatinine test (sole or median value) per chronological age. The index date at each chronological age was set as the date of the last creatinine test.

Using these serum/plasma creatinine tests, we calculated eGFR and constructed charts of population-based eGFR distributions stratified by chronological age and sex. We displayed them graphically to depict the 10th, 25th, 50th, 75th, and 90th percentile curves for each sex across ages 40–100 years. We present our primary findings with eGFR estimated using the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation (assuming all participants to be non-Black).[27] In addition, we

also generated population-based distributions using alternative validated creatinine-based eGFR (eGFRcr) equations: 2021 CKD-EPI (recommended in the United States),[28] European Kidney Function Consortium,[29] and revised Lund-Malmö creatinine equations.[30] These equations are known to yield systematic differences in eGFR, reflecting differences in measurement methods, demographics, and clinical characteristics in the equation development populations and differences in methods for equation development.[31,32]

At each creatinine test (including repeated annual tests when available), we extracted information on demographics (age and sex) and chronic comorbid conditions (hypertension, diabetes, and CVD [composite of myocardial infarction], peripheral arterial disease, cerebrovascular disease, and heart failure history) defined through the presence of International Classification of Diseases, 10th Revision diagnoses in medical records with a look-back period up to 1997 (Supplementary Table S1). We also extracted information on all albuminuria tests performed in the year before or in the year after each eGFR. All methods of albuminuria testing were considered: dipstick albuminuria or proteinuria tests, 24-hour and spot albumin concentrations, and urinary protein-to-creatinine ratio or urinary albumin-to-creatinine ratio tests. Urinary protein-to-creatinine ratio and dipstick tests were approximated to urinary albumin-to-creatinine ratio values using previously validated equations[33] and then categorized (A1, <30 mg/g; A2, 30–300 mg/g; A3, >300 mg/g) according to the Kidney Disease: Improving Global Outcomes (KDIGO) classification,[4] along with a "missing" category if absent. In cases with more than 1 eligible albuminuria test in the year before a given creatinine test, we selected the one closest in time. Comorbid conditions were presented for descriptive purposes or stratification. Because the dataset was compiled from comprehensive and complete regional health records, there were no missing data for the variables used in this analysis.

Supporting analysis and online eGFR percentile calculator. GFR declines because of aging and disease. We chose to develop population-based eGFR distributions and not "normative" eGFR distributions, both because it is difficult to separate aging from disease and because excluding people with certain comorbid conditions would result in selection bias. To support this decision, we plotted the eGFR distribution of the total population and those with selected comorbid conditions known to influence GFR, namely diabetes, hypertension, and CVD. Building on these distributions, we developed a user-friendly online tool that enables clinicians to contextualize an individual's eGFR by comparing it with age- and sex-specific percentile curves (https://scream.meb.ki.se/egfr-percentiles/).

Sensitivity analysis. To evaluate whether our eGFR distributions are representative of the Stockholm population or instead affected by the indications of testing, we accounted for measured characteristics of the nontested population through inverse probability weighting.[13] Briefly, at each calendar year, we weighted the creatinine-tested population for the inverse probability of being tested, assuming that the test indication is adequately measured and accounted for with our selected covariates. This approach assigns higher weights to under-represented groups, making the sample more representative of the target population.

To achieve this, we created 16 calendar year cohorts (from 2006 to 2021) with all residents of the Stockholm region aged 40–100 years. For each calendar year cohort, we separated the populations undergoing or not undergoing creatinine testing and set the index date as the date of the last creatinine test available, as 31 December of that calendar year if no test was performed, as the date of emigration from the region, or as the date of death. We then extracted information on study covariates and calculated the probability (i.e., propensity score) of receiving a creatinine test in each calendar year using multivariable logistic regression conditional on the aforementioned covariates. In each calendar year, the inverse probability weightings were calculated as 1/propensity score if an individual received a creatinine test in that calendar year and 1/(1 – propensity score) if an individual did not receive a test in that calendar year. In this way, we obtained the inverse probability weightings for all the outpatient creatinine tests in each calendar year, and we presented the eGFR distributions based on the eGFR measurements from the weighted pseudo population.

Part II: Validation of eGFR distributions against the risks of kidney failure with replacement therapy and death

We explored associations between age- and sex-specific eGFR percentiles according to the eGFR distributions, and the risks of KFRT and all-cause death, which are well known to be associated with eGFR in middle age and older adults, and were selected because of completeness of ascertainment and importance. The date of KFRT was identified through linkage with the nationwide Swedish Renal Register,[34] and the date of all-cause death through the Cause of Death Register.[35] Patients were followed until the event, emigration from the Stockholm region, or 31 December 2021.

The exposure was the age- and sex-specific eGFR percentile, categorized into intervals of 5 percentiles (e.g., 2.5th–7.5th and 7.5th–12.5th percentiles), except for both extremes (0th–2.5th and 97.5th–100th percentiles), with the central 5 percentiles (e.g., the 47.5th–52.5th percentiles) serving as the reference category. Through this approach, we model the event rates associated with deviations from the median distribution of eGFR given a person's age and sex. The association between the study exposure and the rates of KFRT and all-cause death was evaluated through Cox proportional hazards models, with robust variance estimators to account for repeated measurements within individuals. For the evaluation of relative rates of KFRT, we treated death as a censoring event and report cause-specific hazard ratios. We then calculated hazard ratios and 95% confidence intervals.

Relative risks and 10-year absolute risks, overall and by sex, across 5 eGFR percentile groups were calculated at cohort entry (i.e., at first eGFR observation per individual).

Absolute risks for KFRT were estimated through cumulative incidence curves using the Aalen-Johansen estimator taking into account the competing risk of death. We calculated the 95% confidence interval for the absolute risks using a nonparametric bootstrap with 1000 samples.

Subgroup analysis. We evaluated the robustness of our outcome-analyses across 2 distinct age groups: 40–64 and 65–100 years.

Supporting analysis. We performed descriptive statistics of individuals with at least 1 eGFR below the 25th and the 5th percentiles of the distribution. If there were more than 1 such eGFR test per individual, we selected the first one for descriptives. In this population, we reported the proportion of individuals who received any test of albuminuria or proteinuria (dipstick albuminuria or proteinuria, urinary albumin-to-creatinine ratio, urinary protein-to-creatinine ratio, or albuminuria excretion rates) in any form of care and during the year before or after.

Exploration albuminuria distribution and mediation of albuminuria adjustment on study outcomes. To evaluate whether abnormal albuminuria levels were more likely to accompany low eGFR percentile distributions, we plotted the frequency of testing and distribution of albuminuria KDIGO categories in the year before each eGFR observation.

To evaluate whether albuminuria is, at least in part, the explanation to observed worse outcomes of low eGFR percentiles, we created a subcohort in which participants were selected through one random eGFR conditional on albuminuria testing in the year before the eGFR. We then calculated relative rates of KFRT and death across 5 eGFR percentile groups with and without adjustment for albuminuria.

Patient and public involvement

The Swedish patient organization was invited to comment on our work and provide feedback on our online eGFR percentile calculator but declined to participate.

RESULTS

Population coverage

During 2006–2021, approximately 40% (range: 35%–46%) of Stockholm residents aged 40–100 years underwent at least 1 creatinine test per calendar year. Overall, 80% of the adult population within this age range in Stockholm was represented in our cohort at least once (Supplementary Figure S1).

eGFR distributions

The cohort included 1,179,501 unique individuals with a median age at cohort entry of 54 years (interquartile range: 44–65 years, Supplementary Table S2). Older age categories had a higher proportion of women, lower median eGFR, and a progressively higher prevalence of hypertension, diabetes, and CVD. Participants contributed a total of 6,914,993 repeated eGFR measurements, which were used to construct eGFR distributions. Baseline characteristics using other eGFR equations are displayed in Supplementary Tables S3–S5.

Figure 1 illustrates the eGFR distribution using the CKD-EPI 2009 equation. The median eGFR declined from 104–106 (men-women) ml/min per 1.73 m^2 at age 40 years to 45–50 ml/min per 1.73 m^2 at age 100 years. The median eGFR fell below 60 ml/min per 1.73 m^2 at age 87 years in men and 88 years in women. eGFR percentiles are available in the Supplementary eGFR Key Percentiles.

Accounting for the inverse probability of being tested (Supplementary Figure S2) minimally modified the eGFR distributions, suggesting good representativeness of our cohort for this age range (Supplementary Figure S3). Supplementary Figure S4 displays median eGFR among participants with diabetes, hypertension, or CVD. People with these conditions had lower 50th percentiles than the total population, except for younger adults (<65 years old) with diabetes. eGFR distributions using alternative validated equations are shown in Supplementary Figures S5–S7.

Association between eGFR percentile and study outcomes

During a median follow-up of 10 years (interquartile range: 5–14 years), we identified 2651 KFRT events and 223,875 deaths. Compared with individuals within the central 5 percentiles (47.5th–52.5th) of eGFR distribution, those in lower eGFR percentiles had significantly higher rates of KFRT, with statistical significance ($P < 0.05$) observed below the 25th–30th percentiles (Figure 2a). No significant association was found between higher eGFR percentiles and KFRT risk. Mortality followed a U-shaped association, where both lower and higher eGFR percentiles were linked to increased rates of death (Figure 2b). These trends were consistent when using alternative eGFR equations (Supplementary Figures S8–S10) and across age groups (Figure 3).

The characteristics as well as the relative and 10-year absolute risks across 5 eGFR percentile groups at cohort entry, overall and by sex, are shown in Supplementary Tables S6 and S7. Absolute risks of KFRT were low (on average <1%) but were higher (0.85%) in participants below the 25th percentile of eGFR distribution than in participants within the 45th–55th percentiles (absolute risk 0.04%). Absolute risks were higher (approximately double) in men compared with women. The absolute 10-year risk of death in this population aged 40–100 years was approximately 17%, being higher among participants below the 25th percentile (18.6%) or above the 75th percentile of the distribution than among participants within the 45th–55th percentiles (absolute risk 15.12%).

Characteristics of individuals below the 25th eGFR percentile

Table 1 summarizes the characteristics of individuals with at least 1 eGFR value below the 25th percentile. Among these, 421,547 individuals had an eGFR ≥60 ml/min per 1.73 m^2, whereas 187,415 had an eGFR <60 ml/min per 1.73 m^2. Individuals with low eGFR percentiles but eGFR ≥60 ml/min per 1.73 m^2 were, on average, 21 years younger than those with low eGFR percentiles and eGFR <60 ml/min per 1.73 m^2.

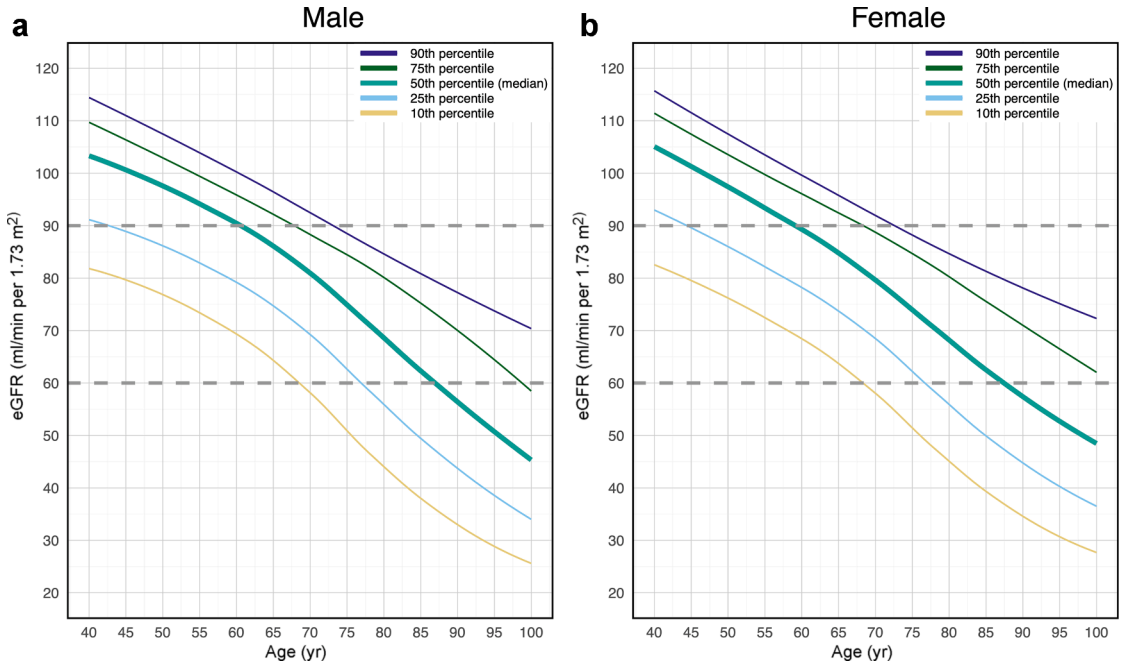

Figure 1 | Estimated glomerular filtration rate (eGFR) distributions for male (a) and female (b) using the Chronic Kidney Disease Epidemiology Collaboration 2009 equation. LOESS (Locally Estimated Scatterplot Smoothing) was applied for the curves.

Albuminuria testing was generally low and more frequent in individuals with high-risk conditions. Overall, 24% of individuals with eGFR ≥60 ml/min per 1.73 m^2 and 39% of those with eGFR <60 ml/min per 1.73 m^2 underwent albuminuria testing within a year before or after the eGFR test. Testing rates were higher in individuals with diabetes, hypertension, or CVD, with little difference between higher and lower eGFR subgroups: 66% versus 64% among individuals with diabetes, 39% versus 44% among those with hypertension, and 33% versus 38% among those with CVD. Among individuals without these comorbid conditions, testing rates were lower, with a larger difference between eGFR groups: 17% for eGFR ≥60 ml/min per 1.73 m^2 versus 28% for eGFR <60 ml/min per 1.73 m^2. For completeness, Supplementary Table S8 describes the characteristics of participants below the 5th percentile, and Supplementary Tables S3–S5 depict participants below the 25th percentile when using other validated eGFR equations.

Exploration of albuminuria distribution and mediation by albuminuria levels

A small proportion (28%) of eGFR observations in our study had records of albuminuria assessment in the year before the eGFR measurement. The distribution of albuminuria testing and KDIGO albuminuria categories across eGFR percentiles is shown in Supplementary Figure S11, observing a trend

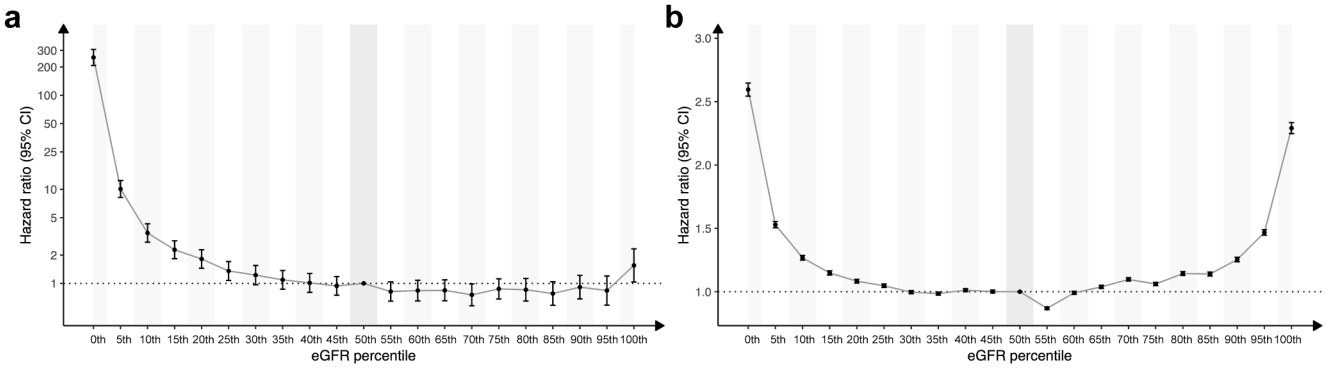

Figure 2 | Association between estimated glomerular filtration rate (eGFR) percentiles and rates of kidney failure with replacement therapy (a) and all-cause mortality (b) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009 equation. Hazard ratios and 95% confidence intervals (CIs) were calculated from a Cox proportional hazard regression model with robust estimators; the central 5 percentile (47.5th–52.5th) served as the reference level. eGFR percentiles were obtained based on eGFR values calculated with the CKD-EPI 2009 equation.

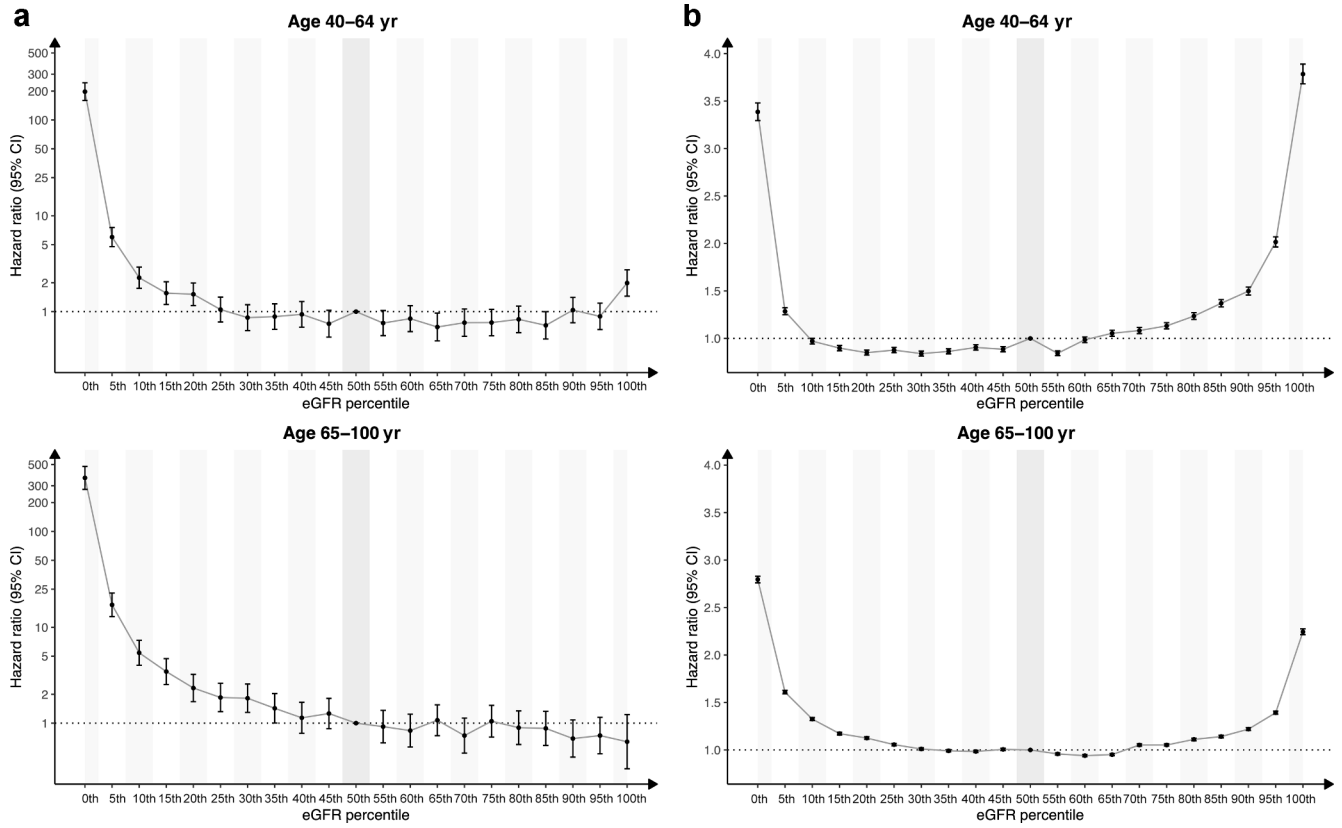

Figure 3 | Association between estimated glomerular filtration rate (eGFR) percentiles and rates of kidney failure with replacement therapy (a) and all-cause mortality (b) across 2 categories of age. Hazard ratios and 95% confidence intervals (CIs) were calculated from a Cox proportional hazard regression model; the central 5 percentile (47.5th–52.5th) served as the reference level. eGFR percentiles were obtained based on eGFR values calculated with the Chronic Kidney Disease Epidemiology Collaboration 2009 equation.

toward a higher proportion of tested participants across lower eGFR percentiles, as well as a trend toward a higher proportion of cases with albuminuria of severity A2 or A3 in them.

The characteristics of the subcohort of participants selected based on one random eGFR measurement conditional on having albuminuria tested in the year before the eGFR measurement are shown in Supplementary Table S9. Explained by the indications for albuminuria testing, we observed that these participants had a higher proportion of people with comorbid conditions, older age, and lower eGFR compared with our main cohort. Relative risks of study outcomes are shown in Supplementary Table S10. Adjustment for albuminuria substantially reduced the magnitude of the KFRT risk associated with participants below the 25th percentile of eGFR distribution, but effect sizes remained high with both statistical and clinical significance.

DISCUSSION

Principal findings

Currently, there are no established strategies for the early identification or primary prevention of CKD. We hypothesized that population-based eGFRcr distributions may help identify individuals at risk. In this study, we analyzed data from 80% of the adult population 40 years and older residing in the Stockholm region to construct age- and sex-specific distributions of eGFR. We found that eGFR values below the 25th percentile were associated with increased risks of KFRT. Furthermore, both lower and upper extremes of the eGFR distribution were linked to elevated mortality rates.

Comparison of previous studies, along with strengths and limitations

This study adds to the current understanding of population-wide eGFRcr distributions and offers several methodological strengths. These include a large sample size, repeated annual eGFR measurements (as opposed to a single observation), and high representativeness of the dataset. Using health care–based data as in our study may overestimate CKD prevalence because of selection biases (i.e., sicker people access health care and have creatinine tested). We tried to mitigate this concern by focusing on outpatient measurements and computing the median eGFR from all tests conducted annually for each individual, and by weighting our estimates against the population without creatinine tests. In doing so, we demonstrated that creatinine testing is common, with 40% of the adult population undergoing tests each year. Moreover, accounting for characteristics of the untested population did not materially alter the eGFR distributions. A recent study by Hussain *et al.*[23] used data from 8.7 million

Table 1 | Characteristics of unique individuals with eGFR below the 25th percentile for their specific age and sex, overall and stratified whether the absolute eGFR value is <60 ml/min per 1.73 m^2 or ≥60 ml/min per 1.73 m^2

Characteristics	Overall	eGFR ≥60 ml/min per 1.73 m^2	eGFR <60 ml/min per 1.73 m^2
No. of individuals	525,458	428,954	177,165
Sex, female, n (%)	280,774 (53)	223,651 (52)	100,059 (56)
Age, yr, median [IQR]	57 [47–68]	53 [45–62]	75 [68–81]
eGFR, ml/min per 1.73 m^2, median [IQR][a]	74 [63–81]	77 [70–83]	52 [44–57]
No. of individuals tested for albuminuria[b], n (%)	138,312 (26)	103,932 (24)	70,214 (40)
No. of individuals tested with albuminuria A1	108,107 (21)	87,310 (20)	45,213 (26)
No. of individuals tested with albuminuria A2	21,210 (4)	12,511 (3)	16,694 (9)
No. of individuals tested with albuminuria A3	8995 (1.7)	4111 (1.0)	8307 (5)
Stratified by comorbid conditions, n (%)			
Diabetes	52,240 (10)	32,180 (8)	38,549 (22)
Tested for albuminuria[c]	32,472 (62)	21,275 (66)	24,827 (64)
Hypertension	172,886 (33)	111,298 (26)	115,483 (65)
Tested for albuminuria	67,291 (39)	43,381 (39)	51,098 (44)
Cardiovascular disease[d]	83,822 (16)	38,715 (9)	69,041 (39)
Tested for albuminuria	28,220 (34)	12,889 (33)	26,463 (38)
Any of the 3	211,702 (40)	135,505 (32)	136,513 (77)
Tested for albuminuria	81,244 (38)	52,686 (39)	58,478 (43)
None of the 3	313,756 (60)	293,449 (68)	40,652 (23)
Tested for albuminuria	57,068 (18)	51,246 (17)	11,736 (29)

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; IQR, interquartile range, UACR, urinary albumin-to-creatinine ratio; UPCR, urinary protein-to-creatinine ratio.
[a]eGFR was calculated using the CKD-EPI 2009 equation.
[b]Proportion of individuals who received at least one test of albuminuria/proteinuria in the year before or after the date of the shown eGFR. We included all albuminuria/proteinuria methods (dipstick, UACR, UCPR, albuminuria excretion rates) performed in both outpatient and inpatient settings.
[c]Proportion of individuals within a given stratum who received at least one test of albuminuria/proteinuria (all such values).
[d]Cardiovascular disease includes myocardial infarction, peripheral vascular disease, cerebrovascular disease, and heart failure.
The table shows the first observation per individual with an eGFR below the 25th of distribution.

younger adults (aged 18–65 years) receiving health care in Ontario, Canada, to construct eGFR distributions. However, creatinine testing in young adults is less frequent, which may introduce concerns regarding selection bias. In our health care system, fewer than 50% of adults aged 18–44 years undergo routine creatinine testing,[26] which led us to focus on adults aged 40–100 years, where most CKD cases are identified.[13]

We provide eGFR distributions using the 4 validated eGFR equations recommended by the 2024 KDIGO guidelines.[4] We note that eGFR distributions were slightly different depending on the equation used, owing to the different assumptions in their modeling and the magnitude of the coefficients for age and sex in their regression formulas. As is well known, European Kidney Function Consortium and revised Lund-Malmö equations tended to systematically provide lower median eGFRs compared with the CKD-EPI 2009 equation, whereas the CKD-EPI 2021 equation tended to systematically provide higher median eGFRs.[27–30,36]

Consistent with prior evidence, eGFR distribution in our study is lower in women versus men, resulting in an increased prevalence of CKD among women.[37] It has been proposed that the longer life expectancy in women combined with a slower natural decline of kidney function with aging is responsible for this. However, it is also possible that eGFR equations produced more biased estimates in women, particularly with the use of a constant body surface area of 1.73 m^2, given that women, on average, tend to be smaller than men (reviewed in the paper by Carrero *et al.*[38]). Also consistent with preceding evidence demonstrating that GFR declines faster in men than in women,[37,38] the absolute risks of KFRT in our study were higher for men.

GFR is lower in older people than in younger people because of aging and disease. Several previous studies have used exclusion criteria to focus on "healthy" populations, but distinguishing health from disease in older adults is inherently challenging. Excluding individuals with selected comorbid conditions led in some studies to rejecting more than 25% of data,[16–18] and few adults in their 80s are free from comorbidity. We opted to develop population-based distributions, without exclusions, and demonstrate instead that individuals with comorbid conditions known to be CKD risk factors typically have eGFR values below the 50th percentile of the population distribution. Recently, Astley *et al.*[16] reported on normative eGFR in a consortium of European cohorts. In part because 72% of the patients included in that consortium came from the SCREAM database, distributions are strikingly similar despite the exclusion of individuals with some comorbidities. For example, the 50th percentile for an 80-year-old woman study using the European Kidney Function Consortium equation was 63 ml/min per 1.73 m^2 in

the Astley study and 62 ml/min per 1.73 m^2 in our study. We acknowledge that eGFR based on serum creatinine is influenced by non-GFR determinants, such as muscle mass, and is subject to measurement error.[39] Nevertheless, it remains the most widely used estimate for guiding clinical decision-making in routine practice. Cystatin C, an alternative filtration marker, is being more widely recommended in clinical practice. Cystatin C–based eGFR often provides different values than eGFRcr, and lower cystatin C–based eGFR is associated with a higher risk than eGFRcr.[40,41] Herold *et al.*[21] compiled data from 3 merged population-based cohorts to compute eGFRcr and cystatin C–based eGFR distributions in 12,000 individuals aged 25–95 years who had both measures. They showed that despite intraindividual variability, population-level eGFR distributions with these 2 filtration markers were remarkably similar. Caution should be exercised when extrapolating our findings to more ethnically diverse populations, but we note that despite differences across studies,[16–21] our observed percentiles are largely consistent with those previously reported. We observed that deviations from the median eGFR distribution—even at eGFR >60 ml/min per 1.73 m^2—were associated with increased risks of KFRT and all-cause mortality. Notably, clinically meaningful and statistically significant associations with KFRT risk were observed in individuals with eGFR values below the 25th percentile. This threshold could help identify individuals at risk of having or developing CKD requiring further evaluation. Interestingly, our data also showed that both lower and higher eGFR percentiles were associated with higher mortality rates, perhaps reflecting the broader role of eGFR as an indicator of overall health status, affected by both kidney function and muscle mass. We speculate that higher eGFRcr percentiles may capture people with disease-induced low muscle mass (i.e., people with frailty or cachexia), or in some cases, possible hyperfiltration in diabetes (as shown indirectly in Supplementary Tables S6 and S9 depicting a higher proportion of participants with diabetes across the highest eGFR percentile distribution categories). Traditionally, normality of a biomarker has been defined using the central 80% or 95% of a distribution. In line with this, Hussain *et al.*[23] reported elevated risks of death and KFRT in young adults with eGFR values below the 10th and 5th percentiles. However, ranges of normality may not necessarily reflect ranges of safety, and our analysis—which evaluated the full continuum of eGFR percentiles—suggests that risk associations become apparent earlier, and that the "optimal" ranges of eGFRcr may lie between the 25th and 75th percentiles of the population distribution.

Interpretation of findings

Our study provides compelling evidence for the clinical utility of population-wide eGFRcr distributions as a complementary tool to automatic eGFR reporting. These distributions can help identify individuals at higher risk of adverse outcomes that need further evaluation, and charts could facilitate discussions between clinicians and patients about kidney function, potential risks, and the need for lifestyle changes. We show that the number of individuals who could benefit from this approach is substantial: over 400,000 adults in our region with eGFR >60 ml/min per 1.73 m^2 were below the 25th percentile of distribution. Even if we observed increasing rates of albuminuria testing in these low percentiles, the rate of albuminuria screening remains unacceptably low, consistent with general trends.[11,12] Although exploratory in nature, our study reports a higher proportion of participants with low eGFR percentiles that have detected albuminuria levels consistent with KDIGO categories A2 or A3 and we speculate that elevated albuminuria may be a feature of people with "low within normal" eGFR. Our sequential adjustment in the survival models suggests that albuminuria may also be a potential explanation for their increased KFRT risk. There is an imperative need to better understand the characteristics of individuals with a low within normal eGFR, including not only other markers of kidney disease (e.g., albuminuria and other markers of kidney damage, such as abnormal urinalysis or kidney ultrasound, cystatin C–based eGFR), but also their comorbid conditions and body composition and size.

A previous study assessing potential kidney donors by age and eGFR also suggested that reference charts could improve the efficiency of living donor selection,[42] and our analysis of associations with mortality suggests that eGFR in high percentiles of distribution (such as above 75th) may also reflect some underlying health issue that requires examination. A randomized vignette study from Australia demonstrated that providing general practitioners with charts of eGFR distributions significantly increased the proportion of practitioners (from 52% to 79%) identifying a clinical problem that required further exploration in young adults with eGFR >60 ml/min per 1.73 m^2.[43] In qualitative research, 89% of practitioners held positive views regarding the incorporation of charts of eGFR distributions in clinical settings (with the remainder expressing neutral opinions). They described the charts as "easy to use" and a "valuable complementary tool" for assessing kidney health.[44] In Supplementary Appendix S1, we provide 3 clinical vignettes and the output from our data visualization tool as examples of how eGFR distribution charts can help inform decisions for further exploration and monitoring.

In clinical practice, especially in older adults, there is often the question of whether lower eGFR values reflect aging or disease. Previous studies have suggested that eGFRcr values at or below 60 ml/min per 1.73 m^2 are less strongly associated with adverse outcomes in older adults compared with younger individuals.[45,46] Although this disparity may be attributed to the limitations of creatinine as a filtration marker rather than to the GFR threshold itself,[41] some nephrologists have expressed concerns that CKD may be overdiagnosed in older patients, advocating for an age-adapted definition of CKD.[47] Our findings further contribute to this ongoing debate by showing that eGFR<60 ml/min per 1.73 m^2 is not a universal finding among older

adults. The majority (>50%) of adults younger than 87–88 years (men-women) had eGFRcr values above the current threshold to define moderate CKD.

Next steps and future research

Our interactive data visualization tool (accessible online at https://scream.meb.ki.se/egfr-percentiles/) is available for academics, clinicians, and patients interested in further exploring this resource. Our data represent the population of the Stockholm region aged 40 years or older, and extrapolation to other regions or countries should be done with caution. Furthermore, there is a need to define eGFR distributions in persons younger than 40 years. We encourage researchers to test our assumptions and develop representative eGFR distributions using local population data from geographically distinct regions. In the absence of region-specific data, researchers are encouraged to use our eGFR distributions and validate whether the risk thresholds identified by our study are similarly associated with adverse health outcomes in geographically distinct health care systems. This would assess the generalizability of our eGFR distributions.

CONCLUSION

We developed population-wide eGFRcr distributions from a representative sample of the Stockholm population and demonstrated that eGFR values below the 25th percentile are associated with adverse clinical outcomes. These distributions could complement automatic eGFR reporting and aid in the early identification and primary prevention of CKD.

DISCLOSURE

The authors have no conflict of interest to report in relation to the topic of this study. Unrelated to the study, JJC reports funding to Karolinska Institutet by AstraZeneca, Boehringer Ingelheim, Vifor Pharma, Novo Nordisk, and MSD, as well as personal honoraria for lectures by Fresenius Kabi and Laboratorios Columbia. ME reports personal honoraria for lectures by AstraZeneca, Astellas Pharma, Vifor Pharma, Fresenius Healthcare, and Baxter Healthcare, and being a member of advisory boards for Astellas, AstraZeneca, and Vifor Pharma. AO reports consultancy or speaker fees or travel support from Astellas, AstraZeneca, Bioporto, Boehringer Ingelheim, Fresenius Medical Care, GSK, Bayer, Sanofi-Genzyme, Sobi, Menarini, Lilly, Chiesi, Otsuka, Novo Nordisk, Sysmex, Vifor Fresenius Medical Care Renal Pharma, and Spafarma and is Director of the Catedra UAM-AstraZeneca of chronic kidney disease and electrolytes. He has stock in Telara Farma. All the other authors declared no competing interests.

DATA STATEMENT

eGFR percentiles of distribution can be accessed through our supplemental materials or explored online (https://scream.meb.ki.se/egfr-percentiles/). The raw data used in this article cannot be shared publicly because of the privacy of individuals who participated in the study. The data may be shared upon reasonable request for academic research collaborations fulfilling General Data Protection Regulation, and national as well as institutional ethics regulations and standards by contacting JJC (juan.jesus.carrero@ki.se).

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AUTHOR CONTRIBUTIONS

YY and JJC had full access to the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. JJC and AO were responsible for the study concept, and JJC, AS, and YY were responsible for the study design. YY performed the statistical analysis with methods supported by AS. AC completed the online application. JJC drafted the manuscript. All authors critically revised the manuscript for important intellectual content. YY and JJC are the guarantors of this study. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Supplementary material is available online at www.kidney-international.org.

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