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Relative risks of Chronic Kidney Disease for mortality and End Stage Renal Disease across races is similar

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Disclosure

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author)

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Author Contributions

All authors had full access to the analysis reports and tables and take responsibility for the integrity of the data and the accuracy of the data analysis

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Abstract

Some suggest race-specific cutpoints for kidney measures to define and stage chronic kidney disease (CKD), but evidence for race-specific clinical impact is limited. To address this issue, we compared hazard ratios of estimated glomerular filtration rates (eGFR) and albuminuria across races using meta-regression in 1.1 million adults (75% Asians, 21% whites, and 4% blacks) from 45 cohorts. Results came mainly from 25 general population cohorts comprising 0.9 million individuals. The associations of lower eGFR and higher albuminuria with mortality and end-stage renal disease (ESRD) were largely similar across races. For example, in Asians, whites, and blacks, the adjusted hazard ratios (95% confidence interval) for eGFR 45–59 vs. 90–104 ml/min/1.73m^2 were 1.3 (1.2–1.3), 1.1 (1.0–1.2) and 1.3 (1.1–1.7) for all-cause mortality, 1.6 (1.5–1.8), 1.4 (1.2–1.7), and 1.4 (0.7–2.9) for cardiovascular mortality, and 27.6 (11.1–68.7), 11.2 (6.0–20.9), and 4.1 (2.2–7.5) for ESRD, respectively. The corresponding hazard ratios for urine albumin-to-creatinine ratio 30–299 mg/g or dipstick 1-positive vs. an albumin-to-creatinine ratio under 10 or dipstick negative were 1.6 (1.4–1.8), 1.7 (1.5–1.9) and 1.8 (1.7–2.1) for all-cause mortality, 1.7 (1.4–2.0), 1.8 (1.5–2.1), and 2.8 (2.2–3.6) for cardiovascular mortality, and 7.4 (2.0–27.6), 4.0 (2.8–5.9), and 5.6 (3.4–9.2) for ESRD, respectively. Thus, the relative mortality or ESRD risks of lower eGFR and higher albuminuria were largely similar among three major races, supporting similar clinical approach to CKD definition and staging, across races.

Introduction

Chronic kidney disease (CKD) is a global public health problem,[1–3] affecting 10 to 16% of the adult population in several continents[4–7] and increasing the risk of adverse outcomes.[8–12] The definition and staging of CKD is based on the level of glomerular filtration rate (GFR) and the presence of kidney damage, usually ascertained as albuminuria.[1, 11, 13] However, the comparability of GFR and albuminuria measures across racial groups and their relationship with risk has not been fully explored,[14] although some have suggested race-specific thresholds for GFR and albuminuria to define and stage CKD.[15] The primary objective of this study was to quantify the associations of GFR and albuminuria with risk for all-cause and cardiovascular mortality, and ESRD among Asians, whites, and blacks, three major races in the world, and assess whether there are any substantial differences across the races.

Results

Study populations

A total of 1,102,581 individuals were studied, including 75% Asians (mostly Eastern Asians), 21% whites and 4% blacks. Majority of the study population, 85% or 933,720 individuals, were from 25 general population cohorts, with remaining 12% or 132,566

individuals from 7 high-risk cohorts, and 3% or 36,295 individuals from 13 CKD cohorts (Table 1). Thus, our primary analyses were conducted in the general population cohorts, and results for the high-risk cohorts and CKD cohorts were shown in supplemental materials separately. Asians comprised the majority of the general population cohorts (87%), but not the high-risk (6%) or CKD (12%) cohorts, and mainly came from cohorts based on data from comprehensive health screening programs for the healthy population. Accordingly, Asians tended to have a lower risk profile (younger age and lower prevalence of comorbid conditions) as compared to whites and blacks. While most Asians were from Asian cohorts, most blacks were from US cohorts. There were differences in the methods for ascertainment of albuminuria among the general population cohorts: only 1% of Asians had ACR data, while ACR data were available in 73% of whites and 100% of blacks included in the meta-analysis, reflecting different medical and research settings.

eGFR and albuminuria distributions by race

In the general population cohorts, the crude prevalence of reduced eGFR (<60 ml/min/1.73 m^2) in Asians, whites and blacks was 5.1%, 15.8%, and 9.4% respectively (Figure S1A). The prevalence of elevated albuminuria (≥30 mg/g by ACR or ≥1+ by urine dipstick) in the three races was 2.8%, 9.7% and 16.8%, respectively (Figure S1B). The difference in prevalence of reduced eGFR and elevated albuminuria across racial groups was attenuated after age standardization, particularly for reduced eGFR (Figure S1C–D). In the high-risk cohorts, the crude prevalence of decreased eGFR and high albuminuria were 11.1% and 23.9% in Asians, 17.8% and 20.4% in whites, and 10.2% and 13.3% in blacks, respectively (Figure S2).

Incidence rates of mortality and ESRD by race

We observed 38,696 all-cause deaths and 9,065 CVD deaths in Asians (mean follow-up of 9.2 years), 20,079 and 7,325 cases in whites (mean follow-up of 8.4 years), and 2,485 and 436 cases in whites (mean follow-up of 6.6 years) (Table S1). Crude rates for all-cause and CVD mortality in the general population cohorts were 5.9 and 1.4 per 1,000 person-years in Asians, 24.1 and 10.4 in whites, and 18.7 and 5.5 in blacks, respectively (Figure S3). After age-standardization, mortality rates were higher in blacks compared to whites, while the lower rates in Asians persisted. The variation in mortality rates was as great among studies within races as among races within studies. Among the studies with data on ESRD, crude incidence rates of ESRD per 1,000 person-years were 0.3 in Asians, 0.8 in whites, and 2.8 in blacks.

Independent relationships of eGFR and albuminuria to clinical risk by race

Figure 2 shows HRs for all-cause mortality, CVD mortality, and ESRD in the general population cohorts by race for eGFR from 15 to 120 ml/min/1.73 m^2 compared to the reference point at eGFR 95 ml/min/1.73 m^2. The patterns for each outcome were qualitatively similar among three races across most of the range of eGFR, with higher risk at lower eGFR. For all-cause and cardiovascular mortality, although there was variation across races in the eGFR thresholds below which the HRs were significantly greater than the reference point, partially due to difference in the precision of estimates across races, the HR reached significance at eGFR between 60 and 75 ml/min/1.73 m^2 in most analyses and did

not differ significantly for a given eGFR among races, except for small ranges noted at the bottom of Figure 1. For ESRD, the threshold eGFR varied from 65 to 83 ml/min/1.73 m^2 for all three races, although the pattern was least steep in blacks for eGFR <30 ml/min/1.73 m^2.

Figure 2 shows HRs for all three outcomes by races according to albuminuria categories (ACR 10–29, 30–299 and ≥300 mg/g or urine dipstick levels negative, trace, 1+ and ≥2+, respectively) (Figure S4 shows the association for ACR as a continuous variable). Again, the patterns for each outcome were similar among races, with higher HRs for higher albuminuria. The only significant difference was higher CVD mortality in blacks with ACR 30–299 mg/g. In all races, the threshold category above which the HRs for mortality outcomes was significantly greater than the reference category was ACR ≥10 mg/g or dipstick ≥trace. Although data were limited, the independent associations of low eGFR and high albuminuria with three outcomes were largely similar across three races in both high-risk and CKD cohorts (Figures S5-S8).

Combined relationships of eGFR and albuminuria to clinical risk by race

Figure 3 shows the adjusted HRs for all-cause mortality, CVD mortality, and ESRD in the general population cohorts by eGFR and albuminuria categories compared to the reference categories of eGFR 90–104 ml/min/1.73 m^2 and ACR <10 mg/g or dipstick negative. Consistent with the results in Figures 1–2, all-cause mortality risks for eGFR categories and albuminuria categories (marginal rows and columns in Figure 3) were similar for Asians, whites, and blacks. For example, in Asians, whites, and blacks, compared to eGFR 90–104 ml/min/1.73 m^2, the HR [95% CI] for eGFR 45–59 ml/min/1.73 m^2 was 1.25 (1.20–1.31), 1.09 (0.97–1.22) and 1.33 (1.07–1.65) for all-cause mortality, 1.59 (1.46–1.75), 1.40 (1.17–1.68), and 1.44 (0.72–2.86) for cardiovascular mortality, and 27.6 (11.1–68.7), 11.2 (6.01–20.9), and 4.05 (2.18–7.51) for ESRD, respectively. The corresponding HRs for ACR 30–299 mg/g or dipstick (1+) compared to ACR <10 mg/g or dipstick (−), were 1.61 (1.41–1.84), 1.68 (1.50–1.88) and 1.84 (1.65- 2.06) for all-cause mortality, 1.66 (1.37–2.02), 1.76 (1.49–2.09), and 2.79 (2.15–3.62) for cardiovascular mortality, and 7.39 (1.98–27.6), 4.04 (2.75–5.94), and 5.55 (3.36–9.18) for ESRD, respectively. The HRs were quantitatively consistent across most of the studies for three outcomes (Figures S9–S11).

The pattern for categories based on eGFR and albuminuria (cells in Figure 3) was also qualitatively similar among the three races, showing a multiplicatively higher risk for lower eGFR and higher albuminuria, with limited interactions. Of note, the category of eGFR 45–59 with lowest albuminuria was associated with a point estimate for the HR >1.0 compared to the reference groups for all three outcomes for all three races (statistically significant in 7 of 9 comparisons). The category of elevated albuminuria (ACR 30–299 mg/g or urine dipstick 1+) with eGFR 90–104 was associated with a point estimate for the HR >1.0 compared to the reference groups for all 9 comparisons (statistically significant in 8). Similar results were observed for cardiovascular mortality and ESRD. Largely similar results were also observed across three races in both high-risk and CKD cohorts (Figures S12 and S13).

Discussion

Low eGFR and high albuminuria were both independently associated with an increased risk of mortality and ESRD. In this unique and large meta-analysis, we observed qualitatively similar adjusted HR for all-cause and cardiovascular mortality and ESRD according to eGFR or albuminuria across three major races, Asian, white and black, in general population cohorts, despite differences in demographic and clinical characteristics (Table 1) and absolute risk (Figure S3) among racial groups and cohorts. The consistency in eGFR and albuminuria risk relationships across races has important implications for clinical practice, research and public health.

The best known racial disparities in kidney disease are the widely different ESRD rates among countries reported by USRDS.[16] Our results describing highest ESRD rates in blacks are consistent with other studies.[17–20] It is more difficult to study racial differences in earlier stages of CKD. There have not been large studies of multi-racial populations that have simultaneously assessed eGFR and albuminuria regarding their associations with mortality and ESRD. In addition, methods to estimate GFR and ascertain albuminuria have varied, and many studies reported only eGFR or albuminuria. While our study has a wide variation in demographic and clinical characteristics among cohorts, the availability of both eGFR and albuminuria measurements permits a more robust analyses.

Prior reports from the CKD-PC, using comparable methods across cohorts, showed similar impact of eGFR and albuminuria categories on relative risks of all-cause and cardiovascular mortality and ESRD across subgroups defined by demographic and clinical characteristics (age,[21] sex,[22] hypertension,[23] and diabetes[24]). The current analysis expands our prior observations to race groups, and establishes a consistency of the relationship of eGFR and albuminuria to important outcomes irrespective of race. Given the increasing interest in variability of incidence rates of ESRD across countries and races and the major resource implications associated with high ESRD rates, it will be important to pursue the causes for the differences in distribution of cardiovascular risk factors, eGFR and albuminuria that we observed among the racial groups. Specifically, it will be important to determine the extent to which social, environmental and genetic differences result in variation in disease expression and outcomes (such as the higher prevalence of IgA nephropathy in Asia and the contribution of economic aspects to variation in dialysis care).[25,26] Better understanding of the similarities and differences across races should direct research to identify modifiable factors.

The GFR thresholds for the definition and staging of CKD were first proposed in 2002, using data derived predominantly from a general US population.[1] In the last decade, these eGFR thresholds have been incorporated into clinical guidelines in other countries.[3, 27, 28] The recognition of albuminuria as an independent risk factor for adverse outcomes has now led to the incorporation of albuminuria categories into CKD staging, and this analysis has utilized the new recommendations for categories of albuminuria and eGFR.[29] The robust relationship of eGFR and albuminuria to outcomes irrespective of race gives additional credence to their use in clinical arenas and beyond. Given the complexity of using race-

specific thresholds of kidney measures in clinical practice, there would need to be strong evidence for justification to support their adoption.

Standardization of methods for ascertainment of GFR and albuminuria remains a challenge. Specification of race improves the accuracy of creatinine-based GFR estimating equations by adjusting for differences in creatinine generation due to variation in muscle mass and diet. Current guidelines recommend the CKD-EPI creatinine equation for use in North American, Europe and Australia, which estimates GFR ~16% higher for blacks compared to other races at a given age, gender and level of serum creatinine.[30] In our study, the CKD-EPI creatinine equation demonstrates similar eGFR-risk association in Asians, whites, and blacks, providing further support for its usefulness across racial groups and encouraging more widespread reporting of eGFR around the world. Other equations have been developed in Japanese, Taiwanese, and Chinese, but their generalizability has not been evaluated in large studies.[31–34] In our consortium, the selection of ACR vs. dipstick for assessment of albuminuria varies across regions/cohorts and is largely based on study objectives and resources (with ACR being used most commonly in North America, Europe and Australia and dipsticks being most used commonly in Asia). Therefore, we could not assess the influence of urinary creatinine per se, which may vary substantially across races, on the association between ACR and clinical risk.[35] Nevertheless, this study confirms the usefulness of both methods in relating albuminuria with outcomes, thus supporting the use of either method in clinical practice.

Strengths of our study include an international consortium with a wide range of cohorts in various settings, comprehensive data on eGFR and albuminuria, a large study population, and the assessment of both mortality and ESRD. The cohorts were not selected for previous publication regarding the study question, thereby minimizing the possibility of publication bias. The analysis was centrally coordinated, and adjustment for important variables was uniformly carried out in all cohorts. Our continuous analysis using splines allowed inspection of the pattern of association across the entire range of eGFR, irrespective of the reference point used. The categorical analysis allowed combining across cohorts that assessed albuminuria using ACR and dipstick and provided clinically useful information.

There are several limitations in our study. Measurements of creatinine and urine albumin were not standardized in all studies, and we did not have data on measured GFR, cystatin C or 24-h albumin excretion rate to confirm eGFR, urine ACR or dipstick.[36] Only a few Asian cohorts had ACR measurements, and none of them ascertained ESRD as an outcome. Most of the blacks in our study were from cohorts in the US and not from the blacks in Africa. Most Asians were in East Asian cohorts, and we could not compare East and South Asians. Few cohorts included multiple racial groups. Further analyses will be required for Hispanics and other racial/ethnic groups not represented in this study. We cannot rule out the possibility of residual confounding due to unevaluated variables in this study such as lifestyle (e.g., diet or physical activity) or socioeconomic status including access to health care.

Despite wide variability in clinical characteristics among cohorts and lower risk profile in Asian cohorts, there were no substantial differences among Asians, whites and blacks in the

independent and joint associations of reduced eGFR, based on the CKD-EPI creatinine equation, and albuminuria, based on ACR or dipstick, with all-cause and CVD mortality and ESRD. These results support the use of existing eGFR equations for risk categorization, and thresholds of eGFR and albuminuria for CKD definition and staging across these racial groups.

Methods

Study design

Details of the Chronic Kidney Disease Prognosis Consortium (CKD-PC) were described previously.[8–12] To be included in the consortium, a study had to have at least 1,000 participants (not applied to studies predominantly enrolling CKD patients [CKD cohorts][9]), information at baseline on eGFR and albuminuria, and a minimum of 50 events for any of the outcomes of interest. This analysis consists of data from 45 cohorts (25 general population cohorts, 7 high-risk cohorts with high-risk participants selected for cardiovascular or kidney disease risk factors, and 13 CKD cohorts) (Table 1, Table S2, and Appendix 1). This study is based on secondary data analysis of pre-existing, de-identified/de-linked dataset, and was approved by the Institutional Review Board at the Johns Hopkins Bloomberg School of Public Health.

Study variables

GFR was estimated using the CKD-EPI creatinine equation:

$$141 \times (\text{minimum of standardized serum creatinine}\,[\text{mg/dL}]/\kappa \text{ or } 1)^{\alpha} \times (\text{maximum of standardized serum creatinine}[\text{mg/dL}]/\kappa \text{ or } 1)^{-1.209} \times 0.993^{\text{age}} \times (1.018 \text{ if female}) \times (1.159 \text{ if black})$$

, where κ is 0.7 if female and 0.9 if male and α is −0.329 if female and −0.411 if male.[37, 38] For studies in which creatinine measurement was not standardized to isotope dilution mass spectrometry (IDMS), we reduced the creatinine levels by 5%, the calibration factor used to adjust non-standardized MDRD Study samples to IDMS.[39] While urine albumin-to-creatinine ratio (ACR) is the preferred measure of albuminuria in the clinical settings,[1, 3] the semi-quantitative measurement using urine dipstick in mass screening the healthy population has also been reported to be highly valuable.[40] A few studies that reported urine albumin excretion or urine protein-to-creatinine ratio (PCR) were also included.[1] Race/ethnicity was categorized as white, Asian, black, Hispanic, and others. Due to sparse data, we could not reliably investigate Hispanics and other racial/ethnic groups (Table S2) and thus their results were not shown. Diabetes mellitus was defined as fasting glucose ≥7.0 mmol/L, non-fasting glucose ≥11.1 mmol/L, hemoglobin A1c ≥6.5%, use of glucose lowering drugs, or self-reported diabetes. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥ 90 mmHg, use of antihypertensive medication or self-reported hypertension. Hypercholesterolemia was defined as total cholesterol ≥5.0 mmol/L in people with prior CVD and as ≥6.0 mmol/L otherwise or use of lipid lowering drugs. CVD history was defined as a history of myocardial infarction, coronary revascularization, heart failure or stroke. Body mass index (BMI) was calculated as weight (kg) divided by square height (m). Smoking was dichotomized as current versus former/non-smokers. All of these study variables were assessed at baseline in every cohort.

Outcomes

The three outcomes of interest were all-cause mortality, cardiovascular mortality, and ESRD. Cardiovascular mortality was defined as death due to myocardial infarction, heart failure, sudden cardiac death, or stroke. ESRD was defined as start of renal replacement therapy or death due to kidney disease. However, death due to acute kidney injury was not included.[41]

Statistical analyses

Analyses were restricted to subjects aged 18 years or older. Any subject with missing values for eGFR, albuminuria, and race/ethnicity was excluded. Missing values for all other covariates were imputed by the cohort mean. Age adjustment for distribution of kidney measures and incidence rate of three outcomes was performed by direct standardization using US NHANES III as reference population, the only cohort in the consortium representing national data by design. The analysis overview and analytic notes for individual studies are described in Appendix 2.

We subsequently conducted a series of analyses stratified by racial/ethnic groups. We used a two-stage approach, in which statistics were first obtained in each study and then were meta-analyzed estimates of each racial/ethnic group across studies by a random-effects model. General population, high-risk and CKD cohorts were meta-analyzed separately. Heterogeneity was quantified using the χ^2 test for heterogeneity and the I^2 statistic. All analyses were conducted using Stata/MP 11.2 software (www.stata.com) and a *P*-value of less than 0.05 was considered statistically significant.

Cox proportional hazards models were used to estimate the hazard ratios (HRs) of clinical outcomes associated with eGFR and albuminuria, adjusted for age, sex, history of CVD, smoking, systolic blood pressure (continuous), diabetes, serum total cholesterol concentration (continuous), BMI (continuous), and either eGFR or albuminuria as appropriate. Death was censored for ESRD analysis. Since few studies have multiple racial/ethnic groups, incorporating interaction terms between kidney measures and race in models was not practical. Therefore, meta-regression analysis with a random-effects model was used to formally compare HRs according to eGFR and albuminuria across racial/ethnic groups.[42] We modeled eGFR and ACR using linear splines with knots at 30, 45, 60, 75, 90, and 105 ml/min/1.73 m^2 (105 is not implemented for CKD cohorts) and 10, 30, and 300 mg/g (30, 300, and 1000 mg/g for CKD cohorts) (to convert to mg/mmol multiply by 0.113), respectively. eGFR 95 ml/min/1.73 m^2 (50 for CKD cohorts) and ACR 5 mg/g (100 for CKD cohorts) were treated as reference points.[8, 9]

We also compared the risk in categories of eGFR (<15, 15–29, 30–44, 45–59, 60–74, 75–89, 90–104, ≥105 ml/min/1.73 m^2) and albuminuria (ACR: <10, 10–29, 30–299, ≥300 mg/g; PCR: <20, 20–49, 50–499, ≥500 mg/g; dipstick: negative [−], trace [±], +, ≥++) and their combination. For CKD cohorts, the following categories were used for eGFR (<15, 15–29, 30–44, 45–74, 75–89, ≥90 ml/min/1.73 m^2) and albuminuria (ACR: <30, 30–299, 300–999, ≥1000 mg/g; PCR: <50, 50–499, 500–1999, ≥2000 mg/g; dipstick: negative/trace, +, ++, ≥+++). The category with eGFR 90–104 ml/min/1.73 m^2 (45–74 for CKD cohorts) and the

lowest albuminuria was used as the reference group.[8, 9] Given that few Asian cohorts had ACR data, results for albuminuria were primarily shown for categories.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix 1. Acronyms or abbreviations for studies included in the current report and their key references linked to the Web references

1. General population cohorts

Aichi	Aichi Workers' Cohort[1]
ARIC	Atherosclerosis Risk in Communities Study[2]
AusDiab	Australian Diabetes, Obesity, and Lifestyle Study[3]
Beaver Dam	Beaver Dam CKD Study[4]
Beijing	Beijing Cohort Study[5]
CHS	Cardiovascular Health Study[6]
CIRCS	Circulatory Risk in Communities Study[7]
COBRA	COBRA Study[8]
ESTHER	ESTHER Study[9]
Framingham	Framingham Heart Study[10]
Gubbio	Gubbio Study[11]
HUNT	Nord Trøndelag Health Study[12]
IPHS	Ibaraki Prefectural Health Study[13]

MESA	Multi-Ethnic Study of Atherosclerosis[14]
MRC Older People	MRC Study of assessment of older people[15]
NHANES III	Third US National Health and Nutrition Examination Survey[16]
Ohasama	Ohasama Study[17]
Okinawa83	Okinawa 83 Cohort[18]
Okinawa93	Okinawa 93 Cohort[19]
PREVEND	Prevention of Renal and Vascular End-stage Disease Study[20]
Rancho Bernardo	Rancho Bernardo Study[21]
REGARDS	Reasons for Geographic And Racial Differences in Stroke Study[22]
Severance	Severance Cohort Study[23]
Taiwan	Taiwan MJ Cohort Study[24]
ULSAM	Uppsala Longitudinal Study of Adult Men[25]

2. High-risk cohorts

ADVANCE	The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial[26]
CARE	The Cholesterol and Recurrent Events (CARE) Trial[27]
KEEP	Kidney Early Evaluation Program[28]
KPHawaii	Kaiser Permanente Hawaii Cohort[29]
MRFIT	Multiple Risk Factor Intervention Trial[30]
Pima	Pima Indian Study[31]
ZODIAC	Zwolle Outpatient Diabetes project Integrating Available Care[32]

3. CKD cohorts

AASK	African American Study of Kidney Disease and Hypertension[33]
BC CKD	British Columbia CKD Study[34]
CRIB	Chronic Renal Impairment in Birmingham[35]
Geisinger	Geisinger CKD Study[36]
GLOMMS-1	GLOMMS-1: Grampian Laboratory Outcomes, Morbidity and Mortality Studies – 1[37]
KPNW	Kaiser Permanente Northwest[38]
MASTERPLAN	Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of a Nurse Practitioner[39]
MDRD	Modification of Diet in Renal Disease Study[40]
MMKD	Mild to Moderate Kidney Disease Study[41]
Nephro Test	NephroTest Study[42]
RENAAL	Reduction of Endpoints in Non-insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan[43]
Steno	Steno Type 1 Diabetes Study[44]
Sunnybrook	Sunnybrook Cohort[45]

Appendix 2. Data analysis overview and analytic notes for some of individual studies

Overview

The participating studies were asked to prepare a dataset with approximately 30 variables (follow-up time, event variable, and several predictors including age, gender, race and serum creatinine to estimate GFR and albuminuria). To minimize heterogeneity, we circulated guidelines for definitions of variables (e.g. hypertension, diabetes, smoking) and dataset preparation. Analyses were restricted to subjects aged 18 years or older. We instructed studies not to impute the two key kidney measures, eGFR (i.e., age, gender, race, and serum creatinine) and albuminuria. For other variables in the models with missing values we imputed with the mean value of the covariate. Individuals with practically impossible values

of covariates, i.e., systolic blood pressure <50 or >300 mmHg or BMI <10 or >100 kg/m^2 were excluded from the analysis (<0.01 %).

For 35 of the 45 studies analysis was done at the Data Coordination Center at Johns Hopkins University; for the remainder the standard code was run in-house at individual study centers, with the output returned to the Data Coordinating Center. The code was written in STATA by the Data Coordinating Center. The standard code was designed to automatically save all output needed for the meta-analysis. The Data Coordinating Center then pooled the estimates across studies using STATA.

Studies were instructed to standardize and calibrate their serum creatinine to their best ability and report the method of standardization. The reported creatinine calibration allows grouping studies into studies that reported using an IDMS traceable method or conducted some serum creatinine calibration to IDMS traceable methods (AusDiab, Beaver Dam, Geisinger, GLOMMS-1, Gubbio, HUNT, KEEP, KPNW, MMKD, NephroTest, NHANES III, Okinawa 83 and 93, Rancho Bernardo, REGARDS) and studies where the creatinine standardization was not done (AASK, ADVANCE, Aichi, ARIC, British Columbia CKD, Beijing, CARE, CHS, CIRCS, COBRA, CRIB, ESTHER, Framingham, IPHS, KP Hawaii, MASTERPLAN, MDRD, MESA, MRC Older People, MRFIT, Ohasama, Pima, PREVEND, RENAAL, Severance, STENO, Sunnybrook, Taiwan, ULSAM, ZODIAC). Retrospective assessment of creatinine calibration without direct collection of laboratory data is limited since substantial creatinine calibration differences have been documented even within a single laboratory using the same method over time.

The reference range of eGFR (90–104 ml/min/1.73 m^2) was chosen based on the optimal level of GFR (≥90 ml/min/1.73 m^2) reported in current clinical guidelines[46, 47] and the fact that some studies have reported higher mortality risk at high eGFR.[48–50] The reference point of eGFR (95 ml/min/1.73 m^2) was then arbitrarily chosen within the reference range but not in the knots (90 and 105) used to create splines.

Following the published results from individual studies, we assumed the proportional hazards model provided the best summary of the data in each study and did not summarize statistics on deviations from proportionality across the covariates.

Notes for individual studies

1. General population cohorts

CHS: This study consists of participants only aged 65 or older and thus did not contribute to the subgroup analysis of younger population.

COBRA: Current smokers in this study include chewable tobacco users.

ESTHER: This study only measured urine albumin excretion with the minimum detection value of 11.3 mg/L (equivalent to ACR 17 mg/g) and thus its reference proteinuria group (≤11.3 mg/L) was likely to contain individuals with ACR ≥10 mg/g. Therefore, this study was meta-analyzed with the dipstick studies, translating urine albumin excretion (≤11.3, 11.4–19.9, 20–199 and ≥200 mg/L to −, ±, +, and ≥++).

Gubbio: This study consists of participants aged between 45 and 64 and thus did not contribute to the subgroup analysis of older population.

HUNT: This study is a general-population study overall but measured urine albumin mainly in participants with treated hypertension or diabetes. However, this study was categorized as a general population cohort, since they measured albuminuria in a 5% random sample out of ≈65,000 participants and, thus, the relationship between kidney measures and risk was maintained. This study has not collected use of anti-diabetic medication and use of statins (and thus hypercholesterolemia). Most of the glucose measurements were non-fasting.

IPHS: This study categorized their dipstick data − and ± into the same group. Therefore, dipstick data − and ± were treated as a reference group, and this study did not contribute to estimates of dipstick ±.

MRC Older People: This study categorized their dipstick data − and ± into the same group. Therefore, dipstick data − and ± were treated as a reference group, and this study did not contribute to estimates of dipstick ±. This study has not collected total cholesterol. This study consists of participants aged ≥75 years old and thus did not contribute to the subgroup analysis of younger population.

NHANESIII: This study did not collect data on total cholesterol, hypercholesterolemia, or use of anti-diabetic medications.

Ohasama: This study has not collected data on use of anti-diabetic medications.

Okinawa 83: This study has not collected data on fasting glucose, smoking, history of cardiovascular disease, anti-diabetic or anti-hypertensive medications.

Okinawa 93: This study has not collected data on fasting glucose, smoking, history of cardiovascular disease, anti-diabetic or anti-hypertensive medications.

ULSAM: This study measured urinary albumin excretion rate (μg/min), which was converted to mg/day by multiplying 1.44. All participants aged 65 or older and thus this study did not contribute to the subgroup analysis of younger population. This study consists of only men, thus did not contribute to the subgroup analysis of women.

2. High-risk cohorts

ADVANCE: This study is an intervention study which includes participants with diabetes only.

CARE: This study is an intervention study in which all patients had a previous myocardial infarction. This study did not include dipstick category “+++”. Due to many missing values, data for fasting glucose and BMI were not included.

KP Hawaii: In this study for participants with only ACR, PCR was imputed by ACR * 1.5.

MRFIT: This study is an intervention study which includes men only and thus did not contribute to the subgroup analysis of women.

Pima: This study consists entirely of Pima and the closely-related Tohono O'odham Indians. ACR was measured in a spot urine specimen. History of cardiovascular disease was not recorded in this study.

ZODIAC: This study includes only individuals with type 2 diabetes. This study has not collected data on fasting glucose or hypercholesterolemia.

3. CKD cohorts

AASK: This study is an intervention study which includes African American participants only. All participants were free of diabetes.

Geisinger: This study includes all Geisinger primary care recipients, 18 years or older as of index date, and who have CKD, defined as two or more outpatient eGFR values < 60 by CKD-EPI equation. Covariates obtained most closely to index date within a past year were included in models.

GLOMMS-1: This study did not collect data on use of anti-diabetic or anti-hypertensive medication, total cholesterol, systolic or diastolic blood pressure, or BMI. Diabetes and hypertension status were coded based on hospital physician or general practitioner diagnosis recorded in case notes. The ethnicity of the Grampian population is relatively homogenous with overall 98.3% of males and 98.4% of females being white. Indians account for 0.2% of the population, Pakistani and other South Asian individuals account for 0.3%, Chinese 0.3% and 0.8% are recorded as other.[51]

KPNW: This study defined diabetes using their own clinical tool that includes diagnosis codes, treatment codes, and laboratory values. This study has not collected use of anti-diabetic medications.

MASTERPLAN: This study measured ACR in patients with albuminuria in the low range, PCR in patients with overt proteinuria. Thus, for those participants with only ACR, PCR was imputed by ACR * 1.5.

MDRD: This study has not collected use of anti-diabetic or anti-hypertensive medications, use of statins, or hypercholesterolemia.

MMKD: This study measured 24h proteinuria.

RENAAL: This was a randomized controlled trial to determine whether the angiotensin receptor blocker losartan confers renoprotection in patients with type 2 diabetes and nephropathy.

Steno: Although this study has recruited type 1 diabetes mellitus patients with and without diabetic nephropathy, only participants with ACR ≥ 30 mg/g at baseline were included in this study as a CKD cohort. All participants had hypercholesterolemia.

Appendix 3. Acknowledgements and funding for collaborating cohorts

Study List of sponsors

Study	List of sponsors
AASK	NIDDK
ADVANCE	National Health and Medical Research Council of Australia program grant 571281; Servier
Aichi	KAKENHI (09470112, 13470087, 17390185, 18590594, 20590641, 20790438, 22390133)
ARIC	The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C). The authors thank the staff and participants of the ARIC study for their important contributions.
AusDiab	The Baker IDI Heart and Diabetes Institute, Melbourne, Australia, their sponsors, and the National Health and Medical Research Council of Australia (NHMRC grant 233200), Amgen Australia, Kidney Health Australia and The Royal Prince Alfred Hospital, Sydney, Australia.
BC Cohort	BC Provincial Renal Agency, an Agency of the Provincial Health Services Authority in collaboration with University of British Columbia.
Beaver Dam	NIH/NIDDK DK73217 NIH/NEI EY 006594
Beijing	The research for this study was supported by the Program for New Century Excellent Talents in University (BMU2009131) from the Ministry of Education of the People's Republic of China, and the grants for the Early Detection and Prevention of Non-communicable Chronic Diseases from the International Society of Nephrology Research Committee.
CARE	Alberta Heritage Foundation for Medical Research/Alberta Innovates Health Solutions Interdisciplinary Team Grants Program
CHS	The research reported in this article was supported by contracts HHSN268201200036C, N01-HC-85239, N01-HC-85079 through N01-HC- 85086, N01-HC-35129, N01 HC-15103, N01 HC-55222, N01-HC-75150, N01-HC-45133, and grant HL080295 from the National Heart, Lung, and Blood Institute (NHLBI), with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided through AG-023629, AG-15928, AG-20098, and AG-027058 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at http://www.chs-nhlbi.org/pi.htm.
CIRCS	N/A
COBRA	Wellcome Trust, UK
CRIB	British Renal Society Project Grant Award British Heart Foundation Project Grant Award.
ESTHER	Ministry of Research, Science and the Arts Baden-Württemberg (Stuttgart, Germany), Federal Ministry of Education and Research (Berlin, Germany), Federal Ministry of Family Affairs, Senior Citizens, Women and Youth (Berlin, Germany), European Commission FP7 framework programme of DG-Research (CHANCES Project). Measurement of urinary albumin was funded by Dade-Behring, Marburg, Germany.
Framingham	NHLBI Framingham Heart Study (N01-HC-25195).
Geisinger	Geisinger Clinic
GLOMMS-1	Chief Scientist Office CZH/4/656
Gubbio	Merck Sharp & Dohme – Italy; Municipal and Health Authorities of Gubbio, Italy; Center of Preventive Medicine, Gubbio, Italy; Istituto Superiore di Sanità, Rome, Italy; Federico II University, Naples, Italy; University of Milan, Milan, Italy; Northwestern University, Chicago, USA; University of Salerno, Italy.
HUNT	N/A
IPHS	N/A
KEEP	US National Kidney Foundation
KP Hawaii	N/A

Study	List of sponsors
KPNW	Amgen
MASTERPLAN	The MASTERPLAN study is a clinical trial with trial registration ISRCTN registry: 73187232. Sources of funding: The MASTERPLAN Study was supported by grants from the Dutch Kidney Foundation (Nierstichting Nederland, number PV 01), and the Netherlands Heart Foundation (Nederlandse Hartstichting, number 2003 B261). Unrestricted grants were provided by Amgen, Genzyme, Pfizer and Sanofi-Aventis.
MDRD	NIDDK UO1 DK35073 and K23 DK67303, K23 DK02904
MESA	This research was supported by contracts N01-HC-95159 through N01-HC-95169 from the National Heart, Lung, and Blood Institute. The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.
MMKD	The MMKD study was funded by the Austrian Heart Fund and by the Innsbruck Medical University.
MRC Older People	UK Medical Research Council, Department of Health for England, Wales and the Scottish Office and Kidney Research UK
MRFIT	The Multiple Risk Factor Intervention Trial was contracted by the National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH), Bethesda, Md. Follow-up after the end of the trial was supported with NIH/NHLBI grants R01-HL-43232 and R01-HL-68140. The principal investigators and senior staff of the clinical centers, coordinating center, other support centers and key committees are listed in a previous report (JAMA 1982; 248: 1465–1477).
NHANES III	United States Center for Disease Control
NephroTest	The NephroTest CKD cohort study is supported by grants from: Inserm GIS-IReSP AO 8113LS TGIR; French Ministry of Health AOM 09114 and AOM 10245; Inserm AO 8022LS; Agence de la Biomédecine R0 8156LL, AURA, and Roche 2009-152-447G. The Nephrotest initiative was also sponsored by unrestricted grants from F. Hoffman-La Roche Ltd. The authors thank the collaborators and the staff of the NephroTest Study: Gauci C, Karras A, Maruani G, Daugas E, d'Auzac C, Jacquot C, Thervet E, Roland M, Letavernier E, Boffa JJ, Ronco P, Fessi H, du Halgouet C, Vrtovsnik F, Urena P.
Ohasama	Grant-in-Aid(H20-22Junkankitou[Seishuu]-Ippan-009, 013 and H23-Junkankitou [Senshuu]-Ippan-005) from the Ministry of Health, Labor and Welfare, Health and Labor Sciences Research Grants, Japan; Japan Atherosclerosis Prevention Fund.
OKINAWA 83	N/A
OKINAWA 93	N/A
Pima	This work was supported by the Intramural Research Program of the National Institute of Diabetes and Digestive and Kidney Diseases
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Rancho Bernardo	NIA AG07181 and AG028507 NIDDK DK31801
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Study	List of sponsors
Severance	Seoul city R&BD program (10526), Korea, The National R&D Program for Cancer Control, Ministry for Health, Welfare and Family affairs, Republic of Korea (1220180), and The National Research Foundation of Korea(NRF) grant funded by the Korea government(MEST) (2011-0029348).
STENO	N/A
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ZODIAC	N/A

Appendix

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CKD-PC Steering Committee: Brad C Astor, Josef Coresh (Chair), Ron T Gansevoort, Brenda R Hemmelgarn, Paul E de Jong, Andrew S Levey, Adeera Levin, Kunihiro Matsushita, Chi-Pang Wen, Mark Woodward

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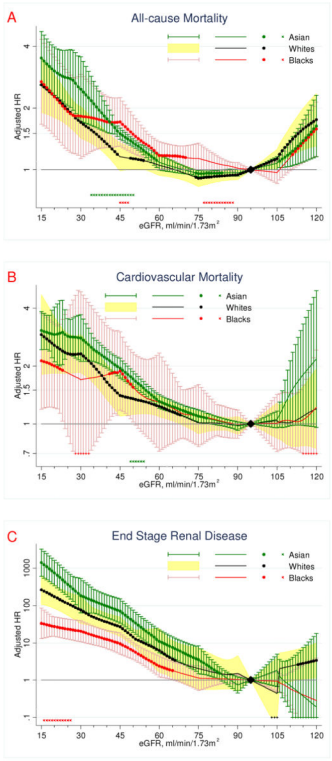


Figure 1.

Association of eGFR with all-cause mortality (A), cardiovascular mortality (B), and ESRD (C) across three racial groups in general population cohorts. The shaded area or whiskers represent 95% CIs. The reference (diamond) is eGFR 95 mL/min/1.73m2. Dots represent statistically significant points. Difference in HR among racial groups were tested using meta-regression with whites as a reference, and stars along the bottom of each panel indicate a significant interaction at P<0.05. HRs were adjusted for age, sex, smoking, systolic blood pressure, history of cardiovascular disease, diabetes, serum total cholesterol concentration, body mass index, and albuminuria.

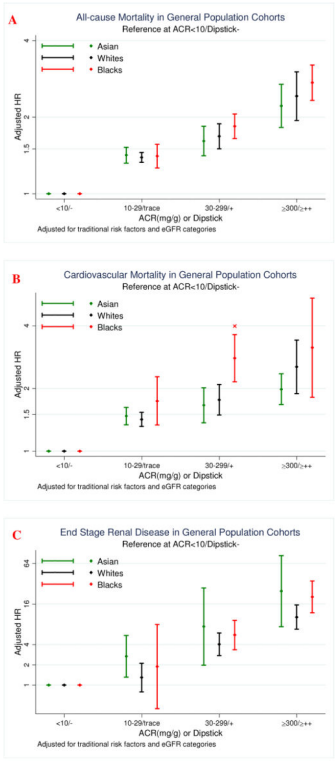
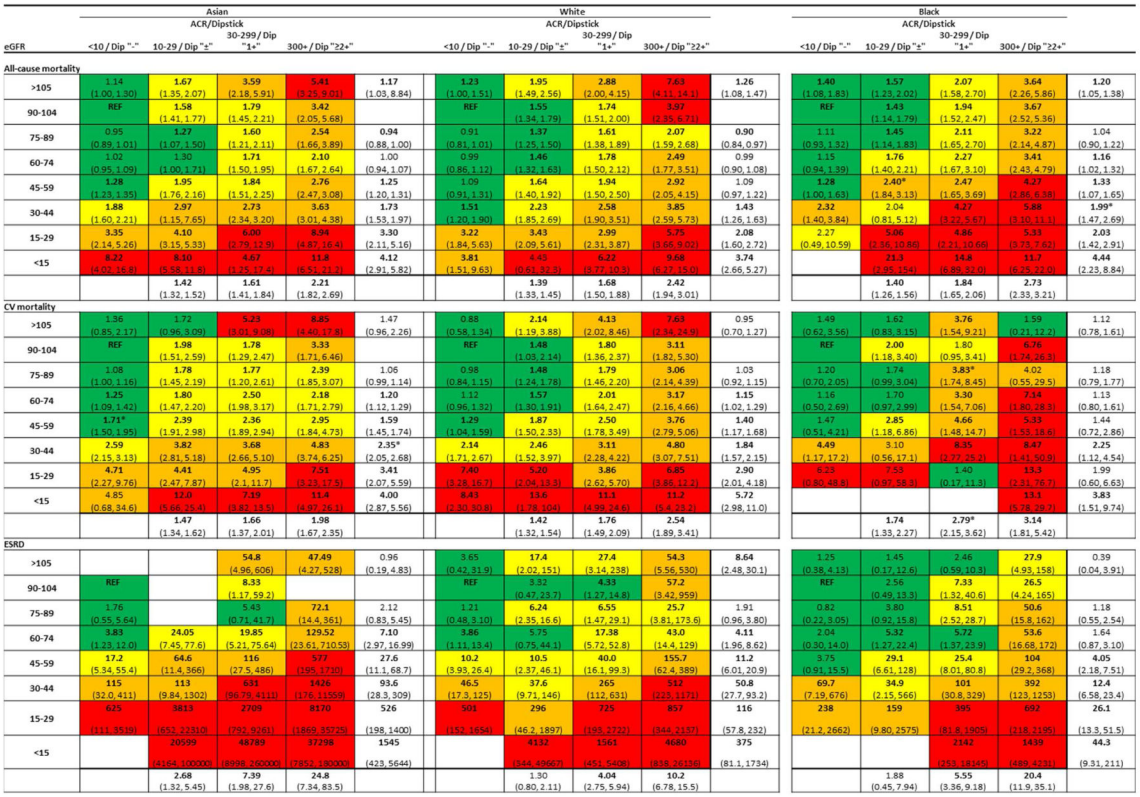


Figure 2.

Association of albuminuria with all-cause mortality (A), cardiovascular mortality (B), and ESRD (C) across three racial groups in general population cohorts. The whiskers represent 95% CIs. The reference category is ACR <10 mg/g or dipstick negative. Dots represent statistically significant points. Difference in hazard ratios (HR) among racial groups were tested using meta-regression with whites as a reference. HRs were adjusted for age, sex, smoking, systolic blood pressure, history of cardiovascular disease, diabetes, serum total cholesterol concentration, body mass index, and eGFR categories.



eGFR	Asian ACR/Dipstick <10 / Dip "-"	Asian 10-29 / Dip "±"	Asian 30-299 / Dip "1+"	Asian 300+ / Dip "2+"	Asian	White ACR/Dipstick <10 / Dip "-"	White 10-29 / Dip "±"	White 30-299 / Dip "1+"	White 300+ / Dip "2+"	White	Black ACR/Dipstick <10 / Dip "-"	Black 10-29 / Dip "±"	Black 30-299 / Dip "1+"	Black 300+ / Dip "2+"	Black
All-cause mortality															
>105	1.14 (1.00, 1.30)	**1.67** (1.35, 2.07)	**3.59** (2.18, 5.91)	**5.41** (3.23, 9.01)	**1.17** (1.03, 8.84)	**1.23** (1.00, 1.51)	**1.95** (1.49, 2.56)	**2.88** (2.00, 4.15)	**7.63** (4.11, 14.1)	**1.26** (1.08, 1.47)	**1.40** (1.08, 1.83)	**1.57** (1.23, 2.02)	**2.07** (1.58, 2.70)	**3.64** (2.26, 5.86)	**1.20** (1.05, 1.38)
90-104	REF	**1.58** (1.41, 1.77)	**1.79** (1.45, 2.21)	**3.42** (2.05, 5.68)		REF	**1.55** (1.34, 1.79)	**1.74** (1.51, 2.00)	**3.97** (2.35, 6.71)		REF	**1.43** (1.14, 1.79)	**1.94** (1.52, 2.47)	**3.67** (2.52, 5.36)	
75-89	0.95 (0.89, 1.01)	**1.27** (1.07, 1.50)	**1.60** (1.21, 2.11)	**2.54** (1.66, 3.89)	**0.94** (0.88, 1.00)	0.91 (0.81, 1.01)	**1.37** (1.25, 1.50)	**1.61** (1.38, 1.89)	**2.07** (1.59, 2.68)	**0.90** (0.84, 0.97)	1.11 (0.95, 1.32)	**1.45** (1.14, 1.83)	**2.11** (1.65, 2.70)	**3.22** (2.14, 4.87)	1.04 (0.90, 1.22)
60-74	1.02 (0.95, 1.09)	1.30 (1.00, 1.71)	**1.71** (1.50, 1.95)	**2.10** (1.67, 2.64)	1.00 (0.94, 1.07)	0.99 (0.86, 1.12)	**1.46** (1.32, 1.63)	**1.78** (1.50, 2.12)	**2.49** (1.77, 3.51)	0.99 (0.90, 1.08)	1.15 (0.94, 1.39)	**1.76** (1.40, 2.21)	**2.27** (1.67, 3.10)	**3.41** (2.43, 4.79)	**1.16** (1.02, 1.32)
45-59	**1.28** (1.25, 1.35)	**1.95** (1.76, 2.16)	**1.84** (1.51, 2.25)	**2.76** (2.47, 3.08)	**1.25** (1.20, 1.31)	1.09 (0.91, 1.31)	**1.64** (1.40, 1.92)	**1.94** (1.50, 2.50)	**2.92** (2.05, 4.15)	1.09 (0.97, 1.22)	**1.28** (1.00, 1.63)	**2.40*** (1.84, 3.13)	**2.47** (1.65, 3.69)	**4.27** (2.86, 6.38)	**1.33** (1.07, 1.65)
30-44	**1.88** (1.60, 2.21)	**2.97** (2.15, 7.65)	**2.73** (2.34, 3.20)	**3.63** (3.01, 4.38)	**1.73** (1.53, 1.97)	**1.51** (1.20, 1.90)	**2.23** (1.85, 2.69)	**2.58** (1.90, 3.51)	**3.85** (2.59, 5.73)	**1.43** (1.26, 1.63)	**2.32** (1.40, 3.84)	2.04 (0.81, 5.12)	**4.27** (3.22, 5.67)	**5.88** (3.10, 11.1)	**1.99*** (1.47, 2.69)
15-29	**3.35** (2.14, 5.26)	**4.10** (3.15, 5.33)	**6.00** (2.79, 12.9)	**8.94** (4.87, 16.4)	**3.30** (2.11, 5.16)	**3.22** (1.84, 5.63)	**3.43** (2.09, 5.61)	**2.99** (2.31, 3.87)	**5.75** (3.65, 9.02)	**2.08** (1.60, 2.72)	2.27 (0.49, 10.59)	**5.06** (2.36, 10.86)	**4.86** (2.21, 10.66)	**5.33** (3.73, 7.62)	**2.03** (1.42, 2.91)
<15	**8.22** (4.02, 16.8)	**8.10** (5.58, 11.8)	**4.67** (1.25, 17.4)	**11.8** (6.51, 21.2)	**4.12** (2.91, 5.82)	**3.81** (1.51, 9.63)	4.43 (0.61, 32.3)	**6.22** (3.77, 10.3)	**9.68** (6.27, 15.0)	**3.74** (2.66, 5.27)		**21.3** (2.95, 154)	**14.8** (6.89, 32.0)	**11.7** (6.25, 22.0)	**4.44** (2.23, 8.84)
		1.42 (1.32, 1.52)	**1.61** (1.41, 1.84)	**2.21** (1.82, 2.69)			**1.39** (1.33, 1.45)	**1.68** (1.50, 1.88)	**2.42** (1.94, 3.01)			**1.40** (1.26, 1.56)	**1.84** (1.65, 2.06)	**2.73** (2.33, 3.21)	
CV mortality															
>105	1.36 (0.85, 2.17)	1.72 (0.96, 3.09)	**5.23** (3.01, 9.08)	**8.85** (4.40, 17.8)	1.47 (0.96, 2.26)	0.88 (0.58, 1.34)	**2.14** (1.19, 3.88)	**4.13** (2.02, 8.46)	**7.63** (2.38, 24.4)	0.95 (0.70, 1.27)	1.49 (0.62, 3.56)	1.62 (0.83, 3.15)	**3.76** (1.54, 9.21)	1.59 (0.21, 12.2)	1.12 (0.78, 1.61)
90-104	REF	**1.98** (1.51, 2.59)	**1.78** (1.29, 2.47)	**3.33** (1.71, 6.46)		REF	**1.48** (1.03, 2.14)	**1.80** (1.36, 2.37)	**3.11** (1.82, 5.30)		REF	**2.00** (1.18, 3.40)	1.80 (0.95, 3.41)	6.76 (1.74, 26.3)	
75-89	1.08 (1.00, 1.16)	**1.78** (1.45, 2.19)	**1.77** (1.20, 2.61)	**2.39** (1.85, 3.07)	1.06 (0.99, 1.14)	0.98 (0.84, 1.15)	**1.48** (1.24, 1.78)	**1.79** (1.46, 2.20)	**3.06** (2.14, 4.39)	1.03 (0.92, 1.15)	1.20 (0.70, 2.05)	1.74 (0.99, 3.04)	**3.83*** (1.74, 8.45)	4.02 (0.55, 29.5)	1.18 (0.79, 1.77)
60-74	**1.25** (1.09, 1.42)	**1.80** (1.47, 2.20)	**2.50** (1.98, 3.17)	**2.18** (1.71, 2.79)	**1.20** (1.12, 1.29)	1.12 (0.96, 1.32)	**1.57** (1.30, 1.91)	**2.01** (1.64, 2.47)	**3.17** (2.16, 4.66)	**1.15** (1.02, 1.29)	1.16 (0.50, 2.69)	1.70 (0.97, 2.99)	**3.30** (1.54, 7.06)	**7.14** (1.80, 28.3)	1.13 (0.80, 1.61)
45-59	**1.71*** (1.50, 1.95)	**2.39** (1.91, 2.98)	**2.36** (1.89, 2.94)	**2.95** (1.84, 4.73)	**1.59** (1.45, 1.74)	**1.29** (1.04, 1.59)	**1.87** (1.50, 2.33)	**2.50** (1.78, 3.49)	**3.76** (2.79, 5.06)	**1.40** (1.17, 1.68)	1.47 (0.51, 4.21)	**2.85** (1.18, 6.86)	**4.66** (1.48, 14.7)	**5.33** (1.53, 18.6)	1.44 (0.72, 2.86)
30-44	**2.59** (2.15, 3.13)	**3.82** (2.81, 5.18)	**3.68** (2.66, 5.10)	**4.83** (3.74, 6.25)	**2.35*** (2.05, 2.68)	**2.14** (1.71, 2.67)	**2.46** (1.52, 3.97)	**3.11** (2.28, 4.22)	**4.80** (3.07, 7.51)	**1.84** (1.57, 2.15)	**4.49** (1.17, 17.2)	3.10 (0.56, 17.1)	**8.35** (2.77, 25.2)	**8.47** (1.41, 50.9)	**2.25** (1.12, 4.54)
15-29	**4.71** (2.27, 9.76)	**4.41** (2.47, 7.87)	**4.95** (2.1, 11.7)	**7.51** (3.23, 17.5)	**3.41** (2.07, 5.59)	**7.40** (3.28, 16.7)	**5.20** (2.04, 13.3)	**3.86** (2.62, 5.70)	**6.85** (3.85, 12.2)	**2.90** (2.01, 4.18)	6.23 (0.80, 48.8)	2.53 (0.97, 58.3)	1.40 (0.17, 11.3)	**13.3** (2.31, 76.7)	1.99 (0.60, 6.63)
<15	4.85 (0.68, 34.6)	**12.0** (5.66, 25.4)	**7.19** (3.82, 13.5)	**11.4** (4.97, 26.1)	**4.00** (2.87, 5.56)	**8.43** (2.30, 30.8)	**13.6** (1.78, 104)	**11.1** (4.99, 24.6)	**11.2** (5.4, 23.2)	**5.72** (2.98, 11.0)				**13.1** (5.78, 29.7)	**3.83** (1.51, 9.74)
		1.47 (1.34, 1.62)	**1.66** (1.37, 2.01)	**1.98** (1.67, 2.35)			**1.42** (1.32, 1.54)	**1.76** (1.49, 2.09)	**2.54** (1.89, 3.41)			**1.74** (1.33, 2.27)	**2.79*** (2.15, 3.62)	**3.14** (1.81, 5.42)	
ESRD															
>105			**54.8** (4.96, 606)	**47.49** (4.27, 528)	0.96 (0.19, 4.83)	**3.65** (0.42, 31.9)	**17.4** (2.02, 151)	**27.4** (3.14, 238)	**54.3** (5.56, 530)	**8.64** (2.48, 30.1)	1.25 (0.38, 4.13)	1.45 (0.17, 12.6)	2.46 (0.59, 10.3)	**27.9** (4.93, 158)	0.39 (0.04, 3.91)
90-104	REF		**8.33** (1.17, 59.2)			REF	**3.52** (0.47, 23.7)	**4.33** (1.27, 14.8)	**57.2** (3.42, 959)		REF	2.56 (0.49, 13.3)	**7.33** (1.32, 40.6)	**26.5** (4.24, 165)	
75-89	1.76 (0.55, 5.64)		5.43 (0.71, 41.7)	**72.1** (14.4, 361)	2.12 (0.83, 5.45)	1.21 (0.48, 3.10)	**6.24** (2.35, 16.6)	**6.55** (1.47, 29.1)	**25.7** (3.81, 173.6)	1.91 (0.96, 3.80)	0.82 (0.22, 3.05)	3.80 (0.92, 15.8)	**8.51** (2.52, 28.7)	**50.6** (15.8, 162)	1.18 (0.55, 2.54)
60-74	**3.83** (1.23, 12.0)	**24.05** (7.45, 77.6)	**19.85** (5.21, 75.64)	**129.52** (23.61, 710.53)	**7.10** (2.97, 16.99)	**3.86** (1.11, 13.4)	**5.75** (0.75, 44.1)	**17.38** (5.72, 52.8)	**43.0** (14.4, 129)	**4.11** (1.96, 8.62)	2.04 (0.30, 14.0)	**5.32** (1.27, 22.4)	**5.72** (1.37, 23.9)	**53.6** (16.68, 172)	1.64 (0.87, 3.10)
45-59	**17.2** (5.34, 55.4)	**64.6** (11.4, 366)	**116** (27.5, 486)	**577** (195, 1710)	**27.6** (11.1, 68.7)	**10.2** (3.93, 26.4)	**10.5** (2.37, 46.1)	**40.0** (16.1, 99.3)	**155.7** (62.4, 389)	**11.2** (6.01, 20.9)	3.75 (0.91, 15.5)	**29.1** (6.61, 128)	**25.4** (8.01, 80.8)	**104** (29.2, 368)	**4.05** (2.18, 7.51)
30-44	**115** (32.0, 411)	**113** (9.84, 1302)	**651** (86.75, 4111)	**1426** (176, 11559)	**93.6** (28.3, 309)	**46.5** (17.3, 125)	**37.6** (9.71, 146)	**265** (112, 631)	**512** (225, 1171)	**50.8** (27.7, 93.2)	**69.7** (7.19, 676)	**34.9** (2.15, 566)	**101** (30.8, 329)	**392** (123, 1253)	**12.4** (6.58, 23.4)
15-29	**625** (111, 3519)	**3813** (652, 22310)	**2709** (792, 9261)	**8170** (1869, 35725)	**526** (198, 1400)	**501** (152, 1654)	**296** (46.2, 1897)	**725** (193, 2722)	**857** (344, 2137)	**116** (57.8, 232)	**238** (21.2, 2662)	**159** (9.80, 2575)	**395** (81.8, 1905)	**692** (218, 2195)	**26.1** (13.3, 51.5)
<15		**20599** (4164, 100000)	**48789** (8998, 260000)	**37298** (7852, 180000)	**1545** (423, 5644)		**4132** (344, 49667)	**1561** (451, 5408)	**4680** (838, 26136)	**375** (81.1, 1734)			**2142** (253, 18145)	**1439** (489, 4231)	**44.3** (9.31, 211)
		2.68 (1.32, 5.45)	**7.39** (1.98, 27.6)	**24.8** (7.34, 83.5)			**1.30** (0.80, 2.11)	**4.04** (2.75, 5.94)	**10.2** (6.78, 15.5)			**1.88** (0.45, 7.94)	**5.55** (3.36, 9.18)	**20.4** (11.9, 35.1)	

Figure 3.

Hazard ratios (HRs) of clinical outcomes according to eGFR and albuminuria categories across three racial groups in general population cohorts. Each number represents a pooled HR from meta-analysis adjusted for covariates and compared with the reference cell (REF) within each race. Bold numbers indicate statistical significance at P<0.05. Color shading indicates the strength of association (approximately one quarter of all cells across racial groups are shaded in each color; Green: low; yellow: mild; orange: moderate; red: high). Difference in HR among racial groups were tested using meta-regression with whites as a reference, and stars (*) indicate a significant interaction at P<0.05.

White										Black									
male	%DM	% HTN	% Hx of CVD	% HC	% Smoking	eGFR mean	% Alb[a]	% eGFR <60	% N	Age	% Female	%DM	% HTN	% Hx of CVD	% HC	% Smoking	eGFR mean	% Alb[a]	% eGFR <60
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
%	14%	42%	13%	37%	14%	83	7%	7%	22%	62	64%	27%	67%	15%	33%	18%	90	14%	7%
%	8%	33%	8%	45%	16%	86	7%	6%	-	-	-	-	-	-	-	-	-	-	-
%	10%	51%	15%	54%	20%	80	4%	15%	0.02%‡	56	100%	0%	100%	0%	0%	100%	89	0%	0%
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
%	14%	61%	31%	37%	7%	73	20%	21%	17%	77	35%	22%	77%	32%	41%	12%	77	23%	21%
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
%	19%	60%	17%	46%	16%	84	12%	14%	-	-	-	-	-	-	-	-	-	-	-
%	10%	40%	6%	22%	15%	88	12%	7%	-	-	-	-	-	-	-	-	-	-	-
%	5%	39%	5%	48%	31%	84	4%	1%	-	-	-	-	-	-	-	-	-	-	-
%	18%	82%	23%	N/A	21%	85	12%	11%	-	-	-	-	-	-	-	-	-	-	-
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
%	6%	39%	0%	31%	12%	78	6%	11%	28%	62	55%	18%	59%	0%	26%	18%	85	12%	8%
%	8%	76%	18%	N/A	11%	57	7%	57%	-	-	-	-	-	-	-	-	-	-	-
%	10%	35%	15%	N/A	24%	90	11%	11%	27%	42	55%	13%	31%	8%	N/A	32%	108	13%	5%
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
%	4%	34%	5%	40%	34%	88	11%	4%	1%‡	43	54%	6%	36%	2%	20%	29%	103	15%	2%
%	12%	56%	10%	29%	8%	73	15%	22%	0.07%‡	84	100%	0%	100%	0%	100%	0%	48	0%	100%
%	15%	51%	33%	N/A	12%	82	12%	11%	40%	64	62%	29%	71%	33%	N/A	17%	89	19%	11%

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Asian																		
Study	**Total N**	**%N**	**Age**	**% Female**	**%DM**	**% HTN**	**% Hx of CVD**	**% HC**	**% Smoking**	**eGFR mean**	**% Alb[a]**	**% eGFR <60**	**% N**	**Age**	**% Female**	**%DM**	**% HTN**	**C**
Severance	76201	100%	46	49%	6%	25%	1%	37%	29%	90	5%	2%	-	-	-	-	-	
Taiwan	515573	100%	42	50%	5%	17%	4%	13%	24%	93	2%	4%	-	-	-	-	-	
ULSAM*	1103	-	-	-	-	-	-	-	-	-	-	-	100%	71	0%	19%	75%	3
Overall GP	940366	87%	46	53%	5%	23%	4%	16%	25%	90	3%	5%	11%	63	53%	12%	52%	1
Percent using ACR		1%											73%					
High Risk																		
ADVANCE*	10595	39%	65	46%	100%	75%	22%	45%	14%	81	36%	14%	59%	67	40%	100%	87%	2
CARE	4098	-	-	-	-	-	-	-	-	-	-	-	93%	59	13%	13%	85%	1
KEEP	77902	6%	54	62%	29%	56%	9%	N/A	7%	88	13%	10%	46%	58	66%	31%	68%	1
KP Hawaii†	39884	-	-	-	-	-	-	-	-	-	-	-	100%	59	50%	48%	N/A	1
MRFIT	12854	1%	46	0%	10%	71%	0%	55%	36%	88	8%	0%	90%	46	0%	4%	65%	
Pima*	5066	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
ZODIAC*	1095	-	-	-	-	-	-	-	-	-	-	-	100%	68	57%	100%	87%	3
Overall HR	151494	6%	59	53%	63%	66%	15%	45%	10%	85	24%	12%	65%	58	48%	39%	71%	1
Percent using ACR		48%											7%					
CKD																		
AASK†	1094	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
BC CKD*	17426	24%	70	43%	39%	77%	20%	16%	2%	35	91%	92%	65%	69	46%	38%	83%	3
CRIB*	308	6%	53	25%	10%	100%	30%	N/A	N/A	20	95%	100%	88%	63	34%	16%	94%	4
Geisinger ACR*	3361	0.2%‡	67	33%	100%	100%	17%	100%	0%	51	50%	100%	98%	70	54%	96%	88%	3
Geisinger dipstick	4509	0.06%‡	70	33%	33%	33%	67%	0%	0%	40	67%	100%	99%	72	62%	27%	76%	3
GLOMMS-1 ACR*	537	-	-	-	-	-	-	-	-	-	-	-	100%	73	51%	93%	64%	4
GLOMMS-1 PCR†	470	-	-	-	-	-	-	-	-	-	-	-	100%	70	48%	48%	61%	3
KPNW	1627	2%‡	63	40%	40%	96%	36%	20%	8%	45	52%	92%	94%	72	56%	38%	93%	4
MASTERPLAN*	636	4%‡	57	46%	12%	96%	23%	81%	15%	38	85%	73%	92%	61	30%	35%	95%	2

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Asian																		
Study	**Total N**	**%N**	**Age**	**% Female**	**%DM**	**% HTN**	**% Hx of CVD**	**% HC**	**% Smoking**	**eGFR mean**	**% Alb[a]**	**% eGFR <60**	**% N**	**Age**	**% Female**	**%DM**	**% HTN**	**C**
MDRD[†]	1730	-	-	-	-	-	-	-	-	-	-	-	80%	51	38%	5%	N/A	1
MMKD[†]	202	-	-	-	-	-	-	-	-	-	-	-	100%	47	34%	N/A	89%	1
NephroTest[*]	928	-	-	-	-	-	-	-	-	-	-	-	90%	61	32%	27%	93%	1
RENAAL[*]	1513	17%	60	32%	100%	98%	19%	64%	21%	39	100%	95%	49%	61	33%	100%	97%	3
STENO[*]	886	-	-	-	-	-	-	-	-	-	-	-	100%	44	43%	100%	64%	
Sunnybrook[*]	3385	-	-	-	-	-	-	-	-	-	-	-	100%	68	44%	51%	86%	4
Overall CKD	38612	12%	69	43%	42%	7%	21%	4%	4%	35	91%	92%	78%	68	48%	47%	50%	3
Percent using ACR		99%											73%					

Abbreviations: eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; ACR, urine albumin-to-creatinine ratio; PCR, urine protein-to-creatinine ratio.

[*] Studies with ACR,

[†] Studies with PCR.

[‡] Not included in meta-analysis due to small number of events (<10) in this racial group.

[a] Proportion of participants with ACR ≥30 mg/g or PCR ≥50 mg/g or dipstick protein ≥1.

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