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Age and the Association of Kidney Measures with Mortality and End-Stage Renal Disease

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Abstract

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Author Contributions: Dr. Coresh had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Matsushita, Astor, Gansevoort, Levin, Wen, Coresh.

Acquisition of data: Matsushita, Coresh for CKD-PC with CKD-PC investigators/collaborators listed below.

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Study supervision: Matsushita, Gansevoort, Coresh.

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Context—Chronic kidney disease (CKD) is prevalent in older individuals, but the risk implications of low estimated glomerular filtration rate (eGFR) and high albuminuria across the full age range are controversial.

Objective—To evaluate possible effect modification (interaction) of age on the association of estimated GFR and albuminuria with clinical risk examining both relative and absolute risk.

Design, Setting, Participants—We investigated 2,051,244 participants from 33 general population or high-risk (of vascular disease) cohorts and 13 CKD cohorts from Asia, Australesia, Europe, and North/South America conducted during 1972–2011 with mean follow-up time of 5.8 years (range 0–31 years).

Main Outcome Measures—Hazard ratios (HRs) of mortality and end-stage renal disease (ESRD) according to eGFR and albuminuria were meta-analyzed across age categories after adjusting for sex, race, cardiovascular disease, diabetes, systolic blood pressure, cholestserol, body mass index, and smoking. Absolute risks were estimated using HRs and average incidence rates.

Results—Mortality (112,325 deaths) and ESRD (8,411 events) risk were higher at lower eGFR and higher albuminuria in every age category. In general/high-risk cohorts, relative mortality risk for reduced eGFR decreased with increasing age: e.g., adjusted HRs (95% CI) at eGFR 45 vs. 80 ml/min/1.73m^2 were 3.50 (2.55–4.81), 2.21 (2.02–2.41), 1.59 (1.42–1.77), and 1.35 (1.23–1.48) in age categories 18–54, 55–64, 65–74 and 75+ years, respectively (*P-values* for age interaction <0.05). Absolute risk differences for the same comparisons were higher at older age (9.0 [95% CI, 6.0–12.8], 12.2 [10.3–14.3], 13.3 [9.0–18.6], and 27.2 [13.5–45.5] excess deaths per 1,000 person-years, respectively). For increased albuminuria, reduction of relative risk with increasing age were less evident, while differences in absolute risk were higher in the older age categories (7.5 [95% CI, 4.3–11.9], 12.2 [7.9–17.6], 22.7 [15.3–31.6], and 34.3 [19.5–52.4] excess deaths per 1,000 person-years, respectively by age category, at ACR 300 mg/g compared to 10 mg/g). In CKD cohorts, adjusted relative hazards of mortality did not decrease with age. In all cohorts, ESRD relative risks and absolute risk differences at lower eGFR or higher albuminuria were comparable across age categories.

Conclusions—Both low eGFR and high albuminuria were independently associated with mortality and ESRD regardless of age across a wide range of populations. Mortality showed lower relative risk but higher absolute risks differences at older age.

Chronic kidney disease (CKD) is defined by reduced glomerular filtration rate (GFR < 60 ml/min/1.73m^2) or kidney damage (usually detected by high albuminuria ≥ 30 mg albumin per gram of creatinine).[1] CKD affects 10 to 15% of adults in the US, Europe and Asia,[2–4] and the prevalence increases dramatically with age (from 4% at age 20–39 to 47% at age 70+ years in the US).[2] Recently, it has been suggested that the definition and staging of CKD and corresponding clinical risk should be determined by the combination of estimated GFR (eGFR) and albuminuria levels.[5–7] These kidney measures are also used for cardiovascular risk stratification in clinical guidelines.[8,9] However, there is controversy whether age modifies their independent and combined association with clinical risk, partly due to different analytic approaches.[10–14] The resulting uncertainty about the comprehensive impact of age on CKD-risk relationship hampers optimal clinical practice and public health initiatives for this large patient group.

Before general implementation of the recently revised CKD classification system, acceptable clinical risk performance must be demonstrated in all age groups. The purpose of the current study was therefore to evaluate possible effect modification (interaction) of age on the association of estimated GFR and albuminuria with clinical risk examining both relative and absolute risk. We analyzed data from 2 million participants in 46 different

cohorts to characterize the mortality and end-stage renal disease (ESRD) risk across the full age range (18–108 years) using a uniform analytic approach.

METHODS

The Chronic Kidney Disease Prognosis Consortium (CKD-PC) consists of cohorts worldwide from general, high-risk (for vascular risk), and CKD populations with baseline information on eGFR and albuminuria, at least 1000 participants (not applied to CKD cohorts) and ≥50 events for any outcome of interest during follow-up (eAppendix 1).[7,15–17] The CKD-EPI equation with serum creatinine values standardized to Isotope Dilution Mass Spectrometry (IDMS) traceable methods was used to estimate GFR.[18] For studies in which creatinine measurements were not standardized to IDMS, we reduced the creatinine levels by 5%, as previously reported.[19,20] Albuminuria was preferably measured as albumin-to-creatinine-ratio (ACR), but studies with urine albumin excretion rate, urine protein-to-creatinine ratio (PCR), or dipstick protein were also included. Information on demographic and cardiovascular risk factors was also obtained for all subjects (eAppendix 2). Age was categorized as 18–54, 55–64, 65–74, and 75+ years. Participants with missing values for either eGFR or albuminuria were excluded. Missing values for other adjustment variables were replaced by the cohort mean, as more advanced imputation methods were not feasible within this large consortium. Our primary endpoints were all-cause mortality and ESRD. ESRD was defined as starting dialysis, kidney transplantation or death coded as because of kidney disease other than acute kidney injury. The results for cardiovascular mortality (death due to myocardial infarction, heart failure, sudden cardiac death, or stroke) are shown in the Appendix only given the similarity to results for all-cause mortality. The study was based on deidentified information from studies previously approved by individual ethical boards, and the current meta-analysis was approved by the institutional review board at the Johns Hopkins Bloomberg School of Public Health.

In each study cohort, eGFR linear splines (knots at every 15 ml/min/1.73m^2 from 30 to 105 ml/min/1.73m^2 [90 ml/min/1.73m^2 in CKD cohorts]) and their product terms with age category were incorporated in Cox proportional hazards models, providing hazard ratios (HRs) with eGFR 80 ml/min/1.73m^2 (50 ml/min/1.73m^2 in CKD cohorts) selected as a stable reference for all age categories (eAppendix 2). Reference ranges are important for conducting statistical significance tests but do not alter the shape of the association across the full range of exposure. CKD-PC usually uses the reference range of eGFR 90–104 ml/min/1.73m^2 (95 for continuous analysis) for general population and high-risk cohorts. However, given that few people in the oldest age category had eGFR in this range (2.3%) and thus very few events (particularly ESRD) were observed in this eGFR range, we selected a lower eGFR category of 80 ml/min/1.73m^2 as the reference for the present study. Other covariates in the models were sex, race/ethnicity (black vs. non-black), history of cardiovascular disease, diabetes, systolic blood pressure, serum total cholesterol, body mass index, smoking, albuminuria (log-transformed ACR or PCR or dipstick categories) and for clinical trials the randomized intervention. Interactions, i.e. effect modifications, were evaluated as the ratio of HRs in each age category compared to the age category of 55–64 years at each 1 ml/min/1.73m^2 of eGFR from 15 to 120 ml/min/1.73m^2 (point-wise interaction). Overall interaction for each age category compared to age 55–64 years across the full range of eGFR was assessed by averaging the coefficients for product terms between eGFR splines and age categories using inverse-variance weighting. Estimates from each cohort were pooled using random effects models. The same approach was applied to log-ACR risk associations, with knots at 10, 30, and 300 mg/g (30, 300, and 1000 mg/g in CKD cohorts) and the reference point of 10 mg/g (20 mg/g in CKD cohorts). Point-wise interaction of the ACR-risk association was assessed at approximate 8% increments of ACR.

The adjustment for eGFR was conducted using its spline terms. See eAppendix 2 for more details on analytical methods and individual cohorts.

We estimated the adjusted average absolute risk using the weighted average incidence rates in the reference age category (55–64 years) at the reference range of eGFR (75–89 ml/min/1.73 m^2) or ACR (<30 mg/g) combined with the meta-analyzed adjusted HRs for each level of eGFR and ACR. The weights were from the random effects meta-analysis for HRs at adjacent points to the reference eGFR (80 ml/min/1.73m^2) and ACR (10 mg/g) point in the spline models. For additive interaction, we tested whether the incidence rate difference was equal across age groups and its sign (direction) was noted. The standard errors for additive interaction (incidence rate differences) were calculated using the delta method and the variance-covariance matrix of all the spline regression coefficients obtained using multivariate meta-analysis and restricted maximum likelihood.[21] Since a single reference average incidence rate is combined with the adjusted hazard ratios to get all the adjusted average risks, the reference average incidence rate itself does not affect statistical tests of risk differences or interactions and was assumed to be constant in standard error calculations.

Categorical analyses comparing the risk in 32 categories of eGFR (<15, 15–29, 30–44, 45–59, 60–74, 75–89, 90–104, ≥105 ml/min/1.73m^2) and albuminuria (ACR: <10, 10–29, 30–299, ≥300 mg/g; PCR: <15, 15–49, 50–499, ≥500 mg/g; or dipstick test results: negative, trace, 1+, ≥2+) were done in general and high-risk cohorts. For mortality we used eGFR 75–89 and the lowest albuminuria category as the reference. For ESRD, we used the no-CKD definition (eGFR ≥60 and ACR<30 or equivalent proteinuria) as the reference since ESRD is rare at optimal kidney function.[1] Differences in absolute risks were calculated, and their standard errors were calculated using the delta method using the variance-covariance matrix of the main effects and interactions obtained with multivariate meta-analysis.[21] Since there were few participants with eGFR <15 ml/min/1.73m^2 in the general population (<0.1%) and high-risk (0.2%) cohorts, we only reported results for this eGFR category in the CKD cohorts. Heterogeneity was estimated by the χ^2 test for heterogeneity and the I^2 statistic. In all analyses, two-sided P-values less than 0.05 were considered significant. All analyses were done with Stata 11.2 (StataCorp LP, College Station, Texas).

RESULTS

Forty-six cohorts (20 from North America, 12 from Europe, 10 from Asia, 1 from Australia, and 3 international) with 2 million adults were included and followed for a mean period of 5.8 years during 1972–2011. Mean age was 49.4 years (range 18–103 with 148,951 (7.3%) subjects above age 75). The prevalences of diabetes, treated hypertension and current smoking were 10.7, 27.9, and 21.5 %, respectively. In general population and high risk cohorts, older age was associated with lower mean GFR and a higher prevalence of albuminuria (Table 1), history of cardiovascular disease, hypertension, diabetes, and other risk factors (eTable 1). There were a total of 112,325 deaths and 2,766 ESRD events among the general population and high risk cohorts, and an additional 9,037 deaths and 5,962 ESRD events in the CKD cohorts.

Figure 1 panels A and B show adjusted relative hazards of all-cause mortality for eGFR and ACR. Mortality risk was higher at lower eGFR and higher ACR within each age category (18–54, 55–64, 65–74 and 75+ years), but adjusted HRs were progressively lower at older age. For example, HRs at eGFR 45 (vs. 80 ml/min/1.73m^2) were 3.50 (95% CI, 2.55–4.81) in 18–54 years, 2.21 (2.02–2.41])in 55–64 years, 1.59 (1.42–1.77) in 65–74 years, and 1.35 (1.23–1.48) in 75+ years (see eFigure 1 for study-specific results). Interaction was assessed both for each point in the graphs and overall compared to age 55–64 years as a reference. Point-wise age-interaction was significant in a broad range of eGFR (symbols in the bottom

of Figure 1 panel A show significant positive interaction, stronger effect, for younger ages, and negative interaction, weaker effect, for older ages). The difference in the four age categories were due to the difference in the slopes between eGFR 45 and 75 ml/min/1.73m^2; the slopes at <45 ml/min/1.73m^2 were largely parallel across the age categories. Nevertheless, the overall interaction was significant in all age categories compared to 55–64 years (all P<0.004, eFigures 2–4). Despite this significant age interaction, mortality risk always started to increase in the eGFR range 60–75 ml/min/1.73m^2, although in age 75+ it only reached statistical significance at eGFR of 56 and lower. Age-interaction with ACR was less evident, and significant point-wise interaction was only observed at higher ACR ranges (Figure 1, panel B). For example, HRs of all-cause mortality at ACR 300 (vs. 10 mg/g) were 2.53 (95% CI 2.13–3.03) in 18–54 years, 2.30 (1.84–2.88) in 55–64 years, 2.10 (1.83–2.44) in 65–74 years, and 1.73 (1.45–2.05) in 75+ years. Overall interaction reached significance only for age categories 65–74 (P=0.020) and 75+ (P=0.002) showing lower relative hazards than age 55–64 years (eFigures 5–7). The associations were consistent across subgroups detmined by race, sex, and hypertension and diabetes status (eFigure 8–11).

Figure 1 panels C-D show all-cause mortality rate (absolute risk) for eGFR and ACR by age categories based on weighted average across the cohorts adjusted for covariates. A steeper slope at older age indicates a higher absolute risk difference associated with low eGFR as compared with younger age categories. For example, at eGFR 45 (vs. 80 ml/min/1.73m^2) there was 9.0 [95% CI, 6.0–12.8] extra deaths per 1,000 person-years in 18–54 years, 12.2 [10.3–14.3] in 55–64 years, 13.3 [9.0–18.6] in 65–74 years, and 27.2 [13.5–45.5] in 75+ years. This pattern of higher absolute risk difference at older age for a worse kidney marker profile than the reference (positive interaction) and lower risk difference at younger age (negative interaction) was statistically significant for most eGFR values below 40 ml/min/1.73m^2. Panel D shows similar trends for high albuminuria with the additive interaction reaching statistical significance at all ACR values; the absolute risk difference of ACR 300 mg/g compared to 10 mg/g were 7.5 [4.3–11.9] in age 18–54 years, 12.2 [7.9–17.6] in 55–64 years, 22.7 [15.3–31.6] in 65–74 years, and 34.3 [19.5–52.4] in age 75+ years. Studies with only older individuals demonstrated similar relative risk of mortality as other studies contributing to Figure 1 (eFigure 12). Relative and absolute risks for cardiovascular mortality were similar to all-cause findings (eFigure 13).

Figure 2 shows relationships for ESRD. For ESRD, the adjusted relative hazard started to increase around eGFR 70 ml/min/1.73m^2 and ACR 10 mg/g in all age categories (panels A and B). With the exception of slightly stronger association in the youngest age group within a limited range of eGFR (41–51 ml/min/1.73m^2) and ACR (81–440 mg/g), no significant point-wise interactions were observed. Similar results were observed in the subset of cohorts where we conducted competing risk ananalysis (eFigure 14). The oldest age category had the lowest hazard ratio associated with eGFR at 45 ml/min/1.73m^2 but demonstrated steeper slope at eGFR<45, catching up with other age categories by 15 ml/min/1.73m^2 (Figures 2 and eFigure 15). Overall interactions for eGFR and ACR were not significant in age categories of 18–54, 65–74, and 75+ compared with the reference age category of 55–64 years (P-values ranged from 0.113 to 0.730, eFigures 16–21). The adjusted average ESRD incidence rate at a given level of eGFR or ACR was lower in the oldest age group (Panels C-D). However, the differences in absolute risk were not significant except for a limited GFR range where adjusted average ESRD incidence rate was higher in the youngest age group.

Similar findings were observed when we tested age-interactions with combined categories of eGFR and albuminuria (Figure 3 and eTable 2). Specifically, relative associations with all-cause mortality were often strongest (red cells) in the youngest; conversely absolute risks were highest at older age with low eGFR and high albuminuria, although differences

compared to age 55–64 were only statistically significant for a subset of the cells. For ESRD the associations with both eGFR and ACR were very strong in all age groups with effect modification by age being more subtle with three of 15 cells showing weaker relative hazards at older ages (65–74 and 75+ years) and fewer (three at age 65–74 and none at age 75+) showing lower ESRD risk difference compared to the same cell at age 55–64 (eFigure 22).

Figure 4 shows a separate analysis of CKD cohorts using a lower reference point for eGFR (50 ml/min/1.73m^2) (Panels A and C for all-cause mortality and panels B and D for ESRD). The slopes for relative risk of mortality were largely parallel across age categories indicating no age interaction. Somewhat steeper slope was observed at older age category for ESRD, although overall interaction was of borderline significance (p=0.04, 0.07 and 0.08 for ages 18–54, 65–74 and 75+ vs. 55–64 years). Absolute mortality risk was higher at older age, but the risk difference (additive interaction) was largely non-significant (panel C). For ESRD, at moderately reduced eGFR the youngest age group had the highest adjusted average incidence rate but similar relative hazards with the other age categories due to a higher risk at the reference eGFR. The risk increased steeply among older individuals leading to comparable absolute risks around eGFR 15 ml/min/1.73m^2. Analysis of increasing levels of albuminuria in CKD patients showed similar patterns with the caveat that only a few CKD cohorts measured ACR (eFigure 23).

DISCUSSION

In this large collaborative meta-analysis, low eGFR and high albuminuria were associated with mortality and ESRD regardless of age. We found that mortality risk associations were weaker on the relative scale but stronger on the absolute scale at older ages in general population and high risk cohorts. In cohorts specifically selected for CKD age did not modify the mortality associations. For ESRD risk, age did not significantly influence relative and absolute risk gradients. Thus, eGFR and albuminuria were strongly associated with both mortality and ESRD in a wide range of studies across the full age range. Importantly, the results were largely consistent across diverse cohorts in terms of demographic and clinical characteristics.

In principal, CKD diagnosis could be based on i) “normal” values based on the distribution in appearantly healthy individuals or ii) kidney marker levels associated with increased risk for future adverse outcomes.[22] Supporters of the former approach have cited a dramatic rise in the prevalence of nephrosclerosis with age in kidney biopsies, even among healthy kidney donors, and suggested the concept of natural inevitable senescence of the kidneys suggesting age specific cutoffs for defining normal kidney function.[14] Several studies suggesting that the mortality relative risk associated with low eGFR is reduced at older age have also been used as arguments for age specific CKD diagnosis and staging.[10,12,13,23] In contrast, our meta-analysis documents that risk of mortality and ESRD is increased at approximately 60 ml/min/1.73m^2, the threshold used for defining CKD over the last 10 years, across all age groups. In fact, at the oldest age group while relative risks of mortality are lowest, attributable risks are highest. Therefore, while economic and other considerations should be taken into account, in terms of risks of mortality and ESRD our data support the current thresholds for defining and staging CKD.

We provided both relative and absolute risk estimates as they complement each other. Relative risks are more generalizable across different settings[24] (high and low baseline risk and varying duration of follow-up) while absolute risks are concrete easy-to-understand estimates which guide cost-benefit analyses and estimates of the potential for prevention. An attenuation of the relative mortality risk associated with low eGFR is found with increasing

age, as shown for traditional cardiovascular risk factors.[25] This lower relative risk at older age may result from higher comorbidities, even at optimal kidney function. On the other hand, absolute risk differences (excess deaths per 1,000 person years) is higher among older people. Similar relative risk attenuations but absolute risk increases have been found with older age for cardiovascular risk factors such as hypertension, hypercholesterolemia, and obesity,[26] yet clinical guidelines do not advocate age-specific "normality" based cutoffs for these risk factors but rather use "risk based" cutoffs. The similarity of our results for eGFR support a similar approach for defining CKD. For example, even at age 75+ persons with eGFR 45–59 ml/min/1.73m^2 and optimally low albuminuria had significantly increased mortality risk, though they had lower relative hazards and higher absolute risks than at younger ages. Furthermore, our CKD cohorts displayed no attenuation of relative risks with age. On the other end of the eGFR spectrum, our study confirms that very high eGFR values are associated with increased relative and absolute moratlity risk in subjects above age 55 years. This is likely caused by the influence of patients with reduced muscle mass due to malnutrition and other effects associated with cancer or other significant comorbidities. Risk implications of high eGFR values should therefore be interpreted with caution.

Most,[10,11,16,27–29] but not all,[30,31] studies found a significant association of mortality risk with higher levels of albuminuria among older individuals. The higher risk with albuminuria has been found across all age groups and eGFR levels,[10] and in elderly subjects from diabetic, non-diabetic and community based cohorts.[10,11,27,28] It has been suggested that the optimal cut-off for predicting death is lower than the cutoff for defining CKD.[29] The current meta-analysis did not assess the most optimal cutoff, but established that the risk association is linear on the log-log scale with no thresholds. Variation in relative hazards with age was modest and limited to very high albuminuria while excess mortality associated with albuminuria was consistently higher at older ages.

Lower ESRD risk for a given level of eGFR has been reported at old age,[13,15,32] and treatment recommendations have been cautious in patients above age 70 with moderately reduced eGFR.[1,33] We found a trend towards lower ESRD risk at 75+ years, which may be partially due to higher mortality risk at the older age (competing risk). Also, several clinical or social factors other than kidney function, may affect the decision to initiate kidney replacement therapy, particularly in older individuals. A recent analysis of the Alberta Kidney Disease Network focused on showing that untreated kidney failure and its ratio to ESRD increased dramatically with age.[34] Importantly, the adjusted HRs for ESRD associated with low eGFR were similar across age groups in our analysis. Neither did we find age differences in the ESRD risk gradient associated with high albuminuria. The current analysis expands on previous work by looking at both eGFR and albuminuria and contrasting mortality and ESRD associations. Importantly, using individual level reanalysis of data from 40 countries we are able to obtain definitive results with a global context.

Our findings have several important implications. First, our study shows that the kidney measures used for defining and staging CKD are strong predictors of clinical risk across the full age range, including the age 75+ years in many cohorts. This contradicts concerns raised by some that current CKD guidelines should be used with caution in older individuals and that low eGFR only reflects natural aging.[12,30,32,35,36] Relating variation in kidney function at older age to subsequent outcomes is the best way to distinguish kidney health from disease without relying on theoretical arguments of what is natural. Second, our data supports the recommendations from several investigators that CKD measures should be added to mortality risk equations.[37,38] This is, however, still debated,[39,40] and our meta-analysis did not assess the incremental prognostic value of adding CKD markers. Third, the strong increase in mortality rate along with kidney measures at older ages suggests that older adults should not be left out from management strategies of CKD. Previous data show that

low eGFR in the very old is associated with classical CKD complications like anemia, acidosis, hyperparathyroidism and hyperphosphatemia.[41] There is also an increasing risk of untreated kidney failure with age,[34] which may be more common in general population cohorts than cohorts selected for CKD, further supporting this view. Overall, the current risk based system for defining and stageing CKD is supported by robust evidence across the full age range.[5–7] Relying on one common CKD classification system for all age groups facilitates implementation in general practice, but clearly intensity and type of treatment could differ by age due to remaining lifetime and comorbidities. Nevertheless, further studies are needed to elucidate whether interventions to prevent CKD progression or CKD-related outcomes are similarly effective and cost-effective across age categories. Although we evaluated critical clinical outcomes, studies taking into account quality of life would be warranted particularly for older age groups.

Some limitations of our study need to be discussed. Serum creatinine measurements were not standardized in all studies. However, we observed similar results when we limited our analysis to studies with serum creatinine measurements standardized to IDMS (data not shown). There is also concern about validity of the CKD-EPI equation in older individuals. However, a recent paper reported that the CKD-EPI equation may be as accurate in older individuals as in younger individuals.[42] Furthermore, there is no internationally accepted gold-standard method for measuring urine albumin, and sampling and storage of urine were not standardized. Many cohorts also used dipstick, which is a semi-quantitative method, for assessing albuminuria, limiting numbers of participants in the analysis for ACR as a continuous variable. Therefore, misclassification of albuminuria, particularly for categorical analysis, might exist. Heterogeneity across cohorts in absolute and relative risks is present and needs to be considered, but our random effects meta-analysis conservatively incorporates heterogeneity into its confidence interval calculations. Likewise, differences in study quality could have influenced our results. Furthermore, results were consistent across cohort type and after exclusion of the largest cohort. Our results need to be carefully interpreted given that they were based on models adjusting for traditional risk factors. However, the results were largely similar when we only adjusted for sex and race (data not shown). Absolute risk at the reference point calculated as a weighted average of the cohorts may not directly apply to any single setting. The shape of the associations and tests for interactions in the present meta-analysis are independent of the exact risk at the reference point. However, the current meta-analysis is not intended to develop an individual risk prediction tool. The incidence rate differences reported are conservative since they adjust for covariates, and unadjusted differences may be larger. We did not confirm the validity of proportional hazards assumption for every study although some of the collaborating cohorts individually comfirmed this assumption for clinical risk with eGFR and/or albuminuria as predictors.[16] Thus, the pooled HRs in this study estimate the average HR over follow-up time.

The study is strengthened by showing consistent results across ACR, PCR, and dipstick cohorts. We evaluated CKD-age interaction on both relative and absolute scale. Moreover, inclusion of 2 million subjects world-wide increases precision and generalizability of estimates to a level that previously has not been possible, particularly for the very old and ESRD. Individual level data, common definitions of covariates, and uniform analysis with adjustment for major risk factors further strengthens our study. We also used the CKD-EPI formula for estimating GFR, which improves the accuracy of kidney function estimates and overall risk prediction[19,43] and has not been examined for age interaction in most cohorts.

In summary, our analysis of 2 million individuals from 46 cohorts across the world shows that CKD markers were associated with risk across the full age spectrum. There was no effect modification for ESRD risk, while relative mortality risk decreased with age.

However, absolute mortality risk difference tended to increase with age. While some variation in management of CKD should be considered by age based on cost and benefits, with respect to risk of mortality and ESRD, our data supports a common definition and staging of CKD based on eGFR and albuminuria for all age groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Role of the Sponsor: The sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

Appendix

CKD-PC investigators/collaborators (study acronyms/abbreviations are listed in eAppendix 1 p 4–5):

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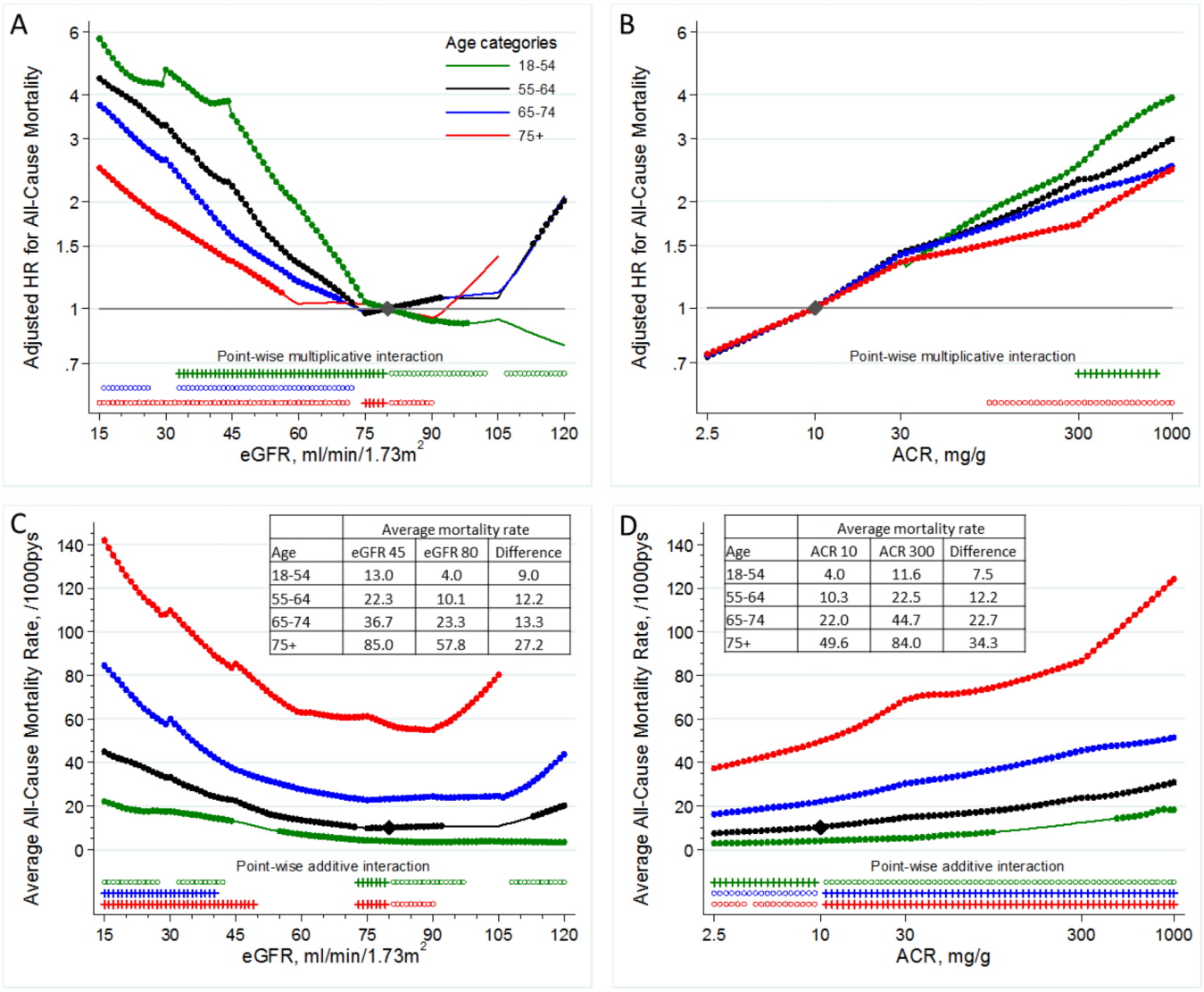

Figure 1.

Adjusted hazard ratios (panels A and B) for all-cause mortality and average mortality rate (panels C and D) according to eGFR (A and C) and ACR (B and D) within each age category. The filled circles note statistical significance ($p<0.05$) compared to the reference (black diamond) eGFR of 80 ml/min1.73m^2 or ACR of 10 mg/g within each age category in panels A and B and compared to age category 55–64 years in panels C and D. Plus signs and open circles on the bottom of each panel represent significantly positive (greater effect size) and negative (smaller effect size) point-wise interactions ($p<0.05$), respectively, compared to age 55–64 years. Gaps indicate no significant point-wise interaction. Models are meta-analysis of general population and high risk cohorts adjusted for sex, race, body mass index, systolic blood pressure, total cholesterol, history of cardiovascular disease, diabetes, smoking status, and albuminuria (panels A and C) or eGFR (panels B and D).

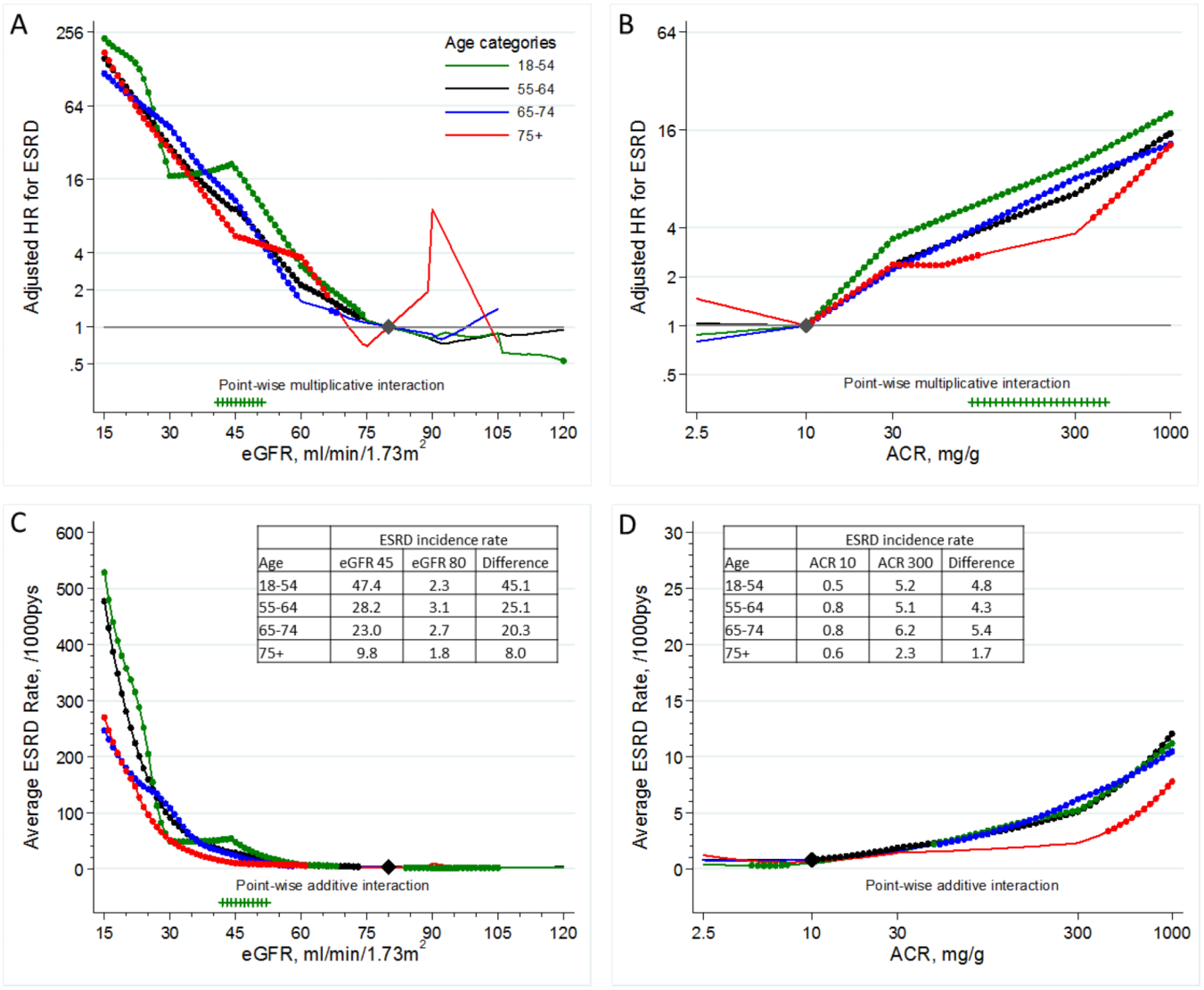

Figure 2.

Adjusted hazard ratios (panels A and B) and average incidence rate (panels C and D) for ESRD according to eGFR (A and C) and ACR (B and D) within each age category. The filled circles note statistical significance ($p<0.05$) compared to the reference (black diamond) eGFR of 80 ml/min1.73m2 or ACR of 10 mg/g within each age category in panels A and B and compared to age category 55–64 years in panels C and D. Plus signs and open circles on the bottom of each panel represent significantly positive (greater effect size) and negative (smaller effect size) point-wise interactions ($p<0.05$), respectively, compared to age 55–64 years. Gaps indicate no significant point-wise interaction. Models are meta-analysis of general population and high risk cohorts adjusted for sex, race, body mass index, systolic blood pressure, total cholesterol, history of cardiovascular disease, diabetes, smoking status, and albuminuria (panels A and C) or eGFR (panels B and D).

	18-54				55-64				65-74				75+			
	ACR/Dipstick				ACR/Dipstick				ACR/Dipstick				ACR/Dipstick			
eGFR	<10 / Dip "-"	10-29 / Dip "±"	30-299 / Dip "1+"	300+ / Dip "≥2+"	<10 / Dip "-"	10-29 / Dip "±"	30-299 / Dip "1+"	300+ / Dip "≥2+"	<10 / Dip "-"	10-29 / Dip "±"	30-299 / Dip "1+"	300+ / Dip "≥2+"	<10 / Dip "-"	10-29 / Dip "±"	30-299 / Dip "1+"	300+ / Dip "≥2+"
A. Adjusted Hazard Ratios																
>105	0.89^{O}	1.37	**2.83**	**5.62**	**1.58**	**2.17**	**3.64**	**5.68**	1.61	**2.28**	**2.83**	**12.21**	1.63	0.76	**24.27**	
90-104	1.04^{O}	**1.78**	**2.23**	**3.68**	**1.14**	**1.42**	**2.10**	**4.48**	1.01^{O}	**1.62**	**1.83**	**2.98**	0.97	**1.88**	**2.18**	**6.77**
75-89	**Ref**	**1.78**	**2.25***	**3.77***	**Ref**	**1.47**	**1.80**	**3.42**	**Ref**	**1.38**	**1.92**	**2.85**	**Ref**	**1.49**	**1.91***	**2.73**
60-74	**1.37***	**2.25***	**3.60***	**7.30***	**1.08**	**1.55**	**2.60**	**4.24**	1.04^{O}	**1.50**	**1.89**^{O}	**2.95**^{O}	1.04	**1.48**	**1.83**^{O}	**2.66**^{O}
45-59	**2.79***	**4.33***	**10.05***	**9.48***	**1.58**	**2.55**	**3.38**	**5.16**	**1.19**^{O}	**1.86**^{O}	**2.49**^{O}	**3.49**^{O}	**1.20**^{O}	**1.75**^{O}	**1.91**^{O}	**2.76**^{O}
30-44	**8.19***	**12.59***	**12.62***	**15.48***	**3.39**	**4.03**	**6.96**	**6.49**	**2.00**^{O}	**3.18**	**4.14**^{O}	**4.56**^{O}	**1.71**^{O}	**2.41**^{O}	**2.73**^{O}	**3.41**^{O}
15-29	**11.98**	**16.13**	**17.35***	**19.40***	**7.01**	**6.78**	**8.27**	**9.89**	**3.86**^{O}	**4.44**	**5.83**	**6.19**^{O}	**2.90**^{O}	**3.69**^{O}	**3.67**^{O}	**5.29**^{O}
B. Incidence Rate Difference, per 1000 person years																
>105	-0.35^{O}	**1.18**	**5.77**^{O}	**14.56**	**5.34**	**10.76**	**24.31**	**43.07**	13.92	**29.12**	**41.51**	**254.86**	33.80	-13.18	**1254.90**	
90-104	0.12^{O}	**2.46**^{O}	**3.87**^{O}	**8.44**^{O}	**1.26**	**3.83**	**10.14**	**31.98**	0.33	**14.18***	**18.87**	**45.03**	-1.56	**47.37**	**63.45**	**310.90**
75-89	**Ref**	**2.45**^{O}	**3.92**^{O}	**8.72**^{O}	**Ref**	**4.31**	**7.32**	**22.24**	**Ref**	**8.62**	**20.85***	**42.00***	**Ref**	**26.55***	**49.08***	**93.29***
60-74	**1.17**	**3.93**	**8.18**^{O}	**19.85**^{O}	**0.73**	**5.08**	**14.68**	**29.77**	0.97	**11.26***	**20.30**	**44.38***	2.32	**25.74***	**44.98***	**89.47***
45-59	**5.62**	**10.50**	**28.49**	**26.72**^{O}	**5.35**	**14.25**	**21.88**	**38.24**	**4.36**	**19.61**	**33.91***	**56.58***	**10.99**	**40.57***	**48.89***	**94.98***
30-44	**22.63**	**36.49**	**36.59**	**45.60**	**21.97**	**27.92**	**54.85**	**50.49**	**22.86**	**49.57***	**71.36**	**80.91***	**38.03***	**75.88***	**93.18**	**129.99***
15-29	**34.58**^{O}	**47.64**	**51.48**	**57.95**^{O}	**55.30**	**53.16**	**66.85**	**81.76**	**65.09**	**78.22**	**109.80***	**118.00**	**102.23**	**145.14***	**143.83***	**231.47***

Figure 3.

Adjusted hazard ratio (panel A) and incidence rate difference (panel B) for all-cause mortality by categories of eGFR and albuminuria across age groups. Each number represents a pooled estimate from meta-analysis in 34 general population and high risk cohorts. All results are adjusted for covariates. Bold numbers indicated statistical significance at *P<0.05* compared to the reference cell and circles (^{O}) indicate a significant negative interaction and stars (*) indicate a significant positive interaction at *P<0.05* compared to the corresponding cell in the 55–64 year age group. Color shading indicates the strength of association (approximately one quarter of all cells are shaded in each color; Green: low; yellow: mild; orange: moderate; red: high) measured as either hazard ratios (panel A) or incidence rate difference (panel B). Confidence intervals are provided in eTable 2.

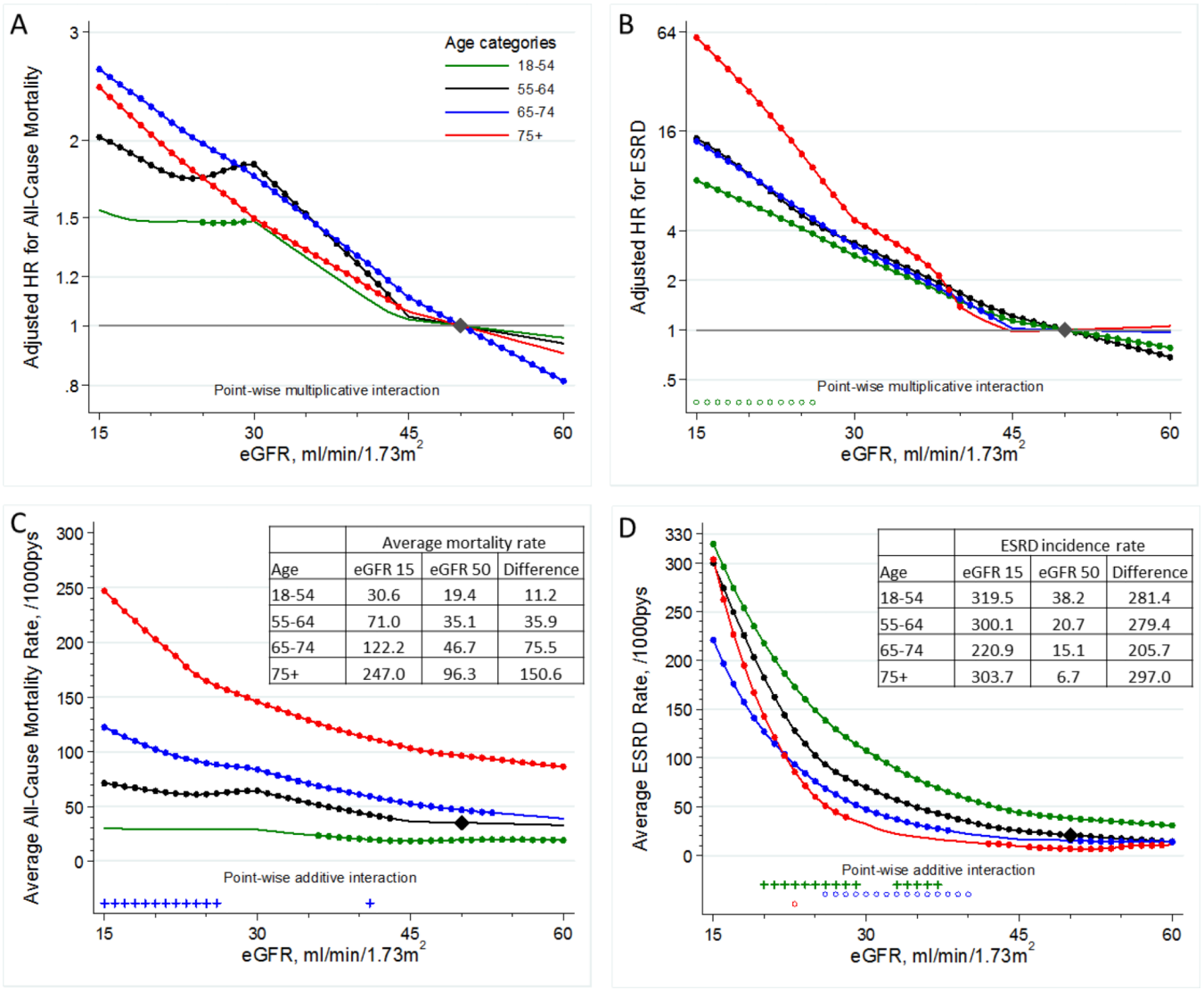

Figure 4.

Adjusted hazard ratios (panels A and B) and average incidence rate (panels C and D) for all-cause mortality (A and C) and ESRD (B and D) in CKD cohorts according to eGFR within each age category. The filled circles note statistical significance ($p<0.05$) compared to the reference (black diamond) eGFR of 50 ml/min1.73m^2 within each age category in panels A and B and compared to age category 55–64 years in panels C and D. Plus signs and open circles on the bottom of each panel represent significantly positive (greater effect size) and negative (smaller effect size) point-wise interactions ($p<0.05$), respectively, compared to age 55–64 years. Gaps indicate no significant point-wise interaction. Models are meta-analysis of CKD cohorts adjusted for sex, race, body mass index, systolic blood pressure, total cholesterol, history of cardiovascular disease, diabetes, smoking status, and albuminuria.

Table 1

Baseline characteristics of participating general population, high risk and chronic kidney disease cohorts by age group

				18–54			55–64			65–74			75+		
Study	**Region**	**N**	**F/U, yrs**	**% N**	**eGFR mean**	**% alb ‡**	**% N**	**eGFR mean**	**% alb ‡**	**% N**	**eGFR mean**	**% alb ‡**	**% N**	**eGFR mean**	**% alb ‡**
General Population															
Aichi[44]	Japan	4,731	7.4	81%	99	2%	19%	90	3%	<0.01%	94	0%	N/A	N/A	N/A
AKDN (Dip)[45]	Canada	920,686	2.7	66%	93	4%	16%	77	4%	10%	68	6%	8%	58	10%
ARIC*[46]	USA	11,441	10.6	6%	93	6%	55%	87	7%	40%	78	11%	<0.01%	72	33%
AusDiab*[47]	Australia	11,179	9.9	61%	94	4%	18%	81	6%	14%	72	11%	7%	63	24%
Beaver Dam CKD[48]	USA	4,857	11.6	31%	91	3%	27%	82	3%	26%	74	5%	16%	63	7%
Beijing*[49]	China	1,559	3.9	34%	93	5%	30%	82	5%	32%	76	7%	4%	68	7%
CHS*[50]	USA	2,988	8.4	N/A	N/A	N/A	N/A	N/A	N/A	25%	80	18%	75%	72	21%
CIRCS[51]	Japan	11,871	17.0	51%	96	3%	36%	84	3%	14%	78	4%	N/A	N/A	N/A
COBRA*[52]	Pakistan	2,872	4.1	66%	110	6%	19%	96	14%	11%	87	14%	4%	78	23%
ESTHER[53]	Germany	9,641	5.0	17%	92	9%	44%	86	11%	38%	78	14%	1%	70	20%
Framingham*[54]	USA	2,956	10.5	37%	99	7%	33%	88	10%	25%	77	19%	5%	67	30%
Gubbio*[55]	Italy	1,681	10.7	50%	88	3%	50%	81	5%	N/A	N/A	N/A	N/A	N/A	N/A
HUNT*[3]	Norway	9,659	12.0	30%	103	5%	20%	87	9%	30%	78	14%	21%	69	23%
IPHS[56]	Japan	95,451	14.0	34%	96	2%	31%	85	2%	30%	78	3%	5%	70	4%
MESA*[57]	USA	6,733	6.2	28%	92	5%	28%	84	8%	30%	77	11%	14%	69	18%
MRC[31]	UK	12,371	6.4	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	100%	57	7%
NHANES III*[58]	USA	15,563	8.5	65%	113	7%	13%	88	15%	13%	77	20%	10%	66	27%
Ohasama[59]	Japan	1,956	10.4	17%	94	12%	42%	85	6%	31%	79	5%	10%	69	19%
Okinawa83[60]	Japan	9,599	16.9	58%	84	15%	19%	69	24%	15%	62	29%	8%	55	36%
Okinawa93[61]	Japan	93,216	6.9	46%	87	3%	25%	74	4%	19%	67	5%	10%	58	6%
PREVEND*[62]	Netherlands	8,385	9.7	66%	95	7%	18%	81	15%	16%	73	25%	0.01%	61	35%
Rancho Bernardo*[63]	USA	1,474	10.5	11%	88	4%	25%	81	9%	26%	73	15%	39%	64	21%
REGARDS*[64]	USA	27,306	5.1	12%	100	10%	38%	91	12%	32%	80	16%	17%	70	22%

				18–54			55–64			65–74			75+		
Study	**Region**	**N**	**F/U, yrs**	**% N**	**eGFR mean**	**% alb ‡**	**% N**	**eGFR mean**	**% alb ‡**	**% N**	**eGFR mean**	**% alb ‡**	**% N**	**eGFR mean**	**% alb ‡**
Severance[65]	Korea	76,201	10.0	74%	93	5%	20%	82	6%	5%	75	7%	1%	66	13%
Taiwan[23]	Taiwan	515,573	8.1	79%	98	1%	13%	79	4%	6%	70	6%	1%	61	7%
ULSAM*[66]	Sweden	1,103	11.6	N/A	N/A	N/A	N/A	N/A	N/A	100%	76	16%	N/A	N/A	N/A
Subtotal∩		**1,861,052**	**5.9 (0.003–20.8)**	**65%**	**95 (16)**	**3%**	**18%**	**79 (15)**	**4%**	**11%**	**71 (15)**	**7%**	**6%**	**60 (16)**	**11%**
High Risk Cohorts															
ADVANCE*[67]	Multiple	10,595	4.8	0.01%	83	24%	40%	85	32%	50%	75	29%	9%	66	33%
AKDN (ACR)* [45]	Canada	102,639	3.0	44%	90	20%	24%	76	23%	19%	65	28%	12%	55	39%
CARE[68]	Canada	4,098	4.8	32%	86	10%	37%	75	14%	30%	67	17%	1%	59	30%
KEEP[69]	USA	77,902	4.2	50%	98	10%	23%	81	12%	17%	72	15%	10%	61	21%
KP Hawaii†[70]	USA	39,884	2.4	38%	94	34%	27%	78	29%	20%	68	32%	16%	58	40%
MRFIT[71]	USA	12,854	24.9	91%	88	4%	9%	80	3%	N/A	N/A	N/A	N/A	N/A	N/A
Pima*[72]	USA	5,066	13.8	91%	124	17%	6%	91	46%	3%	82	53%	1%	72	53%
ZODIAC*[73]	Netherlands	1,095	7.9	13%	92	23%	21%	78	30%	34%	69	42%	31%	59	50%
Subtotal∩		**254,133**	**4.4 (0.003–32.0)**	**46%**	**94 (20)**	**17%**	**24%**	**79 (17)**	**21%**	**19%**	**69 (17)**	**25%**	**11%**	**58 (17)**	**34%**
CKD Cohorts															
AASK†[74]	USA	1,094	8.8	48%	45	72%	33%	47	54%	20%	46	49%	N/A	N/A	N/A
BC CKD[75]	Canada	17,426	3.3	15%	47	87%	17%	41	79%	28%	37	72%	40%	31	71%
CRIB*[76]	UK	308	6.1	30%	24	95%	21%	23	83%	29%	22	84%	21%	20	81%
Geisinger ACR*[77]	USA	3,361	3.5	7%	49	62%	20%	51	44%	36%	51	41%	38%	50	42%
Geisinger Dip[77]	USA	4,509	3.9	7%	45	45%	14%	49	28%	28%	50	23%	50%	49	23%
GLOMMS-1 ACR*[78]	Scotland	537	4.2	5%	38	71%	14%	36	59%	34%	34	47%	47%	30	48%
GLOMMS-1 PCR†[78]	Scotland	470	4.2	16%	32	92%	13%	31	100%	27%	30	91%	44%	27	97%
KPNW[79]	USA	1,627	4.6	6%	47	54%	14%	49	38%	36%	48	31%	44%	44	27%
MASTERPLAN*[80]	Netherlands	636	4.1	29%	37	94%	28%	37	84%	34%	36	79%	9%	35	84%
MDRD†[81]	USA	1,730	14.1	57%	43	86%	28%	38	78%	15%	38	74%	N/A	N/A	N/A
MMKD†[82]	Multiple	202	4.0	67%	52	95%	31%	39	95%	1%	16	100%	N/A	N/A	N/A

				18–54			55–64			65–74			75+		
Study	**Region**	**N**	**F/U, yrs**	**% N**	**eGFR mean**	**% alb ‡**	**% N**	**eGFR mean**	**% alb ‡**	**% N**	**eGFR mean**	**% alb ‡**	**% N**	**eGFR mean**	**% alb ‡**
NephroTest*[83]	France	928	2.6	34%	49	71%	25%	42	63%	25%	40	58%	16%	33	57%
RENAAL*[84]	Multiple	1,513	2.8	22%	44	100%	44%	41	100%	34%	39	100%	N/A	N/A	N/A
STENO*[85]	Denmark	886	8.8	85%	86	52%	11%	77	33%	4%	65	41%	1%	73	0%
Sunnybrook*[86]	Canada	3,385	2.3	13%	43	88%	16%	41	84%	26%	38	83%	44%	33	84%
Subtotal∩		**38,612**	**4.2 (0.003–18.9)**	**19%**	**49 (27)**	**79%**	**19%**	**43 (18)**	**70%**	**28%**	**41 (16)**	**62%**	**35%**	**37 (14)**	**59%**
Overall Total		2,051,158													

*Studies with ACR,

†Studies with PCR

‡Proportion of participants with ACR ≥30 mg/g or PCR ≥50 mg/g or dipstick protein ≥1+.

∩Overall mean with range or SD for continuous variables.

●All participants are included in AKDN with ACR were counter in the larger Dipstick entry and thus are not accounted for in the total and median.