

Title: Longitudinal comparison of outcomes across the International Network of Chronic Kidney Disease (iNET-CKD) cohorts: a collaborative, individual-level analysis

Running Title: CKD progression in iNET-CKD

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Abstract

Rates of CKD progression, ESRD, all-cause mortality, and cardiovascular (CVD) events among individuals with CKD vary widely across countries. Well-characterized demographic, comorbidity, and laboratory markers captured for prospective cohorts may explain, in part, such differences. To investigate whether core characteristics of individuals with CKD explain differences in rates of outcomes, we conducted an individual-level analysis of 8 cohort studies that are part of iNET-CKD, an international network of CKD cohort studies. Overall, the rate of CKD progression was 40 events/1000 persons-year (95%CI 39 - 41), 28 (95%CI 27 - 29) for ESRD, 41 (95%CI 40 - 42) for death, and 29 (95%CI 28 - 30) for CVD events, but standardized rates were highly heterogeneous across studies ($I^2 > 92.5\%$). Interactions by study group on the association between baseline characteristics and outcomes were identified. For example, the adjusted HR for CKD progression was 0.44 (95% CI 0.35 – 0.56) for women vs. men among the Japanese (CKD-JAC), while it was 0.66 (95%CI 0.59 – 0.75) among the Uruguayan (NRHP). Also, the adjusted HR for ESRD was 2.02 (95% CI 1.88 – 2.17) per 10 units lower baseline eGFR among Americans (CRIC), while it was 3.01 (95% CI 2.57 - 3.53) among Canadians (Can-PREDDICT) (interaction p-value<0.001 for comparisons across all studies). The risks of CKD progression, ESRD, death, and CVD vary across countries even after accounting for the distributions of age, sex, comorbidities, and laboratory markers. These findings support the need for a better understanding of specific factors in different populations that explain this variation.

Key words: CKD, international comparisons, risk factors, CKD progression, epidemiology

Introduction

The prevalence of chronic kidney disease (CKD) and its complications vary widely around the globe¹⁻³. Comparisons across general-population registries from different countries have highlighted regional variation in the global burden of CKD^{4,5}. A deeper understanding of such differences, however, requires more granular information than is typically available in population registries. Many prospective cohorts examining CKD patients are underway internationally, gathering detailed information on the phenotypes and outcomes of their participants⁶⁻¹³. Comparing and contrasting their findings represents an important opportunity to explore and explain the differences across countries, potentially identifying factors associated with adverse consequences of CKD.

The prevalence of CKD and end-stage renal disease (ESRD) vary, at least in part, because of variations in the incidence of CKD, use of renal replacement therapy, and death across countries^{14,15}. Cohort studies and prospective registries are a valuable resource for such comparisons as they characterize their population in detail, including a range of baseline characteristics, and ascertain outcomes in a standardized fashion. ESRD and halving of estimated glomerular filtration rate (eGFR) serve as surrogate markers for CKD progression¹⁶, while death and cardiovascular (CVD) events represent other important and common clinical outcomes in the CKD population. When compared internationally, the rates of ESRD may differ because the definitions may differ (initiation of dialysis versus achievement of a certain threshold of kidney function), because of differences in patterns of practice (preferred choice for early versus late initiation of dialysis) and because of differences in the availability of

healthcare resources (public versus private kidney transplantation and dialysis programs)¹⁷ .

Likewise, mortality in the general population varies from country to country. These variations influence differences in the background risk of death among patients with CKD who live in different countries. Overall, differences in health outcomes for populations with CKD may reflect contrasts in access and quality of health care, beyond environmental^{18,19} , nutritional²⁰ , socioeconomic²¹⁻²³ , and genetic factors²⁴ . Unless such differences are explored, opportunities for improved understanding of reasons for differences in outcomes are limited²⁵⁻²⁷ .

Another relevant aspect of the global contrasts of CKD and its associated outcomes is the variation in prevalence of well-characterized risk factors for CKD progression, like diabetes and hypertension^{3,28} . Such differences, which are easily identifiable in prospective studies of individuals with CKD may, in large part, explain differences in rates of outcomes. Beyond the opportunity to describe these cross-sectional differences, comparing international CKD studies may also show that the relationship between established risk factors and outcomes differ across the various populations over time. The connection between well-characterized risk factors and local aspects of climate, culture, health practice, nutritional habits, and genetics may inform particular levels of risk. Exploring how the magnitude of association between risk factors and outcomes differs from country to country may reveal how the biological impact of such factors interacts with the environment. Characterizing this phenomenon might help us understand different patterns of CKD progression made possible through comparisons across country borders.

In addition to the opportunity to generate new hypotheses, international comparisons of CKD may help promote our understanding of health disparities. Even though most cohorts do not perfectly resemble their country's source population of individuals with CKD, they provide an opportunity to implement a detailed evaluation of kidney disease as it exists in varied geographic settings.

Motivated by the goal of enhancing the capacity to evaluate international comparisons in CKD, the International Society of Nephrology (ISN) established iNET-CKD in 2012. iNET-CKD studies are able to contribute both study and individual-level data toward meta-analyses and promise to enhance our understanding of the genesis of differences in the patterns of CKD across national boundaries. Within a subset of iNET-CKD cohort studies, we sought to describe the variation in outcomes in geographically distinct CKD populations to enhance our understanding of the sources of variability in CKD progression, death, and CVD events.

Results:

Baseline contrasts across cohorts. A total of 23,484 participants with CKD from 8 iNET-CKD studies were analyzed. Median age of participants was 68 years (IQR 59 - 75) with a median duration of follow-up of 4.1 years (IQR 2.5 - 6.8). The proportion of women in these cohorts varied from 35% in ICKD (India) to 48% in CKD-QLD (Australia). The prevalence of diabetes ranged from 24% in ICKD (India) to 52% in CRIC (USA). A history of hypertension varied from 73% in RIISC (GBR) to 99% in KNOW-CKD (Korea), while history of CVD ranged from 7% in KNOW-CKD (Korea) to 58% in CKD-QLD (Australia). The proportion of current smokers varied

from 6% of participants in NRHP (Uruguay) to 17% in CKD-JAC (Japan). Further details on baseline characteristics are provided in **Table1**, **Fig1**, and **FigS1**.

Rates of events. Crude incidence rates of CKD progression, ESRD, death, and CVD events were highly heterogeneous across studies. Even after adjustments for age, sex, entry levels of eGFR, and albuminuria, comparing the incidence rates for all four outcomes provided I^2 statistics above 92.5% (95%CI 88.5 - 99.5%) and Cochran's Q p-value<0.05 (**Fig2** and **FigS2A-C**).

Population attributable risk percent (PARP). We used PARP to assess the unadjusted association between baseline characteristics and the development of outcomes. For example, in **Fig3C**, the PARP associated with diabetes was between 40 and 50% among Koreans (KNOW-CKD), meaning that in the hypothetical scenario that diabetes was eradicated from this population, the risk of all-cause mortality would be potentially reduced by 40 to 50%. PARP for CKD progression and ESRD were, overall, lower for age \geq 65 years and higher for eGFR \leq 30ml/min/1.73m², urinary albumin-over-creatinine ratio (uACR) \geq 300mg/dL, hemoglobin \leq 12mg/dL, and serum albumin \leq 4mg/dl (**Fig3A-B**). For the outcomes of death and CVD events, the PARP were higher among those aged \geq 65 years, with a history of diabetes, and with a history of CVD (**Fig3C-D**). The patterns of association between risk factors and outcomes differed, suggesting that they were influenced by the setting and/or differences in populations across cohorts. The point estimates (95%CI) for all PARPs are presented in **TableS1A-D**.

Interactions by study. Various interactions by study on the association between selected baseline characteristics and the risk of CKD progression, ESRD, all-cause mortality, and CVD were identified (**Table2A-D**). For example, a 10-unit lower baseline eGFR in CRIC (US) was

associated with an adjusted hazard ratio (HR) for CKD progression of 1.60 (95%CI 1.51 - 1.71), while in NRHP (Uruguay) the adjusted HR was 1.88 (95%CI 1.78 - 1.99), representing a 18% higher relative risk in NRHP for individuals with same sex, age, body mass index, diabetes, CVD status, and laboratory markers. In another example, for the outcome ESRD, in KNOW-CKD (Korea), a 1-unit higher level of log-transformed uACR was associated with a HR of 1.16 (95%CI 1.07 - 1.25), while in CKD-JAC (Japan), this HR was 1.98 (95%CI 1.69 – 2.31), representing a 71% higher relative risk in CKD-JAC. Likewise, for death, the adjusted HR of a 1-unit higher level of serum albumin in NRHP was 1.19 (95%CI 1.06 – 1.34), while in CKD-JAC it was 3.15 (95%CI 1.74 – 5.70). Moreover, some of the risk factors studied were significantly related to outcomes in some of the cohorts but not in others. The association between history of diabetes and CVD events was substantial in KNOW-CKD (HR 1.87, 95%CI 1.15 – 3.04) and CKD-JAC (HR 2.18, 95%CI 1.53 - 3.10), but not significant in RIISC (GBR) or Can-PREDDICT (Canada).

To confirm these results, we pooled data on baseline characteristics from all studies and identified three latent-classes, or groups of participants, ignoring study origin. On average, group 1 was characterized by lower prevalence of diabetes (18%) and lower systolic blood pressure (124 +/- 15 mmHg). Group 2 was characterized by older age (median 70, IQR 64 – 75 years), and higher prevalence of history of CVD events at baseline (53%). Group 3 was characterized by lower eGFR (28, IQR 21- 37 mL/min/1.73m²) and higher uACR (median 1009, IQR 455-2240 mg/g) (**TableS2A**). We then tested for the interaction by study on the association between latent class and outcome using Cox proportional hazards models. Interactions by study group were confirmed for all outcomes (**TableS2B**).

As another secondary approach, we replicated all analyses including only individuals followed for at least one year before withdrawal or death (not shown). With this strategy, we aimed to attenuate differences in population composition imposed by disparate inclusion criteria across studies (**Table3**), reducing the impact of events experienced by sicker patients soon after enrolling into health system registries. Finally, we repeated the Cox Models excluding the NRHP cohort (Uruguay), which comprised half of the total population in the main analysis. Results for all sensitivity analyses were consistent with the main analytic approach.

Discussion

We hypothesized that commonly assessed characteristics would substantially explain the differences in incidence rates of four clinical outcomes across CKD follow-up studies implemented in various countries around the globe. While distributions of age, sex, and body mass reflect the core demographic distributions of each study, history of comorbidities and laboratory markers served as proxies for health status, diet, and health care quality. However, we observed that differences in the rates of CKD progression, ESRD, death, and CVD events across studies were not substantially attenuated after adjustment for individual-level characteristics, indicating that other factors potentially related to study setting strongly influence outcomes across these diverse populations. In addition, we observed that the magnitude of the association of individual-level predictors with clinical outcomes varied substantially from study to study.

Interactions by study. It has been widely recognized that lower levels of eGFR and higher levels of albuminuria are associated with an increased risk of ESRD, and CKD progression²⁹⁻³². It has

also been observed that the magnitudes of such associations were quantitatively different across studies²⁹⁻³². Here, we were able to directly compare these associations integrating individual-level data from studies that included diverse populations with CKD. Consistent with previous reports, eGFR and ACR were the stronger predictors of CKD progression and ESRD across all studies. However, the strength of association between these predictors and outcomes were variable. This variability was also observed for other well-established predictors. Our key finding was that levels of association were highly variable from one CKD population to another, despite adjustments for well-established risk factors for disease progression.

Contrast with other international comparisons. Previous studies have compared the prevalence of comorbidities and incidence of CKD complications across populations with CKD from different countries^{1,5,33,34}. A study of five international CKD cohorts reported a variable prevalence of masked and sustained hypertension assessed by 24-hour blood pressure monitoring despite adjustments for comorbidities and levels of eGFR³³. Another study explored differences in the incidence of ESRD between white individuals in the US and those from Norway, standardized for age and sex⁵. Although Norwegians had a slightly lower prevalence of CKD compared to Americans, the incidence of ESRD was up to three times higher among Americans, indicating a higher rate of CKD progression in the US²³. The higher prevalence of hypertension, obesity, and diabetes among Americans was a potential explanation for the augmented risk of CKD progression in the US. Also, differences in care of CKD complications in Norway, reflected by higher levels of hemoglobin and serum albumin, were proposed as explanations for the observed disparity. Another study showed that even within the same continent, where racial diversity is attenuated, differences across studies occur³⁴. The European

CKD Burden Consortium compared the risk of death and eGFR decline across nine cohorts from five European countries. Again, despite adjustments for comorbidities and kidney function, findings varied extensively country-to-country. In contrast to previous studies, we implemented adjustments beyond eGFR and comorbidities, including core laboratory markers of kidney function and metabolism. Despite these adjustments, the associations between predictors and outcomes varied across iNET-CKD studies.

Between-study variability. The sizeable between-study variability observed in this study confirms that each study represents a different source population. Differences in genetics, culture, lifestyle, socioeconomic status, health care, and health access may be underlying causes for observed inter-study differences. For example, in the US, individuals of African ancestry with high-risk variants for Apol1, present an increased risk of developing poor outcomes. Individuals with this genetic background have not been reported in other cohorts included in our study. Also, in the US, access to health insurance coverage depends on individual enrollment, while in Australia and Canada, it is universally covered. Both aspects would tend to increase the risks among the US population compared to others, but they were not evaluated in this study.

Relative burden of death and ESRD. The burden of death in relation to ESRD was heterogeneous across the populations studied. In Asian cohorts, for example, the adjusted rates of death were significantly lower than in the other studies. It has been shown that differences in the mortality rates for the general population may largely explain international differences in mortality for patients on dialysis¹⁵, which may also play a role among individuals

with CKD not on dialysis. Beyond that, as we focused on censored rates of death, the competing risk of ESRD, which reduces the pool of individuals at risk for death, interferes with the risk of death. Still, even among groups with similar risks of death, the rates of CKD progression and ESRD were quite variable.

Limitations. This study has limitations. We studied a subset of iNET-CKD cohorts, which enrolled individuals with CKD according to varied research protocols. Differences in enrollment criteria may have been responsible for differences in the incidence of events across studies. For example, healthier patients might have been selected into cohort studies compared to registry-based studies. While most cohorts excluded individuals with severe comorbidities like cancer or advanced heart failure, such patients were likely represented in registries. To help reduce the impact of this potential problem, in a sensitivity analysis, we began follow-up only after individuals had been in the cohort for one year, thereby reducing the impact of events experienced by sicker patients soon after enrolling into health system registries, with similar findings.

Measurement error associated with differences in creatinine calibration assays across studies was also likely, as well as differences in other laboratory assessments. While we used the CKD-EPI formula to estimate eGFR for all studies, corrections for black race were only applied in the cohorts with mixed populations. Beyond that, CKD-EPI has not been fully validated among Asian populations³⁵. For the Japanese, CKD-EPI has been shown to overestimate kidney filtration, which could increase the likelihood of interactions by country on the association between levels of eGFR and the risk of outcomes. However, as we compared the impact of relative changes in

eGFR instead of absolute values, bias may have been minimized. Moreover, even when limiting the comparisons to western populations, the contrasts in our results remained.

Despite standard definitions of outcomes, they may not have been assessed uniformly across studies. While the assessments of all-cause mortality and ESRD may occur independently of study design, as most studies rely on national registries to obtain such information, halving of eGFR and CVD events were probably susceptible to misclassification. Differences in outcome ascertainment would also increase the likelihood of observing significant interactions on the associations between predictors and outcomes across studies. Despite this concern, CVD events were the outcome for which baseline characteristics demonstrated the highest similarity in their associations across cohorts.

Many potential confounders were unavailable for the analytical approach. Most of the studies included racially homogeneous populations, like the Asian cohorts, in which a contrast within the study was not possible. Also, neither socio-economic status, nor education attainment was assessed by all studies, precluding us from evaluating their association with outcomes. This is noteworthy, as lower socioeconomic status has been associated with an increased risk of CKD and may have accounted for some of the observed inter-study differences operating through variations in access and quality of care.

Given the peculiarities of each study protocol, the reported rates of events may not be generalizable to the correspondent national rates of ESRD, CVD events, or death. Beyond that, except for Uruguay and India, most of the included studies took place in high-income countries, and the information gap for low to middle-income countries was not fully addressed here. Also,

PARP estimates represent maximum potential attribution, assuming causality. Finally, we were not able to examine atherosclerotic CVD versus heart failure-related events separately.

Strengths. Our study also had a number of strengths. We were able to centrally assemble individual-level information from eight studies in different countries while applying common standards for documentation and sharing of data. We evaluated the impact of a range of well-established risk factors into four widely researched and clinically meaningful outcomes. Beyond that, we directly tested the interactions by study on the associations between predictors and outcomes. We also developed a series of sensitivity analyses to further confirm our findings.

Potential Implications. Our findings are relevant for two reasons. First, they suggest that priorities of CKD care should be established locally, promoting tailored health care guidelines for diverse populations. Second, they suggest that the planning of international clinical trials would benefit from the awareness of these contrasts, as interventions for specific comorbidities may result disparate across different levels of background risk. The next steps include more detailed characterization of the cross-national differences that will help understand the basis for heterogeneous exposure – outcome relationships across studies.

Conclusions. The conclusions of this study are threefold. First, individuals with CKD participating in different prospective studies around the globe present, on average, very different baseline profiles defined by clinical history, comorbidities, and laboratory markers. Second, risks of CKD progression, ESRD, death, and CVD events are highly heterogeneous across these studies. These differences in risk, however, were not explained by differences in the distributions of age, sex, eGFR, and ACR. Third, the associations of comorbidities and markers of

metabolic imbalance with clinical outcomes are, on average, quite different from study-to-study. Further studies are necessary to explore reasons for the differences highlighted here. The iNET-CKD, an international network of cohorts with individual-level data, is a promising platform by which to understand some of these contrasts.

Methods

Population. The iNET-CKD is comprised of a group of CKD Studies across the globe committed to collaborative research, exchange of expertise, and mutual training³⁶. With facilitation and endorsement by the ISN, iNET-CKD was formally established in 2012. Prospective cohort studies conducted under a research protocol, collecting bio-samples, and planning to enroll more than a thousand individuals, were eligible to participate in iNET-CKD. All 21 active members of iNET-CKD were invited to participate in this collaborative work in August 2017. A total of 8 studies were able to share de-identified individual-level data by April 2018, representing 23,484 individuals. A Flow-chart on study participation is provided in **FigS4**. Details on the characteristics of the participant studies are provided in **Table3**.

Data Harmonization. The eight datasets were gathered centrally at the University of Pennsylvania, where an IRB protocol was approved (IRB protocol 828,738). Each dataset was built by its research center, based on a shared protocol. Inclusion criteria, which included age 18 years or older and an eGFR between 15 and 60 mL/min/1.73m² (CKD-EPI equation³⁷) at baseline, was checked upon receipt. Data from all studies were reformatted and mapped to one common dataset, verified with investigators, and compared to baseline characteristics

reported in the original publications, whenever available. Only variables defined with similar criteria and commonly assessed across studies were included in the statistical models. Laboratory markers and time-to-event were converted to the same unit of measurement. All covariates were checked for their baseline distributions. Potential outliers or errors were confirmed with the original study and corrected if necessary.

Outcomes. Four primary outcomes were pre-specified for this study. 1) Time to halving of eGFR below the level at study entry; 2) Time to ESRD, defined as the time until dialysis was initiated or when the participant received a kidney transplantation; 3) Time to death, defined as the time until death from any cause; 4) Time to a CVD event, defined by time until the first occurrence of a coronary artery disease, stroke, heart failure or peripheral vascular event diagnosed during a hospitalization. For analyses of renal outcomes, halving of eGFR and ESRD, individuals were censored if they were lost to follow-up or died before reaching the outcome. For the outcomes of death and CVD, individuals were censored if they achieved ESRD or were lost follow-up. Individuals with follow-up longer than 10 years were censored at the end of year 10 to minimize heterogeneity across studies. The initiating time point for all time-to-event analysis was the time of enrollment for each participant into their respective cohort study.

Exposures. All covariates were measured at baseline. Demographic characteristics included age and sex. Clinical characteristics included history of diabetes, hypertension, cardiovascular events, and smoking status. History of diabetes was defined according to at least one of the following criteria: self-reported diagnosis of diabetes, current use of glucose lowering drugs, a fasting serum glucose ≥ 7.0 mmol/L (≥ 126 mg/dL), a non-fasting serum glucose ≥ 11.1 mmol/L

(≥ 200 mg/dL), or glycated hemoglobin A1c $\geq 6.5\%$. History of hypertension was defined as a systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, or reported use of antihypertensive medications. History of cardiovascular disease was identified if the participant reported prior coronary artery disease, revascularization, heart failure, stroke or peripheral vascular disease. Smoking status was defined by self-reported current use of cigarettes. Clinical assessments included systolic blood pressure and body mass index (BMI, Kg/m²), performed according to each study protocol.

Assessment of kidney function included baseline eGFR and urinary albumin-to-creatinine ratio (uACR) or protein-to-creatinine ratio (uPCR), whichever was available. Baseline eGFR was estimated using the CKD-EPI equation using serum creatinine³⁸. For CRIC, CAN-PREDDICT, NRHP, and RIISC, in which part of the population was identified as black, the eGFR was corrected for race. Other laboratory markers included phosphate, calcium, bicarbonate, hemoglobin, total cholesterol, LDL, HDL cholesterol, and triglycerides. A detailed characterization of the studies is provided in the **TableS3**.

Statistical Analysis. Baseline characteristics of the overall population were described using means, standard deviations, and proportions. Baseline characteristics were described for the participants of each CKD study and for all combined (**Table1**). Baseline characteristics with continuous values were graphically depicted across the ranges of baseline eGFR and ACR for each CKD cohort and for the overall population (**Fig1 and FigS2**).

Incidence Rates. Incidence rates of each of the 4 outcomes (composite of halving of eGFR or ESRD, ESRD, cardiovascular events, and death) were calculated as the number of events per 1,000

person-years of follow-up. Adjusted incidence rates were calculated for all four outcomes accounting for differences in baseline distributions of age, gender, and level of eGFR. Adjusted incidence rates were estimated using direct standardization by [producing a weighted average of the stratum-specific rates](#). The total population from all study groups serving as the standard. Strata were defined according to four levels of age (18 to <45; 45 to <60; 60 to <75; 75 years or above), sex, and eGFR (15 to <30; 30 to <45; 45 to <60 ml/min/1.73m²). The I² statistic and the Cochran's Q statistic were calculated for crude and adjusted incidence rates, to evaluate the heterogeneity across iNET-CKD studies. As a secondary approach we repeated the calculation of crude and adjusted incidence rates including only individuals with an assessment of uACR beyond eGFR, age, and sex. For this analysis, levels of uACR (<30; 30 to <300; ≥300mg/dl) were included in the strata definition.

Population Attributable Risk Percent (PARP). To assess the association of the baseline characteristics with the development of outcomes across studies, we estimated the PARP associated with risk factors observed at baseline^{39,40}. In this analysis, we dichotomized all exposures to classify individuals as exposed vs. unexposed. The mean of the overall distribution of each predictor or a clinically meaningful value was used to establish the threshold. The PARP was calculated within each of the eight studies by subtracting the incidence rate of events in the whole study population from the incidence rate in the unexposed and dividing this difference by the incidence rate of events in the whole study population. We estimated the PARP for all available baseline characteristics, assessing their impact on each of the four outcomes.

Cox Proportional Hazards Models. The associations between baseline covariates and the outcomes were assessed using multivariable adjusted Cox PH models. Models were adjusted for age, sex, history of diabetes, cardiovascular disease, BMI, systolic blood pressure, eGFR, ACR, hemoglobin, serum albumin, phosphate, and total cholesterol. We evaluated the heterogeneity of associations between covariates and outcomes across cohorts including interactions between study group and all the covariates. The interactions were eliminated in a backwards selection process when they failed to reach a nominal level of significance of $p \leq 0.1$. Covariates were normally distributed and included in the models in their natural form, except for urinary ACR, which was log-transformed. The proportionality of hazards in each model was examined graphically using plots of scaled Schoenfeld residuals versus time for all covariates. In such plots, a random distribution of the residuals over time was observed.

Sensitivity Analysis. We implemented a latent class analysis (LCA) to create subgroups of all studied iNET-CKD participants to serve as the groups across which we explored for variability of predictor-outcome associations across iNET-CKD cohort studies. LCA is an unsupervised learning method, which classifies subjects according to their predicted probability of group, or latent class membership, estimated using maximum likelihoods. We used the depmixS4 R-package⁴¹ for hidden Markov models to fit on mixed multivariable predictors with binary and normal distributions. We pooled all individual data across studies and identified three classes of participants ignoring study origin. After the latent classes were defined, we tested for the interaction by study on the association between latent class and outcome using Cox PH Models. The choice of three latent classes was made to facilitate comprehension and to preserve the power to detect the interactions.

Multiple imputation. Multiple Imputation was performed for missing values for all covariates included in the Cox PH Models. Twenty imputations were performed using the chained equations method under the assumption that variables were not missing at random. Patterns of missingness are described for each study group in the **TableS4**. Multiple imputation was stratified by study. Analyses were performed in Stata/SE.14.2 for Mac (StataCorp LP, Texas, USA) and R version 3.5.1.

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Funding: Funding of studies contributing to this manuscript are presented in the **TableS5**.

Figures

Figure 1. Distribution of baseline characteristics according to levels of eGFR across iNET-CKD studies. Local cubic polynomial smooths for the distribution of baseline characteristics according to levels of eGFR. Solid black lines indicate the distributions for the overall population with 95% confidence intervals in gray. Dashed colored lines indicate the distributions for each study separately. Age (years); Body mass index (kg/m^2); Systolic blood pressure (mmHg); Hemoglobin (g/dL); Serum phosphate (mg/dL); Serum calcium (mg/dL); Bicarbonate (mg/dL); Serum albumin (mg/dL); I: Total cholesterol (mg/dL); Log-transformed albumin-over-creatinine ratio (mg/g).

Figure 2. Adjusted Incidence rates of CKD Progression (A), ESRD (B), Death (C), and CVD events (D) across iNET-CKD Studies. Adjusted incidence rates were estimated through direct standardization, using the total population from all study groups as the standard. Adjustments included four levels of age (18 to <45; 45 to <60; 60 to <75; 75 years or above), sex, and eGFR (15 to <30; 30 to <45; 45 to <60 $\text{ml}/\text{min}/1.73\text{m}^2$) at baseline. Individuals included were 18 years or older and had an eGFR assessment at baseline between 15 and 60 $\text{ml}/\text{min}/1.73\text{m}^2$. Cochran's Q and I^2 were estimated to assess heterogeneity in incidence rates across iNET-CKD studies. Number of individuals included in each analysis: **A:** 22,476; **B & C:** 22,819; **D:** 21,095.

Figure 3. Population attributable risk percent (PARP) for CKD Progression, ESRD, Death, and CVD according to baseline risk factors across iNET-CKD cohorts. For each column, the population attributable risk percent was calculated as the difference between the rate of events among the

total population and the rate of events among the unexposed divided by the rate of events in the total population. In A, events were time to halving of eGFR/ ESRD; in B, events were time to ESRD, in C, events were time to death; in D, events were time to cardiovascular events. Results are interpretable as the expected change in the rates of events that would occur if all exposed individuals were unexposed. For example, in panel C, the population attributable risk percent for death associated with diabetes was between 40 and 50% among individuals of the Korean cohort KNOW-CKD, meaning that in the hypothetical scenario that diabetes was eradicated from this population, the risk of all-cause mortality would be reduced by 40 to 50%. All predictors were dichotomized according to the mean of their overall distribution across all studies or according to a value considered clinically meaningful. The following levels of predictors are represented in the panels: age \geq 65 years; BMI \geq 30 kg/m²; Systolic blood pressure \geq 130 mmHg; eGFR \leq 30 ml/min/1.73m²; severely increased albumin-over-creatinine ratio (\geq 300mg/dL); phosphate \geq 4 mg/dL; calcium \leq 9 mg/dL; bicarbonate \leq 24 mEq/L; total cholesterol \geq 200 mg/dL.

Tables

Table 1. Baseline characteristics of study participants.

Table 2.A. Adjusted hazard ratios for CKD progression according to baseline risk factors across iNET-CKD cohorts.

Table 2.B. Adjusted hazard ratios for ESRD according to baseline risk factors across iNET-CKD cohorts.

Table 2.C. Adjusted hazard ratios for death according to baseline risk factors across iNET-CKD cohorts.

Table 2.D. Adjusted hazard ratios for cardiovascular events according to baseline risk factors across iNET-CKD cohorts.

Table 3. Description of participant studies

Supplementary Material:

I. Supplementary Figures:

Figure S1. Distribution of baseline characteristics according to levels of urinary albumin-over creatinine ratio across iNET-CKD studies. Local cubic polynomial smooths for the distribution of baseline characteristics according to levels of eGFR. Solid black lines indicate the distributions for the overall population, with 95% confidence intervals in gray. Dashed colored lines indicate the distributions for each separate study. References for log-transformed urinary albumin over creatinine ratio: 0 equals to 1mg/g; 3.4 equals 30 mg/g; 5.7 equals 300 mg/g in the natural scale.

Figure S2.A. Crude Incidence rates of (A) CKD Progression, (B) ESRD, (C) Death, and (D) CVD events across iNET-CKD Studies. Individuals included were 18 years or older, had an eGFR assessment at baseline between 15 and 60 ml/min/1.73m² and **complete information on age and sex**. Cochran's Q and I² were estimated to assess heterogeneity in incidence rates across

iNET-CKD studies. Number of individuals included in each analysis: **A:** 22,476; **B & C:** 22,819; **D:** 21,095.

Figure S2.B. Crude Incidence rates of (A) CKD Progression, (B) ESRD, (C) Death, and (D) CVD events across iNET-CKD Studies. Individuals included were 18 years or older, had an eGFR assessment at baseline between 15 and 60 ml/min/1.73m² and **complete information on age, sex, and urinary albumin-over creatinine ratio (ACR).** Cochran's Q and I² were estimated to assess heterogeneity in incidence rates across iNET-CKD studies. Number of individuals included in each analysis: **A:** 21,396; **B & C:** 21,720; **D:** 20,067.

Figure S2.C. Crude Incidence rates of (A) CKD Progression, (B) ESRD, (C) Death, and (D) CVD events across iNET-CKD Studies. Individuals included were 18 years or older, had an eGFR assessment at baseline between 15 and 60 ml/min/1.73m² and **complete information on age, sex, and urinary albumin-over creatinine ratio (ACR).** Adjusted incidence rates were estimated through direct standardization, using the total population from all study groups as the standard. Adjustments included four levels of age (18 to <45; 45 to <60; 60 to <75; 75 years or above), sex, eGFR (15 to <30; 30 to <45; 45 to <60 ml/min/1.73m²) at baseline, and ACR (<30; 30 to <300; ≥300mg/dl). Cochran's Q and I² were estimated to assess heterogeneity in incidence rates across iNET-CKD studies. Number of individuals included in each analysis: **A:** 21,396; **B & C:** 21,720; **D:** 20,067.

Figure S3. Distributions of the 3 latent classes (described in TableS2A) across each study population.

Figure S4. Flow chart of study participation

II. Supplementary Tables:

Table S1.A. Population attributable risk percent of baseline characteristics for CKD Progression across iNET-CKD Cohorts. Individuals included were 18 years or older and had an eGFR at baseline between 15 and 60 ml/min/1.73m². Participants were censored if they died, lost follow-up or reached 10 years of follow-up before having of eGFR or ESRD. Within each column, population attributable risk percent was calculated as the difference between the rate of CKD progression among the total population and the rate of CKD progression among the unexposed divided by the rate of CKD progression in the total population. Results are interpretable as the potential reduction in the rates of CKD progression expected in case all exposed individuals in the population were unexposed. Values depicted in bold were significantly different than zero (p-value<0.05).

Table S1.B. Population attributable risk percent of baseline characteristics for ESRD across iNET-CKD Cohorts. Individuals included were 18 years or older and had an eGFR at baseline between 15 and 60 ml/min/1.73m². Participants were censored if they died, lost follow-up or reached 10 years of follow-up before ESRD. Within each column, population attributable risk percent was calculated as the difference between the rate of ESRD among the total population and the rate of ESRD among the unexposed divided by the rate of ESRD in the total population. Results are interpretable as the potential reduction in the rates of ESRD expected in case all

exposed individuals in the population were unexposed. Values depicted in bold were significantly different than zero (p-value<0.05).

Table S1.C. Population attributable risk percent of baseline characteristics for all-cause mortality across iNET-CKD Cohorts. Individuals included were 18 years or older and had an eGFR at baseline between 15 and 60 ml/min/1.73m². Participants were censored if they lost follow-up, reached ESRD or 10 years of follow-up before death. Within each column, population attributable risk percent was calculated as the difference between the rate of death among the total population and the rate of death among the unexposed divided by the rate of death in the total population. Results are interpretable as the potential reduction in the rates of death expected in case all exposed individuals in the population were unexposed. Values depicted in bold were significantly different than zero (p-value<0.05).

Table S1.D. Population attributable risk percent of baseline characteristics for cardiovascular events across iNET-CKD Cohorts. Individuals included were 18 years or older and had an eGFR at baseline between 15 and 60 ml/min/1.73m². Participants were censored if they died, lost follow-up, reached ESRD or 10 years of follow-up before a CVD event. Within each column, population attributable risk percent was calculated as the difference between the rate of CVD among the total population and the rate of CVD among the unexposed divided by the rate of CVD in the total population. Results are interpretable as the potential reduction in the rates of CVD expected in case all exposed individuals in the population were unexposed. Values depicted in bold were significantly different than zero (p-value<0.05).

Table S2.A. Distribution of baseline characteristics according to the latent classes defined across the overall population. Distribution of baseline characteristics according to membership

to each of the 3 groups defined in the Latent Class Analysis (LCA). Covariates included in the LCA model: baseline eGFR, log-transformed urinary albumin-to creatinine ratio, age, sex, history of diabetes and cardiovascular disease, body mass index, systolic blood pressure, hemoglobin, and serum albumin. When performing the LCA model, study origin was disregarded. Only subjects with complete data were included in this analysis.

Table S2.B. Interactions by study on the association between latent classes and outcomes.

Individuals included were 18 years or older and had an eGFR at baseline between 15 and 60 ml/min/1.73m². Analysis include 11321 individuals with complete data on eGFR, ACR, age, sex, BMI, systolic blood pressure, diabetes, history of CVD, hemoglobin and serum albumin. Hazard ratios and 95% CI in bold were significantly different than zero (p-value<0.05, not shown). The interactions by study on the association between latent class and the risk of CKD Progression, ESRD, Death, and CVD were considered significant if p-value <0.1. (ACR: Urinary albumin/creatinine ratio).

Table S3.A. Adjusted hazard ratios for CKD progression according to baseline risk factors across iNET-CKD cohorts, including p-values for Z-tests.

Table S3.B. Adjusted hazard ratios for ESRD according to baseline risk factors across iNET-CKD cohorts, including p-values for Z-tests.

Table S3.C. Adjusted hazard ratios for death according to baseline risk factors across iNET-CKD cohorts, including p-values for Z-tests.

Table S3.D. Adjusted hazard ratios for CVD events according to baseline risk factors across iNET-CKD cohorts, including p-values for Z-tests.

Table S4.A. Adjusted hazard ratios for CKD progression according to baseline risk factors across iNET-CKD cohorts, excluding NRHP (Uruguay)

Table S4.B. Adjusted hazard ratios for ESRD according to baseline risk factors across iNET-CKD cohorts, excluding NRHP (Uruguay)

Table S4.C. Adjusted hazard ratios for death according to baseline risk factors across iNET-CKD cohorts, excluding NRHP (Uruguay)

Table S4.D. Adjusted hazard ratios for CVD events according to baseline risk factors across iNET-CKD cohorts, excluding NRHP (Uruguay)

Table S5. Proportion of missing data for each study

Table S6. Funding and Acknowledgments of each study

Supplementary information is available at Kidney International's website.

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Table 1. Baseline Characteristics of Study Participants.

Study	CKD-QLD	RIISC	CRIC	KNOW-CKD	Can-PREDDICT	NRHP	CKD-JAC	ICKD	TOTAL
Country	Australia	GBR	USA	Korea	Canada	Uruguay	Japan	India	
Number of participants	966	766	3,342	1,245	2,284	12,309	2,374	198	23,484
Follow-up [years; median (IQR)]	2.3 (1.3 - 3.2)	3.6 (2.1 - 5.1)	8.1(3.8 - 10)	3.0(1.7- 4.2)	3.8 (2.1 - 5.0)	5.0 (2.7 - 7.5)	3.9 (2.8 - 4.0)	2.7 (1.6 - 3.6)	4.1(2.5-6.8)
Age [years; median (IQR)]	72 [63 - 80]	65 [53 - 76]	61 [53 - 67]	58 [50 - 65]	71 [61 - 77]	72 [64 - 78]	62 [54 - 69]	50 [42 - 58]	68 [59 - 75]
Female Sex [n (%)]	460 (48)	294 (38)	1,508 (45)	449 (36)	845 (37)	5,180 (42)	862 (36)	69 (35)	9,667 (41)
Diabetes [n (%)]	480 (50)	353 (46)	1721 (52)	553 (44)	1,104 (48)	4,481 (36)	868 (37)	48 (24)	9,608 (41)
Hypertension [n (%)]	909 (94)	561 (73)	2,995 (90)	1,232 (99)	2,214 (97)	10,852 (88)	2,194 (92)	173 (87)	21,133 90)
History of CVD [n (%)]	563 (58)	286 (37)	1,210 (36)	91 (7)	1051 (46)	3,995 (32)	552 (23)	14 (7)	7,762 (33)
Smoking [n (%)]	65 (8)	96 (13)	439 (13)	192 (15)	-	757 (6)	336 (17)	16 (8)	1,901 (9)
BMI (kg/m ² ; mean +/- SD)	31 +/- 8	30 +/- 7	32 +/- 8	25 +/- 3	30 +/- 7	29 +/- 6	24 +/- 4	25 +/- 5	29 +/- 7
Systolic BP (mmHg; mean +/-SD)	130 +/- 18	132 +/-21	130 +/- 22	128 +/-16	134 +/- 20	133 +/- 21	131 +/- 18	136 +/-20	132 +/- 21
eGFR [ml/min/1.73m ² ; median (IQR)]	34 [26 - 42]	30 [23 - 39]	40 [31 - 48]	35 [26 - 47]	27 [21 -34]	38 [29 - 46]	31 [23 - 40]	38 [33 - 49]	36 [27 - 45]
45 to <60 ml/min/1.73m ² [n (%)]	194 (20)	106 (14)	1,189 (36)	349 (28)	70 (3)	3,399 (28)	276 (12)	66 (33)	5,651 (24)
30 to <45 ml/min/1.73m ² [n (%)]	422 (44)	270 (35)	1,428 (43)	447 (36)	779 (34)	5,570 (45)	1,005 (42)	94 (47)	10,017 (43)
15 to <30 ml/min/1.73m ² [n (%)]	350 (36)	390 (51)	725 (22)	449 (36)	1,435 (63)	3,340 (27)	1,093 (46)	38 (19)	7,824 (33)
ACR [mg/g; median (IQR)]	80 [13 - 557]	255 [49- 1015]	73 [11 - 561]	39 [11 - 128]	134 [26 - 698]	0 [0 - 0]	408 [89 - 1157]	-	12 [1 - 316]
PCR [mg/g; median (IQR)]	-	-	-	-	-	-	-	409[241 - 956]	-
Normal/mildly increased ACR/PCR	278 (30)	130 (18)	1,252 (39)	485 (41)	591 (28)	9,104 (77)	289 (13)	7 (11)	12,381 (56)
Moderately increased ACR/PCR	311 (33)	256 (35)	887 (27)	570 (48)	742 (35)	711 (6)	655 (30)	32 (49)	4,207 (19)
Severely increased ACR/PCR	353 (37)	338 (47)	1081 (34)	135 (11)	804 (38)	1,965 (17)	1,211 (56)	26 (40)	5,631 (25)
Hemoglobin (g/dl; mean +/- SD)	12.4 +/- 1.9	12.3 +/- 1.7	12.5 +/-1.8	12.4 +/- 1.9	12.4 +/- 1.6	12.7 +/- 1.9	12.3 +/-1.8	12.2 +/- 2.1	12.5 +/- 1.8
Phosphate (mg/dl; mean +/- SD)	3.8 +/- 0.7	3.5 +/-0.7	3.8 +/-0.7	3.7 +/- 0.6	3.7 +/- 0.7	3.9 +/- 1.3	3.4 +/- 0.6	3.8 +/- 0.9	3.7 +/- 0.9
Calcium (mg/dl; mean +/- SD)	9.2 +/- 0.5	9.3 +/- 0.6	9.2 +/- 0.5	9.1 +/- 0.5	9.3 +/- 0.5	9.3 +/- 0.9	9.1 +/- 0.5	9.3 +/-0.9	9.2 +/- 0.7
Bicarbonate (mEq/l; mean +/- SD)	25.5 +/- 3.3	23.8 +/- 3.5	24.2 +/- 3.2	25.0 +/- 3.4	25.6 +/- 3.4	23.9 +/- 3.9	-	-	24.7 +/- 3.5
Serum albumin (g/dl; mean +/- SD)	4.0 +/- 0.3	4.2 +/- 0.5	3.9 +/- 0.5	4.1 +/- 0.4	4.0 +/- 0.4	4.1 +/- 0.5	4.0 +/-0.4	4.5 +/- 0.8	4.0 +/- 0.5
T. Cholesterol (mg/dl; mean +/- SD)	171 +/- 44	183 +/- 52	183 +/- 46	170 +/- 39	165 +/- 45	195 +/- 49	196 +/- 43	171 +/- 53	187 +/- 48

HDL (mg/dl; mean +/- SD)	46 +/- 14	-	47 +/-15	47 +/- 15	46 +/- 17	48 +/- 15	55.0 +/- 19	48 +/- 19	48 +/- 16
LDL (mg/dl; mean +/- SD)	82 +/- 37	-	102 +/- 36	93 +/- 31	86 +/- 33	115 +/- 42	110 +/- 32	100 +/- 42	106 +/- 39
Triglycerides [mg/dl; median (IQR)]	151 [106 - 221]	142 [105 - 213]	131 [92 - 190]	137 [96 - 202]	142 [100 - 213]	140 [102 - 199]	140 [98 - 204]	142 [108 - 206]	139 [99 - 200]

Individuals included were 18 years or older and had an eGFR at baseline between 15 and 60 ml/min/1.73m². History of CVD: History of cardiovascular event; BMI: body mass index; Systolic BP: systolic blood pressure; eGFR: estimated glomerular filtration rate; ACR: Urinary albumin/creatinine ratio; PCR: Urinary protein/creatinine ratio. Levels of ACR and PCR: normal or mildly increased: ACR<30mg/g; PCR < 150mg/g; moderately increased: ACR 30 to 300mg/g; PCR 150 to 1500 mg/g; severely increased: ACR>300 mg/g; PCR >1500 mg/g. Total number of individuals depicted for characteristics with missing observations: smoking status: 20,760; BMI: 20,132; systolic blood pressure: 22,991; ACR or PCR (continuous): 21,632; ACR or PCR (categorical): 22,211; hemoglobin: 20,584; phosphate: 13,194; calcium: 14,302; bicarbonate: 9,085; serum albumin: 13,314; total cholesterol: 17,895; HDL:15,885; LDL:15,452; triglycerides: 17,368.

Table 2.A. Adjusted hazard ratios for CKD progression according to baseline risk factors across iNET-CKD cohorts

	CKD-QLD Australia	RIISC GBR	CRIC USA	KNOW-CKD Korea	Can-PREDDICT Canada	NRHP Uruguay	CKD-JAC Japan	Overall HR	Interaction by study
<i>number of events</i>	63	234	1235	317	583	1260	421	4113	
<i>total of participants</i>	942	660	3023	1190	2095	11778	2155	21843	
	<i>Hazard Ratio (95% CI)</i>								<i>p-value</i>
Age (years) ¹	0.80 (0.67 - 0.95)	0.75 (0.69 - 0.83)	0.85 (0.81 - 0.90)	0.68 (0.62 - 0.76)	0.84 (0.79 - 0.90)	0.71 (0.68 - 0.74)	0.92 (0.84 - 1.01)	—	<0.001
Sex (female)	0.57 (0.32 - 1.02)	1.24 (0.92 - 1.69)	0.75 (0.66 - 0.85)	0.57 (0.44 - 0.73)	0.69 (0.57 - 0.83)	0.66 (0.59 - 0.75)	0.44 (0.35 - 0.56)	—	<0.001
Diabetes	0.96 (0.52 - 1.77)	0.91 (0.67 - 1.23)	1.36 (1.19 - 1.55)	1.16 (0.90 - 1.49)	0.94 (0.78 - 1.14)	1.51 (1.34 - 1.70)	0.94 (0.76 - 1.17)	—	<0.001
History of CVD				—				1.08 (1.01 - 1.16)	0.4207
BMI (kg/m ²)	1.02 (0.99 - 1.06)	0.99 (0.97 - 1.01)	0.99 (0.99 - 1.00)	1.00 (0.97 - 1.04)	0.99 (0.97 - 1.00)	0.99 (0.98 - 1.00)	1.03 (1.00 - 1.06)	—	0.0692
Systolic BP (mmHg) ¹				—				1.09 (1.07 - 1.10)	0.5891
eGFR (ml/min/1.73m ²) ²	2.01 (1.42 - 2.85)	1.81 (1.53 - 2.13)	1.60 (1.51 - 1.71)	1.92 (1.71 - 2.16)	1.97 (1.75 - 2.22)	1.88 (1.78 - 1.99)	1.74 (1.54 - 1.97)	—	0.0029
ACR [mg/g] ³	1.69 (1.32 - 2.16)	1.23 (1.12 - 1.35)	1.55 (1.49 - 1.61)	1.17 (1.10 - 1.25)	1.42 (1.34 - 1.50)	1.17 (1.14 - 1.19)	1.93 (1.73 - 2.16)	—	<0.001
Hemoglobin (g/dl) ⁴	1.07 (0.91 - 1.26)	1.18 (1.07 - 1.30)	1.06 (1.02 - 1.10)	1.12 (1.03 - 1.22)	1.11 (1.05 - 1.18)	1.10 (1.05 - 1.15)	1.24 (1.15 - 1.33)	—	0.0076
Serum albumin (g/dl) ⁴	2.41 (0.79 - 7.35)	1.54 (1.15 - 2.07)	1.43 (1.25 - 1.63)	2.71 (2.13 - 3.44)	1.62 (1.33 - 1.96)	1.25 (1.06 - 1.48)	1.23 (0.98 - 1.54)	—	<0.001
Phosphate (mg/dl)	1.66 (1.10 - 2.52)	1.37 (1.11 - 1.69)	1.06 (0.97 - 1.16)	1.35 (1.12 - 1.63)	1.28 (1.16 - 1.42)	1.02 (0.96 - 1.09)	1.19 (1.01 - 1.41)	—	<0.001
Total Cholesterol (mg/dl) ¹				—				1.01 (1.00 - 1.02)	0.2451

Individuals included were 18 years or older and had an eGFR at baseline between 15 and 60 ml/min/1.73m². Participants were censored if they died, lost follow-up or reached 10 years of follow-up before having of eGFR or ESRD. Hazard Ratios for age, systolic blood pressure, and total cholesterol (1) are provided for a 10 unit increase in their baseline values. Hazard ratios for eGFR (2) are provided for a 10 unit decrease from baseline eGFR. Hazard ratios for ACR (urinary albumin over creatinine ratio) (3) are provided for 1 unit increase in log-transformed ACR. Hazard ratios for serum albumin and hemoglobin (4) are provided for 1 unit decrease from their baseline values. Hazard ratios in bold were significantly different than zero, p-values for interaction by study in bold were considered significant (p<0.1). Non-significant interactions by study group were excluded from the model using a backwards stepwise approach. For the interactions excluded, the p-value indicative of exclusion was reported, and an overall association between the predictor across all study groups was reported according to the final model (Overall HR).

Table 2.B. Adjusted hazard ratios for ESRD according to baseline risk factors across iNET-CKD cohorts

	CKD-QLD Australia	RIISC GBR	CRIC USA	KNOW-CKD Korea	Can-PREDDICT Canada	NRHP Uruguay	CKD-JAC Japan	Overall HR	Interaction by study
<i>number of events</i>	51	228	979	246	419	851	257	3031	
<i>total of participants</i>	942	724	3220	1190	2137	11778	2155	22146	
	<i>Hazard Ratio (95% CI)</i>								<i>p-value</i>
Age (years) ¹	0.73 (0.59 - 0.90)	0.68 (0.62 - 0.75)	0.80 (0.74 - 0.86)	0.72 (0.64 - 0.81)	0.76 (0.70 - 0.82)	0.70 (0.65 - 0.73)	0.94 (0.83 - 1.05)	—	<0.001
Sex (female)	0.52 (0.26 - 1.04)	1.36 (1.00 - 1.84)	0.65 (0.55 - 0.77)	0.43 (0.32 - 0.59)	0.59 (0.47 - 0.74)	0.61 (0.51 - 0.73)	0.37 (0.27 - 0.51)	—	<0.001
Diabetes	0.88 (0.42 - 1.83)	0.84 (0.62 - 1.17)	1.22 (1.01 - 1.48)	1.12 (0.83 - 1.51)	1.04 (0.84 - 1.30)	1.74 (1.47 - 2.07)	0.86 (0.65 - 1.14)	—	<0.001
History of CVD				—				1.17 (1.06 - 1.28)	0.5129
BMI (kg/m ²)	1.03 (0.99 - 1.07)	0.99 (0.97 - 1.01)	0.99 (0.98 - 0.99)	0.99 (0.95 - 1.03)	0.97 (0.96 - 0.98)	0.99 (0.97 - 1.00)	1.01 (0.98 - 1.06)	—	0.0614
Systolic BP (mmHg) ¹				—				1.09 (1.07 - 1.11)	0.956
eGFR (ml/min/1.73m ²) ²	3.12 (1.95 - 4.99)	2.00 (1.69 - 2.36)	2.25 (2.05 - 2.47)	2.46 (2.11 - 2.86)	3.11 (2.65 - 3.66)	2.86 (2.60 - 3.14)	2.52 (2.08 - 3.04)	—	<0.001
ACR [mg/g] ³	1.83 (1.35 - 2.50)	1.36 (1.23 - 1.50)	1.52 (1.43 - 1.61)	1.18 (1.09 - 1.28)	1.40 (1.30 - 1.50)	1.08 (1.06 - 1.10)	1.94 (1.67 - 2.25)	—	<0.001
Hemoglobin (g/dl) ⁴	1.00 (0.82 - 1.22)	1.21 (1.09 - 1.33)	1.05 (1.00 - 1.11)	1.13 (1.03 - 1.25)	1.10 (1.03 - 1.18)	1.12 (1.05 - 1.19)	1.29 (1.17 - 1.42)	—	0.0238
Serum albumin (g/dl) ⁴	3.62 (0.98 - 13.3)	1.40 (1.03 - 1.91)	1.50 (1.25 - 1.81)	3.11 (2.39 - 4.04)	1.88 (1.51 - 2.36)	1.42 (1.09 - 1.85)	1.29 (0.97 - 1.73)	—	<0.001
Phosphate (mg/dl)	1.82 (1.13 - 2.94)	1.57 (1.28 - 1.94)	1.11 (0.99 - 1.25)	1.41 (1.14 - 1.75)	1.42 (1.27 - 1.58)	1.05 (0.97 - 1.15)	1.24 (1.00 - 1.53)	—	<0.001
Total Cholesterol (mg/dl) ¹	1.00 (0.91 - 1.10)	0.99 (0.97 - 1.02)	1.01 (0.99 - 1.02)	1.02 (0.99 - 1.05)	0.98 (0.95 - 1.01)	1.02 (1.01 - 1.04)	0.99 (0.96 - 1.03)	—	0.0918

Individuals included were 18 years or older and had an eGFR at baseline between 15 and 60 ml/min/1.73m². Participants were censored if they died, lost follow-up or reached 10 years of follow-up before ESRD. Hazard Ratios for age, systolic blood pressure, and total cholesterol (1) are provided for a 10 unit increase in their baseline values. Hazard ratios for eGFR (2) are provided for a 10 unit decrease from baseline eGFR. Hazard ratios for ACR (urinary albumin over creatinine ratio) (3) are provided for 1 unit increase in log-transformed ACR. Hazard ratios for serum albumin and hemoglobin (4) are provided for 1 unit decrease from their baseline values. Hazard ratios and 95% CI in bold were significantly different than zero (p-value<0.05, not shown). The interactions by study on the association between each predictor and the risk of death were considered significant if p-value <0.1. Non-significant interactions were excluded from the model using a backwards stepwise approach. For the interactions excluded, the p-value indicative of exclusion was reported, and an overall association between the predictor across all study groups was reported according to the final model (Overall HR).

Table 2.C. Adjusted hazard ratios for death according to baseline risk factors across iNET-CKD cohorts

	CKD-QLD Australia	RIISC GBR	CRIC USA	KNOW-CKD Korea	Can-PREDDICT Canada	NRHP Uruguay	CKD-JAC Japan	Overall HR	Interaction by study
<i>number of events</i>	135	144	592	31	359	3088	57	4406	
<i>total of participants</i>	942	724	3220	1190	2137	11778	2155	22146	
	<i>Hazard Ratio (95% CI)</i>								<i>p-value</i>
Age (years) ¹				–				1.77 (1.71 - 1.84)	0.1707
Sex (female)				–				0.69 (0.64 - 0.73)	0.2209
Diabetes				–				1.25 (1.17 - 1.33)	0.7849
History of CVD	1.18 (0.78 - 1.79)	1.46 (1.05 - 2.05)	2.04 (1.73 - 2.41)	3.20 (1.39 - 7.38)	2.43 (1.93 - 3.07)	1.48 (1.38 - 1.60)	1.36 (0.79 - 2.37)	–	<0.001
BMI (kg/m ²)				–				1.00 (0.99 - 1.00)	0.8143
Systolic BP (mmHg) ¹				–				1.01 (0.99 - 1.02)	0.2007
eGFR (ml/min/1.73m ²) ²				–				1.18 (1.14 - 1.22)	0.224
ACR [mg/g] ³	1.07 (0.96 - 1.19)	1.03 (0.95 - 1.12)	1.08 (1.03 - 1.12)	1.17 (0.97 - 1.42)	1.02 (0.97 - 1.08)	1.05 (1.03 - 1.06)	0.82 (0.71 - 0.94)	–	0.017
Hemoglobin (g/dl) ⁴	1.11 (1.00 - 1.23)	1.06 (0.95 - 1.18)	1.00 (0.95 - 1.06)	1.04 (0.83 - 1.31)	1.16 (1.08 - 1.25)	1.08 (1.06 - 1.11)	1.11 (0.94 - 1.33)	–	0.068
Serum albumin (g/dl) ⁴	2.23 (1.05 - 4.75)	1.69 (1.11 - 2.58)	1.56 (1.26 - 1.93)	1.61 (0.69 - 3.79)	2.07 (1.58 - 2.72)	1.19 (1.06 - 1.34)	3.15 (1.74 - 5.70)	–	<0.001
Phosphate (mg/dl)	1.68 (1.16 - 2.43)	1.18 (0.91 - 1.52)	1.34 (1.17 - 1.54)	1.05 (0.55 - 2.01)	1.20 (1.06 - 1.36)	0.96 (0.91 - 1.02)	0.64 (0.37 - 1.10)	–	<0.001
Total Cholesterol (mg/dl) ¹	1.00 (0.99 - 1.00)	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)	1.00 (0.99 - 1.00)	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)	1.01 (1.00 - 1.01)	–	0.0869

Individuals included were 18 years or older and had an eGFR at baseline between 15 and 60 ml/min/1.73m². Participants were censored if they lost follow-up, reached 10 years of follow-up or ESRD before dying. Hazard Ratios for age, systolic blood pressure, and total cholesterol (1) are provided for a 10 unit increase in their baseline values. Hazard ratios for eGFR (2) are provided for a 10 unit decrease from baseline eGFR. Hazard ratios for ACR (urinary albumin over creatinine ratio) (3) are provided for 1 unit increase in log-transformed ACR. Hazard ratios for serum albumin and hemoglobin (4) are provided for 1 unit decrease from their baseline values. Hazard ratios and 95% CI in bold were significantly different than zero (p-value<0.05, not shown). The interactions by study on the association between each predictor and the risk of death were considered significant if p-value <0.1. Non-significant interactions were excluded from the model using a backwards stepwise approach. For the interactions excluded, the p-value indicative of exclusion was reported, and an overall association between the predictor across all study groups was reported according to the final model (Overall HR).

Table 2.D. Adjusted hazard ratios for CVD events according to baseline risk factors across iNET-CKD cohorts

	RIISC GBR	CRIC USA	KNOW-CKD Korea	Can-PREDDICT Canada	NRHP Uruguay	CKD-JAC Japan	Overall HR	Interaction by study
<i>number of events</i>	29	799	79	185	2029	143	3264	
<i>total of participants</i>	622	3200	1190	2137	11778	2154	21081	
	<i>Hazard Ratio (95% CI)</i>							<i>p-value</i>
Age (years) ¹	1.32 (0.96 – 1.80)	1.27 (1.17 - 1.37)	1.51 (1.18 - 1.93)	1.22 (1.06 - 1.41)	1.11 (1.06 - 1.16)	1.64 (1.32 - 2.03)		<0.001
Sex (female)				–			0.69 (0.64 - 0.75)	0.5433
Diabetes	1.34 (0.62 - 2.90)	1.59 (1.35 - 1.87)	1.87 (1.15 - 3.04)	1.08 (0.80 - 1.46)	1.20 (1.09 - 1.31)	2.18 (1.53 - 3.10)		<0.001
History of CVD				–			2.67 (2.48 - 2.87)	0.8530
BMI (kg/m ²)				–			1.01 (1.00 - 1.01)	0.1334
Systolic BP (mmHg) ¹	0.91 (0.76 - 1.09)	1.02 (0.99 - 1.06)	0.99 (0.86 - 1.15)	1.11 (1.03 - 1.19)	0.99 (0.97 - 1.02)	1.03 (0.94 - 1.13)		0.0565
eGFR (ml/min/1.73m ²) ²				–			1.13 (1.09 - 1.17)	0.3192
ACR [mg/g] ³				–			1.35 (1.06 - 1.70)	0.1095
Hemoglobin (g/dl) ⁴				–			1.04 (1.02 - 1.07)	0.804
Serum albumin (g/dl) ⁴	1.62 (0.75 – 3.52)	1.55 (1.32 - 1.82)	1.07 (0.64 - 1.80)	1.42 (1.00 - 2.00)	1.06 (0.94 - 1.18)	1.19 (0.81 - 1.73)		0.0043
Phosphate (mg/dl)	1.15 (0.66 - 2.00)	1.26 (1.13 - 1.40)	0.86 (0.59 - 1.27)	1.26 (1.07 - 1.49)	1.00 (0.95 - 1.05)	0.96 (0.72 - 1.29)		<0.001
Total Cholesterol (mg/dl) ¹	1.05 (0.98 - 1.12)	1.02 (1.00 - 1.03)	1.04 (0.98 - 1.10)	1.02 (0.99 - 1.06)	0.99 (0.98 - 1.00)	1.02 (0.98 - 1.06)		0.008

Individuals included were 18 years or older and had an eGFR at baseline between 15 and 60 ml/min/1.73m². Participants were censored if they reached ESRD, died, lost follow-up or 10 years of follow-up before a CVD event. Hazard Ratios for age, systolic blood pressure, and total cholesterol (1) are provided for a 10 unit increase in their baseline values. Hazard ratios for eGFR (2) are provided for a 10 unit decrease from baseline eGFR. Hazard ratios for ACR (urinary albumin over creatinine ratio) (3) are provided for 1 unit increase in log-transformed ACR. Hazard ratios for serum albumin and hemoglobin (4) are provided for 1 unit decrease from their baseline values. Hazard ratios and 95% CI in bold were significantly different than zero (p-value<0.05, not shown). The interactions by study on the association between each predictor and the risk of CVD were considered significant if p-value <0.1. Non-significant interactions were excluded from the model using a backwards stepwise approach. For the interactions excluded, the p-value indicative of exclusion was reported, and an overall association between the predictor across all study groups was reported according to the final model (Overall HR).

Table 3. Description of participant studies

Study	Study Design	Age range	Participants older than 65 years [N(%)]	Number of Clinical Sites	First Year of Enrollment	Last Year of Enrollment	Inclusion Criteria to participate in the individual study	Exclusion Criteria to participate in the individual study
CKD-QLD (Australia)	Registry	18 - 95	683 (71)	>10	2011	2018	Prevalent or incident CKD patients not on renal replacement therapy.	Institutionalized or unable or unwilling to provide informed consent
RIISC (GBR)	Cohort	18 - 92	379 (49)	2	2010	2015	CKD stage 3 associated with accelerated CKD progression (eGFR decline steeper than 5mls/min/year or 10mls/min/5years); CKD stage 3 associated with an albumin-creatinine ratio (ACR) ≥ 70 mg/mmol; CKD stages 4 or 5 (pre-dialysis)	Active glomerulonephritis under immunosuppression, renal replacement therapy (dialysis or a functioning kidney transplant), unable or unwilling to provide informed consent.
CRIC (USA)	Cohort	21 - 75	995 (30)	7	2003	2008	Enrollment stratified by age including eGFR between 20 to 70 ml/min/1.73m ²	Polycystic kidney disease; systemic vasculitis or glomerulonephritis under immunosuppression; heart failure (NYHA class III or IV); cirrhosis; HIV infection; pregnant women; previous chemotherapy for systemic cancer; previous multiple myeloma or renal carcinoma; unable to provide informed consent.
KNOW-CKD (Korea)	Cohort	20 - 75	306 (25)	9	2011	2016	CKD stages 1 to 5	Renal replacement therapy (chronic dialysis or organ transplantation); heart failure (NYHA III and IV); past or current history of malignancy; pregnant women; single kidney due to trauma or kidney donation; unable to provide informed consent.
CAN-PREDICCT (Canada)	Cohort	18 - 96	1517 (66)	>10	2007	2008	eGFR between 15 to 45 ml/min/1.73m ²	Organ transplant, immunomodulatory therapy for active vasculitis or glomerulonephritis; life expectancy of less than 1 year (e.g. due to cancer) in the opinion of their attending nephrologist; unable to provide informed consent.

NRHP (Uruguay)	Registry	18 - 98	8794 (71)	>10	2004	2018	eGFR<60 ml/min/1.73m ² , proteinuria 300 mg/day, and/or microalbuminuria 30-300mg/day in diabetic patients, when persistent for more than 3 months.	Unable or unwilling to provide informed consent
CKD-JAC (Japan)	Cohort	21 - 77	930 (39)	>10	2007	2008	eGFR between 10 to 59 ml/min/1.73m ²	Polycystic kidney disease; HIV infection; liver cirrhosis; active cancer or cancer treatment within the last 2 years; transplant recipients; patients who previously received long-term dialysis; unable to provide informed consent.
ICKD (India)	Cohort	18 - 69	12 (6)	>10	2016	2018	eGFR between 30 to 60 ml/min/1.73m ²	Renal replacement therapy (chronic dialysis or organ transplantation); heart failure (NYHA III and IV); past or current history of malignancy; pregnant women; unable to provide informed consent.

NYHA: New York Heart Association