Past Decline versus Current Estimated GFR and Subsequent Mortality Risk

David M. Naimark MD MSc*, Morgan E. Grams MD PhD[†], Kunihiro Matsushita MD PhD[†], Corri Black MBChB MSc[‡], Iefke Drion MD PhD[§], Caroline S. Fox MD MPH[ǁ], Lesley Inker MD[¶], Areef Ishani MD MS**, Sun Ha Jee MHS PhD[††], Akihiko Kitamura MD PhD[‡‡], Janice Lea MD[§§], Joseph Nally MD[ǁǁ], Carmen Peralta MD[¶¶], Dietrich Rothenbacher MD MPH***, Seungho Ryu MD PhD[†††], Marcello Tonelli MD[‡‡‡], Hiroshi Yatsuya MD PhD[§§§], Josef Coresh MD PhD[†], Ron T. Gansevoort MD PhD[ǁǁǁ], David Warnock MD[¶¶¶], Mark Woodward PhD****, Paul E. de Jong MD PhD[ǁǁǁ] for the CKD Prognosis Consortium.

*Division of Nephrology, Sunnybrook Health Sciences Centre and Institute of Health Policy Management and Evaluation, Faculty of Medicine University of Toronto, Ontario, Canada; [†]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, 21205, USA; [‡]University of Aberdeen, United Kingdom; [§]Isala Clinics, Zwolle, the Netherlands; [ǁ]National Heart, Lung, and Blood Institute's Framingham Heart Study and the Center for Population Studies, Framingham, MA; Division of Endocrinology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [¶]Division of Nephrology, Tufts Medical Center, Boston, MA, USA; **Minneapolis VA Health Care System, Minneapolis, MN, USA; [††]Department of Epidemiology and Health Promotion, Institute for Health Promotion, Graduate School of Public Health, Yonsei University, Seoul, Korea; [‡‡]Osaka Center for Cancer and Cardiovascular Disease Prevention, Osaka, Japan; [§§]Renal Division, Emory University School of Medicine, Atlanta, GA, USA; [ǁǁ]Department of Nephrology and Hypertension, Glickman Urological and Kidney Institute, Cleveland, OH, USA; [¶¶]University of California and San Francisco VA Medical Center, San Francisco, CA, USA; ***Division of Clinical Epidemiology and Aging Research, German Cancer Research Center, Heidelberg and Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany; [†††]Kangbuk

Samsung Hospital, Sunkgyunkwan University School of Medicine, Seoul, Korea; ‡‡‡Department of Medicine, University of Alberta, Edmonton, Canada; §§§Department of Public Health, Fujita Health University, Toyoake, Japan; ||||Department of Nephrology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; ¶¶¶Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA; ****The George Institute for Global Health, Nuffield Department of Population Health, University of Oxford, UK and The George Institute for Global Health, University of Sydney, Australia.

Address for Correspondence: Chronic Kidney Disease Prognosis Consortium Data Coordinating Center (Principal Investigator, Josef Coresh, MD, PhD), 615 N. Wolfe Street, Baltimore, MD 21205; Tel: 410-955-9917, Fax: 410-955-8086, E-mail: ckdpc@jhmi.edu

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ABSTRACT

A single determination of estimated glomerular filtration rate (eGFR) is associated with subsequent mortality risk. Prior change in eGFR is used to assess loss of kidney function but its relationship to mortality risk is uncertain. We conducted an individual-level meta-analysis of the risk of mortality associated with antecedent eGFR slope, adjusting for established risk factors including last eGFR, among 1.2 million subjects from 12 chronic kidney disease (CKD) and 22 other (general population and high cardiovascular risk) cohorts within the CKD Progression Consortium. Over a 3-year antecedent period, 12% of participants in the CKD cohorts and 11% in the other cohorts experienced an eGFR slope <-5 ml/min/1.73 m^2/year; a slope >+5 ml/min/1.73 m^2/year was present in 7% and 4%, respectively. Despite heterogeneity, overall, compared to 0 ml/min/1.73m^2/yr, a slope of -6 ml/min/1.73m^2/yr was associated with an adjusted hazard ratio for all-cause mortality of 1.25 (95% CI: 1.09 to 1.44) among CKD cohorts and 1.15 (95% CI: 1.01 to 1.31) among other cohorts during a follow-up period of 3.2 years. Likewise, a slope of +6 ml/min/1.73 m^2/year was also associated with higher mortality risk: 1.58 (95% CI: 1.29 to 1.95) among CKD cohorts and 1.43 (95% CI: 1.11 to 1.84) among other cohorts. Results were similar for cardiovascular (CV) and non-CV causes of death and stronger for longer antecedent periods (e.g., 3 vs. 1 or 2 years). We conclude that prior decline or rise in eGFR is associated with a modest increased risk of mortality, independent of current eGFR.

Key words: chronic kidney disease, estimated glomerular filtration rate, mortality, epidemiology

INTRODUCTION

Chronic kidney disease (CKD) affects 10-16% of the global population.[1, 2] Numerous studies have reported the significant association of low estimated glomerular filtration rate (eGFR) at a single time point with mortality,[3-9] a more frequent occurrence than end-stage renal disease, even among patients with late stages of CKD.[10] Recently, there has been great interest in whether a decline in eGFR adds information to mortality risk assessment beyond eGFR at a single time point. Clinicians are often faced with a situation in which current eGFR is known, as is its past trajectory. Thus, a clinically relevant question is whether past trajectory of eGFR can provide additional information beyond current eGFR.[11, 12]

A surprising finding in previous studies was that an increase in eGFR was associated with an increased risk of mortality. Whether these observations are generalizable is uncertain since they were based on data from single centers[13, 14] and/or in cohorts with mean baseline eGFR values of 50 ml/min/1.73 m^2 or greater.[11-16] Improvement in eGFR in a CKD population might demonstrate different associations with mortality than that in a general population cohort. In addition, the "U-shaped" association might be driven by confounding factors, such as weight loss or heart failure. Thus, a comprehensive investigation about eGFR increase and mortality risk is warranted.

The objective of the current study was to use meta-analysis to address two clinically relevant questions: given patients presenting with a particular eGFR, does the prior eGFR trajectory provide additional prognostic information with respect to mortality risk beyond the present eGFR *per se* and, if so, what is the shape of this relationship?

RESULTS

Associations with estimated glomerular filtration rate slope

Over a 3-year antecedent period, median (inter-quartile range) numbers of creatinine measurements were 7 (7-7) in the CKD and 5 (4-5) in the other (general population/high cardiovascular risk) cohorts. 12% of participants in the CKD and 11% of participants in the other cohorts had an eGFR slope <-5 ml/min/1.73 m^2/year, whereas 7% and 4% experienced an eGFR slope >+5 ml/min/1.73 m^2/year during the antecedent period, respectively. There were no consistent differences in the age or gender distribution between subjects with antecedent slopes of <-5, ≥-5 to ≤+5, and >+5 ml/min/1.73m^2/yr; however, black subjects tended to be in the <-5 ml/min/1.73 m^2 category (Table 1 and Supplemental Table 1). Subjects with annual slopes <-5 ml/min/1.73 m^2/yr had a higher prevalence of elevated albuminuria, were more often diabetic, and were more likely to have a history of CVD compared with subjects in the stable or increasing eGFR slope categories (Supplemental Table 2).

After adjustment, lower current eGFR, younger age, black race, higher total cholesterol, the presence of diabetes, and the presence of albuminuria (severely-increased only in CKD cohorts; moderately-increased and severely-increased the other cohorts) were associated with antecedent slope <-5 ml/min/1.73 m^2/yr (Supplemental Table 3). Factors associated with an eGFR slope >+5 ml/min/1.73 m^2/yr included higher current (last) eGFR, female gender, history of CVD, and the presence of albuminuria (severely-increased only in CKD cohorts; moderately increased and severely increased in the other cohorts).

All-cause mortality

Among cohorts with 3-year antecedent data, 102,477 of 1,277,217 subjects died (8%) over a mean follow-up time of 3.2 years (Table 1 and Supplemental Table 4). Among the 12 CKD cohorts, 57,269 of 249,977 subjects died (23%) while among 22 other cohorts, 45,208 of 1,027,240 subjects died (4%). After antecedent intervals of one and two years, 223,979 of 1,765,589 (13%) and 158,617 of 1,597,849 (10%) subjects died, respectively (Supplemental Table 5).

Risk of all-cause mortality associated with a decline in eGFR

Compared to subjects with no change in eGFR over the antecedent 3-year period, a slope of -6 ml/min/1.73m^2/yr was associated with a HR for all-cause mortality (ACM) of 1.25 (95% CI: 1.09 to 1.44) and 1.15 (95% CI: 1.01 to 1.31) among members of CKD and other cohorts, respectively (Figure 1 and Supplemental Table 6). The risk of ACM associated with an annual eGFR decline was attenuated with shorter antecedent periods (corresponding to smaller absolute eGFR declines) (Supplemental Figure 1).

For both CKD and other cohorts, there was no statistically significant interaction of current eGFR and antecedent eGFR slope with ACM (p for interaction 0.17 and 0.19, respectively) (Figure 2). Higher current albuminuria was associated with higher ACM risk. Among albuminuria strata, the association between antecedent eGFR slope and ACM mortality overlapped only in the extremes of the eGFR slope distribution in the CKD cohorts and was roughly parallel by level of albuminuria in the other cohorts suggesting a similar absence of interaction between current albuminuria and antecedent eGFR decline (p for interaction 0.668

[moderately increased albuminuria] and 0.448 [severely increased albuminuria] for CKD cohorts and 0.444 [moderately increased albuminuria] and 0.144 [severely increased albuminuria] for other cohorts Supplemental Figure 2).

The risk associated with an eGFR slope of -6 ml/min/1.73m^2/yr over the 3-year antecedent period demonstrated heterogeneity (Figure 3). Among CKD cohorts, meta-regression suggested that differences in follow-up time (with higher HR associated with shorter follow-up) and median age (with higher HRs associated with older age) may have accounted for some heterogeneity (Supplemental Figure 3) while for the other cohorts, heterogeneity was not explained by meta-regression (Supplemental Figure 4).

For the CKD cohorts, absolute risk of ACM was higher with greater antecedent decline in eGFR, but current eGFR was relatively more important in determining the absolute mortality risk. Absolute risk of ACM in the other cohorts was low (Supplemental Table 7).

Risk of all-cause mortality associated with an increase in eGFR

ACM risk associations of antecedent eGFR increase were at least as strong as those for eGFR decline and mortality (Figure 1). Compared to subjects with no change in eGFR over the antecedent 3-year period, a slope of +6 ml/min/1.73m^2/yr was associated with a HR for ACM of 1.58 (95% CI: 1.29 to 1.95) for the CKD cohorts and 1.43 (95% CI: 1.11 to 1.84) among members of the other cohorts (Figure 1 and Supplemental Table 6). The risk associated with an eGFR slope of +6 ml/min/1.73 m^2/yr over the 3-year antecedent period demonstrated heterogeneity across both CKD and other cohorts (Figure 4). The absolute risk of ACM was

higher among members of the CKD versus the other cohorts, with current eGFR a more important risk factor than antecedent slope (Supplemental Table 7).

The association of eGFR increase and mortality remained significant in all sensitivity analyses. Participants with positive eGFR slopes in the other cohorts had a trend toward higher risk of both cardiovascular and non-cardiovascular mortality, although risk associations were attenuated (Table 2). Similarly, the increased risk of ACM associated with a positive eGFR slope in the antecedent period persisted when we included a measure, the root mean squared error (RMSE), of each individual's variation around their eGFR slope line, as a covariate in the Cox model (Supplemental Figure 5), or when the model was stratified by RMSE (Supplemental Figure 6). Although weight loss of > 2.0kg was associated with increased odds of eGFR rise, excluding subjects who lost >2.0kg during the antecedent 3 years did not alter the U-shaped relationship between antecedent eGFR slope and all-cause mortality (Supplemental Figure 7). Excluding diabetics and either adjusting for or stratifying by use of renin-angiotensin system inhibiting medications in the antecedent period made no meaningful difference in the risk associations (Supplemental Figures 8 -10).

Analyses using percentage change of eGFR rather than slope are shown in Supplemental Figure 11. Since a given absolute change in eGFR represents a higher percentage change for persons with lower current eGFR values, and since the CKD cohorts had, in general, lower current eGFR, the distribution of percentage decline is shifted to the left for the CKD relative to the other cohorts such that a greater number of persons in the CKD cohorts experienced a 30% or greater reduction in eGFR over three years. Nonetheless, risk associations were similar to

slightly stronger when prior eGFR trajectory was assessed as a percentage change rather than slope (Supplemental Figure 11). Compared to an adjusted Cox model without eGFR slope, the addition of the latter resulted in a marginal improvement in the discrimination with respect to ACM: pooled estimates for the resulting change of c-statistics were 0.003 (95% CI: -0.000 to 0.007) and 0.002 (95% CI: 0.001 to 0.004) for the CKD and other cohorts, respectively (Supplemental Table 8).

DISCUSSION

In the current analysis of more than 1.2 million subjects and more than 100,000 deaths, we found that antecedent eGFR slope over a three year period, whether positive or negative, exhibited a statistically significant association with all-cause, cardiovascular, and non-cardiovascular mortality. These associations were observed even after adjustment for current eGFR (last eGFR in the antecedent period), suggesting that there is modest incremental information in the prior eGFR trajectory beyond eGFR measured at a single time point. In general, large changes in eGFR were associated with the highest risk of mortality, but were unusual (11% for < -5 and 5% for > 5 ml/min/1.73 m^2/yr), while lesser changes were associated with smaller risks, but were more common. Antecedent improvement in eGFR was associated with a mortality risk similar in magnitude as antecedent decline. This association persisted in numerous sensitivity analyses, suggesting that rapid change in creatinine-based eGFR – whether for the worse or for the better - may be a poor prognostic sign. The relationship between antecedent eGFR slope and ACM was apparent across the entire spectrum of current eGFR but, at least within CKD cohorts, current eGFR had a much greater effect on absolute mortality risk than did prior trajectory.

Previous studies have shown that low eGFR measured at a single time point is an important risk factor for ACM.[3, 5, 17-19] We sought to evaluate whether prior change in eGFR contributes independently to ACM prognosis in the clinical setting, where last eGFR value is known. Previous studies have investigated this association from a "clinical trial perspective", adjusting for the first eGFR. The latter is relevant for the situation where two subjects begin a clinical trial at the same eGFR value but one maintains a stable eGFR while the other subject's eGFR either falls or rises.[20] In contrast, adjustment for last eGFR during the antecedent period, as per the current analysis, replicates the clinical scenario whereby ACM risk is compared between two patients who present with the same eGFR value but one has had a stable eGFR and the other has either fallen or risen to that value. Similar to previous work, in which adjustments were made for either the first or last eGFR in the antecedent period, we found a U-shaped relationship between eGFR slope and subsequent ACM risk.[11, 13-16] Direct, quantitative comparison between the results of these investigations and our own are hampered by different indices of renal function change, different antecedent periods and the use of rates, in some studies, rather than HR, to quantify mortality risk. However, Turin *et al.*[12] found an adjusted HR for ACM of 1.14 and 1.68 for a 4 ml/min/1.73m^2/yr declining and increasing slope, respectively, compared to subjects with a stable eGFR value in a Canadian, population-based study. These values are qualitatively similar to those for the other (general population and high risk) cohorts in the current analysis. The small quantitative difference may be due to differences in the set of adjustment factors employed in the two studies. Note that data from the latter cohort was included in the current analysis.

Several mechanisms may underlie the association of antecedent change in eGFR and mortality. In principle, change in creatinine-based eGFR may reflect either change in true GFR – due to progression or remission of CKD or onset or recovery from acute kidney disease - or change in non-filtration determinants of serum creatinine such as muscle wasting or malnutrition. A steeper antecedent eGFR decline has been traditionally held to signify past decline in true GFR. Thus, in the current study, the true GFR for individuals with a steeper eGFR decline in the antecedent period may have continued to decline in the follow-up period, below the last or current true GFR, and lower true GFR *per se* is expected to be associated with mortality. Alternatively, an antecedent decline in true GFR may simply reflect a more severe comorbidity profile.[12, 14] For example, although we adjusted for diabetes and our findings were qualitatively similar after excluding diabetic subjects, we did not adjust for severity of diabetes, a key determinant of both true GFR decline and mortality risk.[21, 22] Similarly, episodes of acute coronary syndrome or congestive heart failure may increase the risk of death and also cause true GFR decline.[23, 24] Yet, we observed similar associations of antecedent eGFR decline with non-CVD mortality as we did with CVD mortality (albeit in the limited cohorts with this data). Previous investigations have suggested that variability in the eGFR itself may be associated with higher ACM risk.[25] However, in the current study, with individual residual eGFR variation expressed as the RMSE, we found little attenuation of the effect of decreasing (or increasing) eGFR slope on ACM.

The association between increasing eGFR and mortality is less intuitive. Rather than indicating improving true GFR, a rising eGFR may be an indicator of declining muscle mass or malnutrition, with the latter being responsible for the increase in ACM risk. However, exclusion of subjects who lost weight attenuated the risk of ACM on both ends of the eGFR slope spectrum

but did not eliminate the U-shape. Furthermore, a previous study reported an association between higher ACM risk and a positive eGFR slope using cystatin C as a filtration marker even though cystatin C levels are less affected by muscle mass than creatinine, suggesting that a rising eGFR may reflect a rising true GFR.[16] A rising prior true GFR may be due to recovery from acute kidney disease associated with an acute illness and it was the latter that was responsible for the observed increase in ACM risk rather than the rising true GFR *per se*. Finally, a rising true GFR could be seen with hyperfiltration in remnant nephrons, which could be associated with subsequent kidney disease progression, but is not generally hypothesized to be associated with mortality. Since single nephron GFR cannot be measured in humans, this mechanism remains speculative.

The strengths of the current analysis include its large sample size with geographically diverse general population, high CVD risk, and CKD cohorts with current eGFR values that spanned a wide spectrum. We used an index of eGFR change that is commonly employed in the clinical setting, the annualized eGFR slope, and in sensitivity analyses used percentage change in eGFR. We estimated ACM risks with a uniform meta-analytic approach using individual-level data across collaborating cohorts. Our study also has limitations. The general/high risk cohorts enrolled generally younger persons, and were less representative with respect to elderly individuals, than the CKD cohorts. As in all observational studies, residual confounding is possible, and we captured only certain comorbidities. Laboratory assays were not uniform, but where possible, serum creatinine measures were calibrated to isotope dilution mass spectrometry standards. Variation in cohort study design as well as study population might introduce heterogeneity, but the relative consistency across cohorts despite these variations points towards

the robustness of our findings. Finally, p-values close to the nominal level of significance may be prone to type I error given the number of statistical tests involved in our analyses.

In conclusion, compared to patients with a stable eGFR, those with either an antecedent rise or fall in values were at increased risk of subsequent mortality. Prior change of eGFR over three years contributed additional information regarding mortality risk beyond the current eGFR itself. However, these incremental risks were clinically meaningful only for large eGFR changes, which were uncommon. Future research could focus on new filtration markers or direct GFR measurement to help to elucidate the nature of the relationship between rising eGFR and mortality risk.

CONCISE METHODS

Cohort selection criteria

The Chronic Kidney Disease Progression Consortium (CKD-PC) includes cohorts in which the presence of CKD was required for cohort entry and those in which entry was determined by factors other than CKD (general population and high cardiovascular disease [CVD] risk cohorts – i.e. 'other' cohorts).[3-5, 8, 18] The present study involved 35 cohorts (13 CKD and 22 other) including subjects ≥18 years of age who had repeated serum creatinine measurements during antecedent intervals from one to three years in duration. For the main analysis, we included 34 cohorts (12 CKD and 22 other) that could provide data for a 3-year antecedent period. This study was approved by the institutional review board at the Johns Hopkins Bloomberg School of Public Health (Baltimore, Maryland, USA).

Antecedent change in estimated glomerular filtration rate

GFR was estimated using the CKD-EPI 2009 creatinine equation.[26] In cohorts without standardization of creatinine measurement to isotope dilution mass spectrometry, reported creatinine levels were multiplied by 0.95.[27] For each participant, annualized eGFR slope (ml/min/1.73m^2/yr) was derived from ordinary least-squares (OLS)[10] regression using all eGFR measurements available during the antecedent period. The present study focuses on the population with available data in the 3-year antecedent interval (results for 1- and 2-year periods are presented in supplemental analyses). Rapidly declining, stable and rapidly increasing eGFR slope were defined as antecedent slopes of <-5, -5 to +5, and >+5 ml/min/1.73m^2/yr, respectively.[28]

Assessment of baseline covariates

Within the antecedent period, we considered the last eGFR as the "current" eGFR. The last eGFR measurement was taken at 3 ± 0.5 years (i.e. between 2.5 and 3.5 years after the first available eGFR). All covariates were assessed within 1 year prior to the last eGFR measurement during the antecedent period. Diabetes was defined as fasting glucose ≥7.0 mmol/L (126 mg/dl), non-fasting glucose ≥11.1 mmol/L (200 mg/dl), hemoglobin A1c ≥6.5%, use of anti-glycemic drugs, or self-reported diabetes. Prior myocardial infarction, coronary revascularization, heart failure, or stroke was considered as a history of CVD. Albuminuria was categorized as none, moderately-increased, and severely-increased.[29]

Assessment of outcomes

The primary study outcome was all-cause mortality (ACM) occurring subsequent to the antecedent time period, with time at risk starting at the last measurement of eGFR (current). In supplemental analyses we analyzed cardiovascular and non-cardiovascular mortality when data were available (i.e. for 14 of the other cohorts).

Statistical analyses

We performed two-stage meta-analyses, whereby each cohort was first analyzed separately and then pooled using random-effect models (Appendix 1). We imputed missing values of covariates (except eGFR) using cohort-specific mean values. Covariates that were completely missing for a particular cohort were excluded from the regression model for that cohort. We assessed heterogeneity with the I^2 statistic[8] and random-effects meta-regression analyses. Since the distributions of antecedent eGFR slope may be different among other and CKD cohorts, we *a priori* designed the meta-analyses to be stratified by cohort type.

Within each cohort, we estimated the adjusted hazard ratios (HRs) of ACM according to GFR slope with piece-wise linear splines (knots at -10, -5, -3, -1, +1, +3 ml/min/1.73m^2/yr). Cox models were adjusted for age, sex, race (black *vs*. non-black), systolic blood pressure, total cholesterol, diabetes, history of CVD, and current eGFR. Adjustment for albuminuria was done only in secondary analyses, as albuminuria was not measured in conjunction with the last available eGFR in several cohorts. Forest plots of HR estimates at eGFR slopes of -6 and +6 ml/min/1.73m^2/yr were constructed (chosen as representative values within the rapid declining and rising eGFR slope categories, respectively). Differential effects of current eGFR and albuminuria on the relationship between change in eGFR and ACM were evaluated with

interaction terms. We computed the base-case cumulative hazard of ACM at 1, 3, 5, and 10 years after baseline (Appendix 2). Absolute risk was calculated by multiplying the meta-analyzed, adjusted HRs for eGFR slopes of -6, -4, -2, 0,+ 2, +4, and +6 ml/min/1.73m^2/yr by the pooled base-case cumulative hazard. The improvement in discrimination with respect to ACM was assessed with the difference in c-statistics for an adjusted model with and without eGFR slope as a covariate.

Because of an observed risk increase with antecedent increase in eGFR, we conducted several sensitivity analyses. First, we evaluated the associations of antecedent eGFR slope with cardiovascular (death due to myocardial infarction, heart failure, stroke, or sudden cardiac death) and non-cardiovascular (all other etiologies) mortality. Second, we assessed the effect of individual, residual, eGFR variability. We used the root mean square error (RMSE) as an indicator of the variation of an individual's eGFR values around his or her OLS regression line. The RMSE was included as a covariate and then as a stratifying variable (categorized as <5, 5-10, and >10). Third, to explore whether increasing eGFR reflected weight loss, we excluded subjects with antecedent weight loss >2kg over the 3-year period. Fourth, to evaluate whether the U-shaped risk relationship might represent diabetes-associated glomerular hyperfiltration, we repeated analyses excluding persons with diabetes mellitus. Finally, analyses were repeated according to whether individuals had ever been exposed to renin-angiotensin-system-blocking (RASb) medications in the antecedent interval as a covariate in the Cox model and then as a stratifying variable. . Analyses were performed using Stata/SE 13 software (www.stata.com). *P*-values < 0.05 were considered statistically significant.

Contributors: DMN, MEG, KM, RTG, DGW, MW, JC and PEdJ, conceived of the study concept and design. KM and JC, the CKD-PC investigators/collaborators listed below acquired the data. MEG, KM, and JC and the Data Coordinating Center members listed below analyzed the data. All authors took part in the interpretation of the data. DMN, MEG, KM, JC, PEdJ drafted the manuscript, and all authors provided critical revisions of the manuscript for important intellectual content. All collaborators shared data and were given the opportunity to comment on the manuscript. JC obtained funding for CKD-PC and individual cohort and collaborator support is listed in Appendix 3.

CKD-PC investigators/collaborators (study acronyms/abbreviations are listed in Appendix 1)**:** **AASK:** Jackson T. Wright, Jr, Case Western Reserve University, United States; Lawrence J. Appel, Johns Hopkins University, United States; Tom Greene, University of Utah, United States; Brad C. Astor, University of Wisconsin, United States; **ADVANCE:** Stephen MacMahon, George Institute, Australia and UK; John Chalmers, George Institute, Australia; Hisatomi Arima, George Institute, Australia; Mark Woodward, George Institute, Australia and UK; **Aichi:** Hiroshi Yatsuya, Fujita Health University, Japan; Kentaro Yamashita, Nagoya Medical Center, Japan; Hideaki Toyoshima, Anjo Kosei Hospital, Japan; Koji Tamakoshi, Nagoya University, Japan; **AKDN:** Marcello Tonelli, University of Alberta, Canada; Brenda R. Hemmelgarn, University of Calgary, Canada; Matthew T. James, University of Calgary, Canada; Tanvir Chowdhury Turin, University of Calgary, Canada; **ARIC:** Josef Coresh, Johns Hopkins University, United States; Kunihiro Matsushita, Johns Hopkins University, United States; Morgan E. Grams, Johns Hopkins University, United States; Yingying Sang, Johns Hopkins University, United States; **AusDiab (Australian Diabetes, Obesity, and Lifestyle Study)**: Robert C. Atkins, Monash

University, Australia; Kevan R. Polkinghorne, Monash University, Australia; Steven Chadban, University of Sydney, Australia; **Beaver Dam CKD Study**: Anoop Shankar, Virginia Commonwealth University, United States; Ronald Klein, University of Wisconsin, United States; Barbara E.K. Klein, University of Wisconsin, United States; Kristine E. Lee, University of Wisconsin, United States; **British Columbia CKD:** Adeera Levin, British Columbia Provincial Renal Agency and University of British Columbia, Canada; Ognjenka Djurdjev, British Columbia Provincial Renal Agency and Provincial Health Services Authority, Canada; **CARE:** Marcello Tonelli, University of Calgary, Canada; Frank M. Sacks, Harvard School of Public Health, United States; Gary C. Curhan, Channing Division of Network Medicine/Renal Division, Brigham and Women's Hospital, Harvard Medical School, Harvard School of Public Health, United States; **CARE FOR HOMe (Cardiovascular and Renal Outcome in CKD 2-4 Patients - The Fourth Homburg evaluation)**: Adam M. Zawada, Saarland University Medical Center, Germany; Kyrill S. Rogacev, Saarland University Medical Center, Germany; Sarah Seiler, Saarland University Medical Center, Germany; Gunnar H Heine, Saarland University Medical Center, Germany; **CCF:** Sankar D. Navaneethan, Cleveland Clinic, United States; Joseph V. Nally, Jr, Cleveland Clinic, United States; Jesse D. Schold, Cleveland Clinic, United States; **CHS:** Michael Shlipak, University of California, San Francisco and San Francisco VA Medical Center, United States; Mark J. Sarnak, Tufts Medical Center, United States; Ronit Katz, University of Washington, United States; **CIRCS:** Hiroyasu Iso, Osaka University, Japan; Akihiko Kitamura, Osaka Center for Cancer and Cardiovascular Disease Prevention, Japan; Hironori Imano, Osaka University, Japan; Kazumasa Yamagishi, University of Tsukuba, Japan; **CRIB:** David C. Wheeler, University College London, United Kingdom; Jonathan Emberson, University of Oxford, United Kingdom; Jonathan N. Townend, Queen Elizabeth Hospital

Birmingham, United Kingdom; Martin J. Landray, University of Oxford, United Kingdom; **ESTHER (Epidemiologische Studie zu Chancen der Verhuetung, Frueherkennung und optimierten Therapie chronischer Erkrankungen in der aelteren Bevölkerung)**: Dietrich Rothenbacher, German Cancer Research Center and University of Ulm, Germany; Hermann Brenner, MPH, German Cancer Research Center, Germany; Heiko Müller, German Cancer Research Center, Germany; Ben Schöttker, German Cancer Research Center, Germany; **Framingham:** Caroline S. Fox, National Heart, Lung, and Blood Institute, United States; Shih-Jen Hwang, National Heart, Lung, and Blood Institute, United States; James B. Meigs, Massachusetts General Hospital, United States; Ashish Upadhyay, Boston University Medical Center, United States; **Geisinger:** Jamie Green, Geisinger Medical Center, United States; H Lester Kirchner, Geisinger Medical Center, United States; Robert Perkins, Geisinger Medical Center, United States; Alex R Chang, Geisinger Medical Center, United States; **GLOMMS-1 Study:** Corri Black, University of Aberdeen, United Kingdom; Angharad Marks, University of Aberdeen, United Kingdom; Nick Fluck, National Health Service (NHS) Grampian, United Kingdom; Gordon J. Prescott, University of Aberdeen, United Kingdom; **Gubbio**: Massimo Cirillo, University of Salerno, Italy; **HUNT (The Nord-Trøndelag Health Study):** Stein Hallan, Norwegian University of Science and Technology and St Olav University, Norway; Knut Aasarød, Norwegian University of Science and Technology and St Olav University Hopstial, Norway; Cecilia M. Øien, Norwegian University of Science and Technology, Norway; Maria Radtke, Norwegian University of Science and Technology and St Olavs University Hospital, Norway; **IPHS:** Fujiko Irie, Ibaraki Prefectural Office, Japan; Hiroyasu Iso, Osaka University, Japan; Toshimi Sairenchi, Dokkyo Medical University School of Medicine, Japan; Kazumasa Yamagishi, University of Tsukuba, Japan; **Kaiser Permanente NW:** David H Smith, Kaiser

Permanente Northwest, United States; Micah L Thorp, Kaiser Permanente Northwest, United States; Eric S Johnson, Kaiser Permanente Northwest, United States; **KP Hawaii:** Brian J Lee, Kaiser Permanente Hawaii Region, United States; **KSHS:** Eliseo Guallar, Johns Hopkins University, United States; Seungho Ryu, Kangbuk Samsung Hospital, Sungkyunkwan University, School of Medicine, Republic of Korea; Yoosoo Chang, Kangbuk Samsung Hospital, Sungkyunkwan University, School of Medicine, Republic of Korea; Juhee Cho, Sungkyunkwan University, Republic of Korea; Hocheol Shin, Kangbuk Samsung Hospital, Sungkyunkwan University, School of Medicine, Republic of Korea; **Maccabi:** Gabriel Chodick, Maccabi Healthcare Services, Israel; Varda Shalev, Maccabi Healthcare Services and Tel Aviv University, Israel; Yair C. Birnbaum, Maccabi Healthcare Services, Israel; Bracha Shainberg, Maccabi Healthcare Services, Israel; **MASTERPLAN:** Jack F. M. Wetzels, Radboud University Medical Centre, Nijmegen, The Netherlands; Peter J Blankestijn, University Medical Center Utrecht, The Netherlands; Arjan D. van Zuilen, University Medical Center Utrecht, The Netherlands; **MDRD:** Mark J. Sarnak, Tufts Medical Center, United States; Andrew S. Levey, Tufts Medical Center, United States; Lesley A Inker, Tufts Medical Center, United States; Vandana Menon, Tufts Medical Center, United States; **MESA:** Michael Shlipak, University of California, San Francisco and San Francisco VA Medical Center, United States; Mark J. Sarnak, Tufts Medical Center, United States; Ronit Katz, University of Washington, United States; Carmen Peralta, University of California, San Francisco and San Francisco VA Medical Center, United States; **MRFIT:** Areef Ishani, Minneapolis VA Health Care System, United States; James D. Neaton, University of Minnesota, United States; **NephroTest:** Marc Froissart, Paris Descartes University, France; Benedicte Stengel, l'Institut National de la Santé et de la Recherche Médicale (Inserm) U1018, University Paris Sud, and l'Université Versailles Saint Quentin

(USVQ), France; Marie Metzger, Inserm U1018 and University of Paris Sud-11, France; Jean-Philippe Haymann, Sorbonne Universités, Université Pierre et Marie Curie (UPMC) Univ Paris 06, Assistance Publique-Hôpitaux de Paris, France; Pascal Houillier, Assistance Publique-Hôpitaux de Paris, Paris Descartes University, France; Martin Flamant, Assistance Publique-Hôpitaux de Paris, France; **NZDCS:** C Raina Elley, University of Auckland, New Zealand; Timothy Kenealy, University of Auckland, New Zealand; Simon A Moyes, University of Auckland, New Zealand; John F Collins, Auckland District Health Board, New Zealand; Paul L. Drury, Auckland District Health Board, New Zealand; **Ohasama:** Takayoshi Ohkubo, Teikyo University, Japan; Hirohito Metoki, Tohoku University, Japan; Masaaki Nakayama, Fukushima Medical University, Japan; Masahiro Kikuya, Tohoku University, Japan; Yutaka Imai, Tohoku University, Japan; **Okinawa 83/93**: Kunitoshi Iseki, University Hospital of the Ryukyus, Japan; **Pima Indian:** Robert G. Nelson, National Institute of Diabetes and Digestive and Kidney Diseases, United States; William C. Knowler, National Institute of Diabetes and Digestive and Kidney Diseases, United States; **PREVEND:** Ron T Gansevoort, University Medical Center Groningen, The Netherlands; Stephan JL Bakker, University Medical Center Groningen, The Netherlands; Hans L Hillege, University Medical Center Groningen, The Netherlands; Pim van der Harst, University Medical Center Groningen, The Netherlands; **Rancho Bernardo:** Simerjot K Jassal, University of California San Diego and VA San Diego Healthcare, United States; Jaclyn Bergstrom, University of California San Diego, United States; Joachim H Ix, University of California San Diego and VA San Diego Healthcare, United States; Elizabeth Barrett-Connor, University of California San Diego, United States; **RENAAL:** Hiddo J Lambers Heerspink, University of Groningen, The Netherlands; Barry E Brenner, Brigham and Women's Hospital and Harvard School of Medicine, United States; Dick de Zeeuw, University of Groningen, The Netherlands;

Severance: Sun Ha Jee, Yonsei University, Republic of Korea; Heejin Kimm, Yonsei University, Republic of Korea; Yejin Mok, Yonsei University, Republic of Korea; **Sunnybrook:** Navdeep Tangri, University of Manitoba, Canada; Maneesh Sud, University of Toronto, Canada; David Naimark, University of Toronto, Canada; **Taiwan:** Chi-Pang Wen, China Medical University Hospital, Taiwan; Sung-Feng Wen, University of Wisconsin, United States; Chwen-Keng Tsao, MJ Health Management Institution, Taiwan; Min-Kuang Tsai, National Health Research Institutes, Taiwan; **ULSAM (Uppsala Longitudinal Study of Adult Men)**: Johan Ärnlöv, Uppsala University, Sweden; Lars Lannfelt, Uppsala University Hospital, Sweden; Anders Larsson, Uppsala University, Sweden; **VA CKD:** Csaba P. Kovesdy, Memphis Veterans Affairs Medical Center and University of Tennessee Health Science Center, United States; Kamyar Kalantar-Zadeh, University of California Irvine Medical Center, United States; **ZODIAC:** Henk J. Bilo, Isala Clinics, The Netherlands; Nanne Kleefstra, Isala Clinics, The Netherlands; Klaas H. Groenier, Isala Clinics, The Netherlands; Hanneke Joosten, University Medical Center Groningen, The Netherlands; Iefke Drion, Isala Clinics, The Netherlands

CKD-PC Steering Committee: Josef Coresh (Chair), Johns Hopkins University, United States; Ron T. Gansevoort, University Medical Center Groningen, The Netherlands; Paul E. de Jong, University Medical Center Groningen, The Netherlands; Kunitoshi Iseki, University Hospital of the Ryukyus, Japan; Andrew S. Levey, Tufts Medical Center, United States; Kunihiro Matsushita, Johns Hopkins University, United States; Mark J. Sarnak, Tufts Medical Center, United States; Benedicte Stengel, Inserm U1018 and University of Paris Sud-11, France; David G. Warnock, University of Alabama at Birmingham, United States; Mark Woodward, George Institute, Australia

CKD-PC Data Coordinating Center: Shoshana H Ballew (Coordinator), Johns Hopkins University, United States; Josef Coresh (Principal investigator), Johns Hopkins University, United States; Morgan E. Grams (Director of Nephrology Initiatives), Johns Hopkins University, United States; Kunihiro Matsushita (Director), Johns Hopkins University, United States; Yingying Sang (Lead programmer), Johns Hopkins University, United States; Mark Woodward (Senior statistician), George Institute, Australia

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Table 1. Cohort characteristics and outcomes - characteristics of the chronic kidney disease (n = 12) and other (general population and high cardiovascular risk, n = 22) cohorts that could provide data for a 3 year (3y) antecedent period.

Variable	Total sample	CKD cohorts	Other cohorts
N	1,277,217	249,977	1,027,240
Median # SCre	5 (4 – 5)	7 (7 – 7)	5 (4 – 5)
Slope < -5 ml/y			
%N	11	12	11
Age (SD),	58 (17)	73 (11)	54 (17)
%Female	49	9	60
%Black	4	15	1
Slope ≥ -5 ml/y to ≤ 5 ml/y			
%N	84	80	85
Age (SD),	59 (17)	76 (10)	55 (16)
%Female	48	9	56
%Black	2	9	0
Slope > 5 ml/y			
%N	5	7	4
Age (SD),	57 (19)	73 (10)	50 (17)
%Female	48	11	63
%Black	3	10	1
Mean (SD)	3.2 (4.0)	3(1)	3 (4)
ACM events	102,477	57,269	45, 208
CVM	8,231	340	7,891

%N – proportion of cohort belonging to a given slope category; Slope <-5ml/yr – declining eGFR group with an annualized eGFR slope of less than minus 5 ml/min/1.73m^2/year; Slope ≥-5ml/y to ≤5ml/y – stable eGFR group with an annualized GFR greater than or equal to minus 5 and less than or equal to plus 5 ml/min/1.73m^2/year; Slope >5ml/yr – increasing eGFR group with an annualized eGFR slope of greater than plus 5 ml/min/1.73m^2/year. ACM – all-cause mortality; CVM – cardiovascular mortality; SD – standard deviation; #Scre – number of serum creatinine measurements available during antecedent period; IQR – inter-quartile range. *Follow-up time refers to the at-risk period subsequent to the 3-year antecedent interval; ** not all cohorts could provide data with respect to CVM (see Supplemental Table 2).

Table 2. Adjusted hazard ratios (HR) for cardiovascular mortality and non-cardiovascular mortality subsequent to an estimated glomerular filtration (eGFR) slope during a 3-year antecedent period for the other (general/high risk) cohorts (among the 14 cohorts with available data)

	Slope change in eGFR (ml/min/1.73m^2/year) during the 3-year antecedent period						
	-9 ml	**-6 ml**	**-3 ml**	**Stable**	**3 ml**	**6 ml**	**9 ml**
Cardiovascular mortality							
Other cohorts	1.33 (1.17, 1.52)	1.10 (0.98, 1.22)	1.08 (0.97, 1.21)	ref	1.12 (1.02, 1.22)	1.27 (1.10, 1.46)	1.46 (1.16, 1.84)
Non Cardiovascular mortality							
Other cohorts	1.29 (1.17, 1.43)	1.09 (1.03, 1.15)	1.03 (0.95, 1.13)	ref	1.02 (0.95, 1.09)	1.08 (0.95, 1.23)	1.31 (1.00, 1.73)

FIGURE LEGENDS

Figure 1. Hazard ratio of all-cause mortality and change in estimated glomerular filtration rate

Analyses are shown for **A.** chronic kidney disease (CKD) cohorts and **B.** other (general population and high cardiovascular risk) cohorts. Panel **C.** depicts the adjusted hazard ratios (HR) for the open circles on each graph. In the top panels, meta-analyzed, HRs for all-cause mortality associated (ACM) with various annualized rates of estimated glomerular filtration rate (eGFR) are depicted. The reference group for calculation of HRs were patients with stable eGFR values (i.e. a slope = 0 ml/min/1.73m^2/yr). Black dots indicate statistical significance compared with the reference (diamond). The HR for eGFR slope was adjusted for age, sex, race (blacks *vs*. non-blacks), systolic blood pressure, total cholesterol, diabetes, history of CVD, and current (last) eGFR. The bottom panels illustrate histograms of the distribution of eGFR slopes among members of the other and CKD cohorts.

Figure 2. **Interaction of estimated glomerular filtration rate slope and current value of eGFR**

Analyses are shown for the other (general population and high cardiovascular risk) cohorts and the chronic kidney disease (CKD) cohorts. In the top panels, meta-analyzed, adjusted hazard ratios (HR) for all-cause mortality associated (ACM) with various annualized rates of estimated glomerular filtration rate (eGFR), within strata of current eGFR, are depicted (**A**: CKD cohorts, **B**: other cohorts). For other and CKD cohorts the current eGFR strata were set at 65, 80 and 95; and 20, 35 and 50 ml/min/1.73m^2, respectively. The reference group for calculation of HRs were patients with stable eGFR values (i.e. a slope = 0 ml/min/1.73m^2/yr). The HR for eGFR slope

was adjusted for age, sex, race (blacks *vs*. non-blacks), systolic blood pressure, total cholesterol, diabetes, history of CVD, and current (last) eGFR. The bottom panels illustrate kernel density plots of the distribution of eGFR slopes with current eGFR strata among members of the cohorts (**C**: CKD cohorts, **D**: other cohorts).

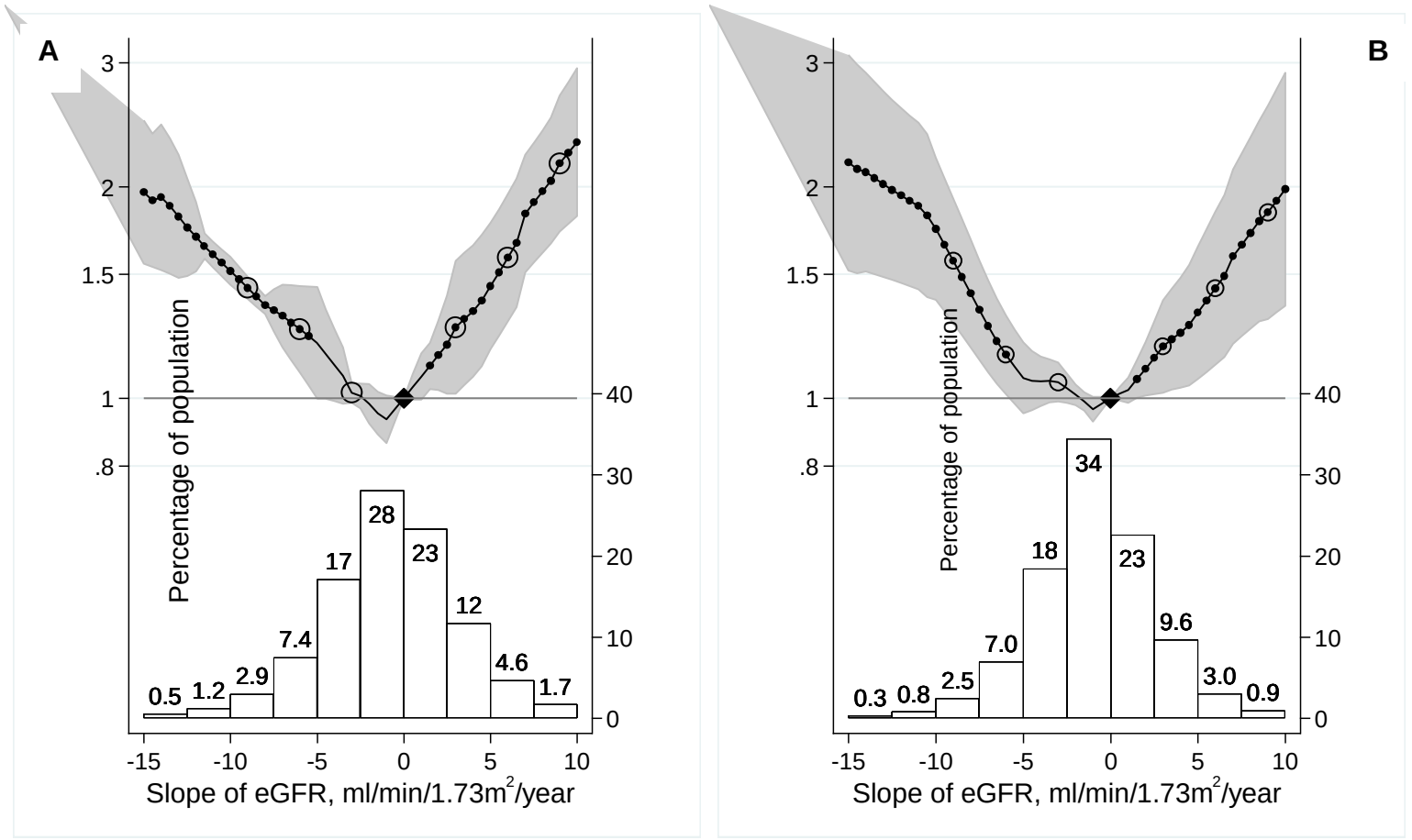
Figure 3. **Forest plot of hazard ratios associated with a 6 ml/min/1.73m^2/yr decline in estimated glomerular filtration rate (an eGFR slope of –6 ml/min/1.73 m2/yr) over a 3-year antecedent period**

Analyses are shown for **A.** chronic kidney disease (CKD) cohorts and **B.** other (general population and high cardiovascular risk) cohorts. Adjusted hazard ratios (HR), within each cohort, for all-cause mortality associated (ACM) with an annualized decline of the estimated glomerular filtration rate (eGFR) of 6 ml/min/1.73m^2/yr are depicted. The reference group for calculation of HRs were patients with stable eGFR values (i.e. a slope = 0 ml/min/1.73m^2/yr). The HR for eGFR slope was adjusted for age, sex, race (blacks *vs*. non-blacks), systolic blood pressure, total cholesterol, diabetes, history of CVD, and current (last) eGFR.

Figure 4. Forest plot of hazard ratios associated with a 6 ml/min/1.73m^2/yr increase in estimated glomerular filtration rate (an eGFR slope of +6 ml/min/1.73 m2/yr) over a 3-year antecedent period

Analyses are shown for **A.** chronic kidney disease (CKD) cohorts and **B.** other (general population and high cardiovascular risk) cohorts. Adjusted hazard ratios (HR), within each cohort, for all-cause mortality associated (ACM) with an annualized increase of the estimated glomerular filtration rate (eGFR) of 6 ml/min/1.73m^2/yr are depicted. The reference group for

calculation of HRs were patients with stable eGFR values (i.e. a slope = 0 ml/min/1.73m^2/yr). The HR for eGFR slope was adjusted for age, sex, race (blacks *vs*. non-blacks), systolic blood pressure, total cholesterol, diabetes, history of CVD, and current (last) eGFR.



C	Slope change in eGFR (ml/min/1.73m^2/year) during the 3-year antecedent period						
	-9 ml	-6 ml	-3 ml	Stable	3 ml	6 ml	9 ml
CKD cohorts	1.43 (1.38, 1.49)	1.25 (1.09, 1.44)	1.02 (0.98, 1.05)	ref	1.26 (1.02, 1.57)	1.58 (1.29, 1.95)	2.17 (1.76, 2.66)
Other cohorts	1.57 (1.28, 1.92)	1.15 (1.01, 1.31)	1.05 (0.99, 1.12)	ref	1.18 (1.02, 1.38)	1.43 (1.11, 1.84)	1.84 (1.30, 2.61)

Figure 1.

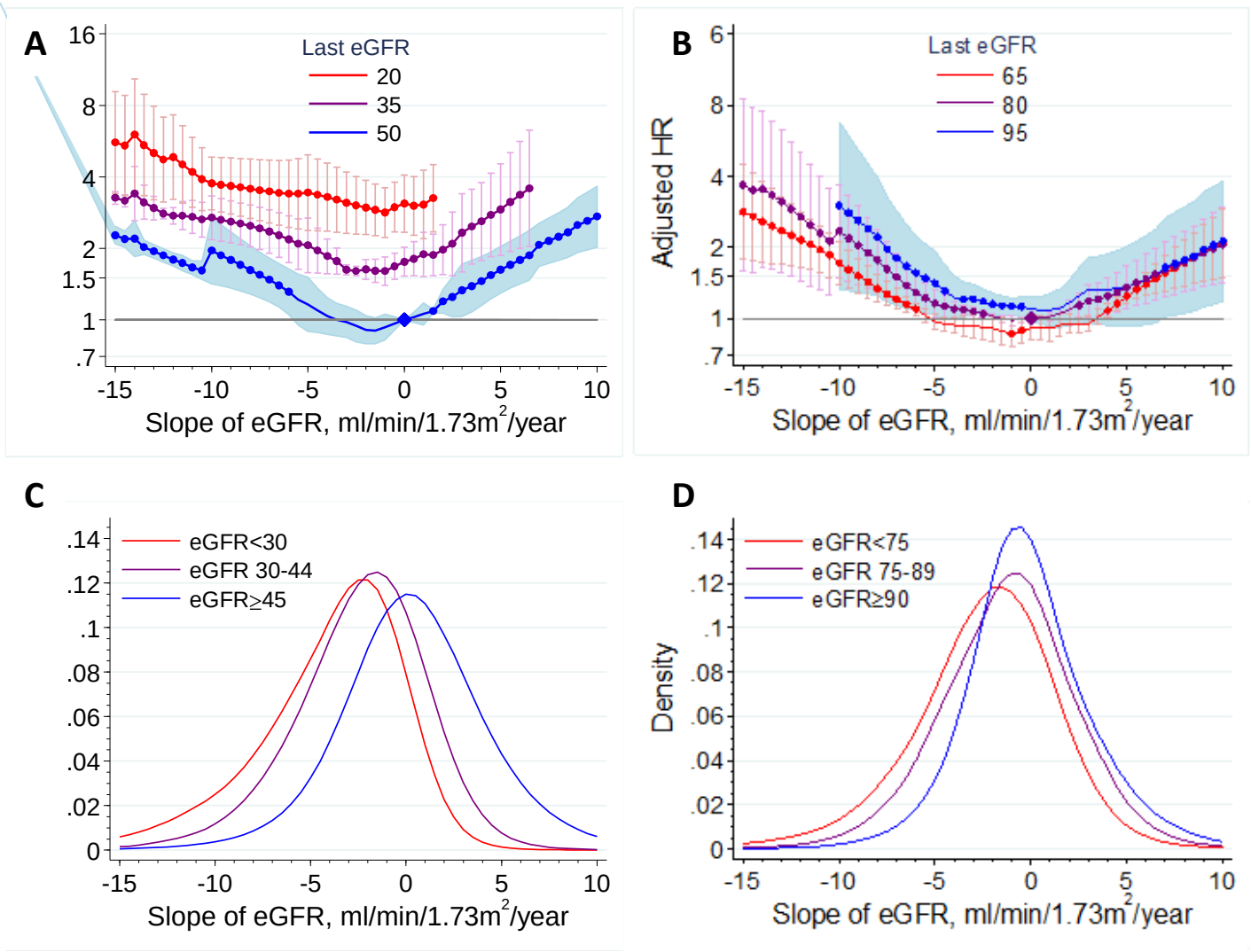

A
Last eGFR
20
35
50
16
8
4
2
1.5
1
.7
-15
-10
-5
0
5
10
Slope of eGFR, ml/min/1.73m2/year
B
Last eGFR
65
80
95
Adjusted HR
6
8
4
2
1.5
1
.7
-15
-10
-5
0
5
10
Slope of eGFR, ml/min/1.73m2/year
C
eGFR<30
eGFR 30-44
eGFR≥45
.14
.12
.1
.08
.06
.04
.02
0
-15
-10
-5
0
5
10
Slope of eGFR, ml/min/1.73m2/year
D
eGFR<75
eGFR 75-89
eGFR≥90
Density
.14
.12
.1
.08
.06
.04
.02
0
-15
-10
-5
0
5
10
Slope of eGFR, ml/min/1.73m2/year

Figure 2.

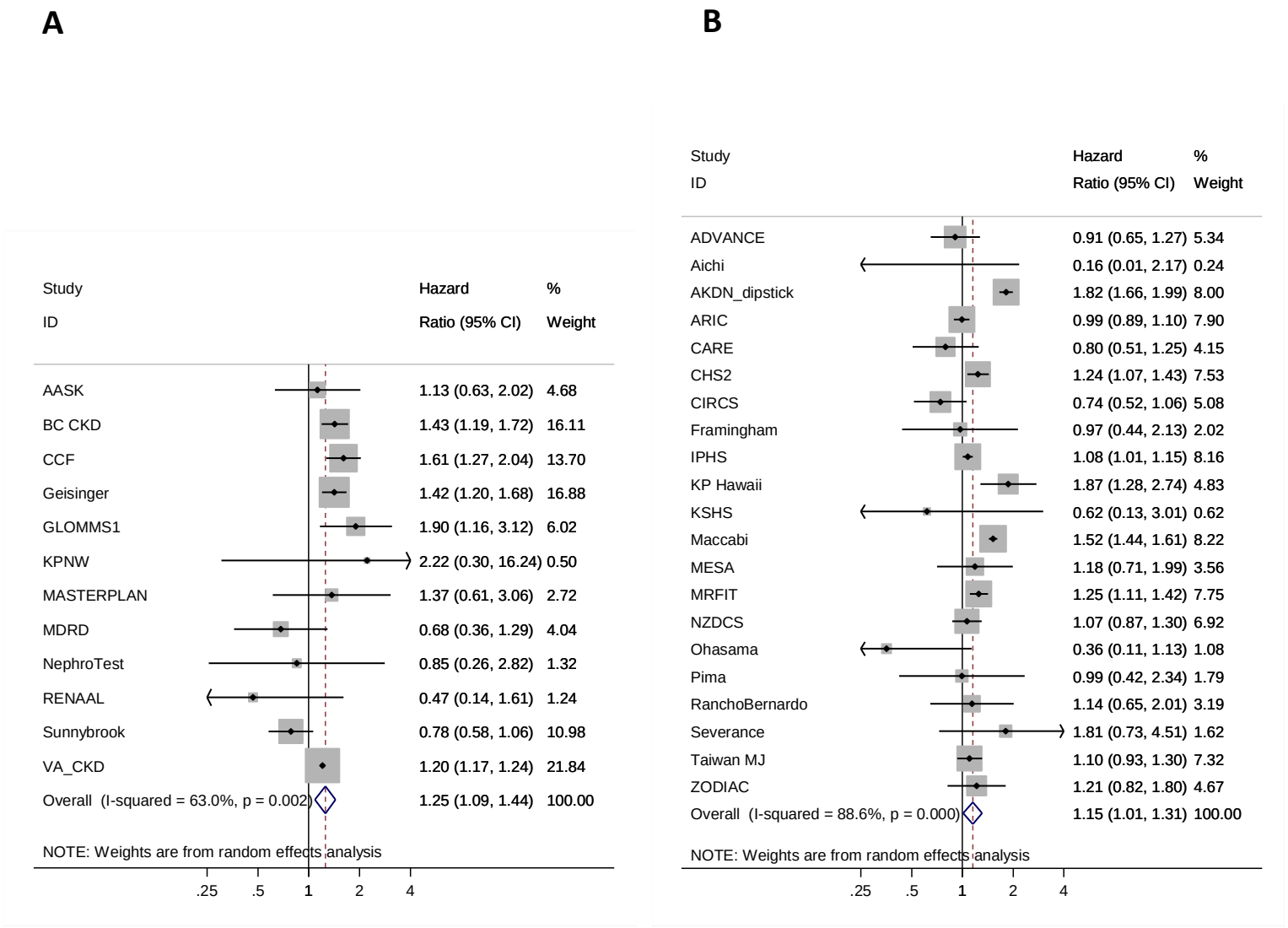

A
Study
ID
Hazard
Ratio (95% CI)
%
Weight
AASK 1.13 (0.63, 2.02) 4.68
BC CKD 1.43 (1.19, 1.72) 16.11
CCF 1.61 (1.27, 2.04) 13.70
Geisinger 1.42 (1.20, 1.68) 16.88
GLOMMS1 1.90 (1.16, 3.12) 6.02
KPNW 2.22 (0.30, 16.24) 0.50
MASTERPLAN 1.37 (0.61, 3.06) 2.72
MDRD 0.68 (0.36, 1.29) 4.04
NephroTest 0.85 (0.26, 2.82) 1.32
RENAAL 0.47 (0.14, 1.61) 1.24
Sunnybrook 0.78 (0.58, 1.06) 10.98
VA_CKD 1.20 (1.17, 1.24) 21.84
Overall (I-squared = 63.0%, p = 0.002) 1.25 (1.09, 1.44) 100.00
NOTE: Weights are from random effects analysis
.25
.5
1
2
4
B
Study
ID
Hazard
Ratio (95% CI)
%
Weight
ADVANCE 0.91 (0.65, 1.27) 5.34
Aichi 0.16 (0.01, 2.17) 0.24
AKDN_dipstick 1.82 (1.66, 1.99) 8.00
ARIC 0.99 (0.89, 1.10) 7.90
CARE 0.80 (0.51, 1.25) 4.15
CHS2 1.24 (1.07, 1.43) 7.53
CIRCS 0.74 (0.52, 1.06) 5.08
Framingham 0.97 (0.44, 2.13) 2.02
IPHS 1.08 (1.01, 1.15) 8.16
KP Hawaii 1.87 (1.28, 2.74) 4.83
KSHS 0.62 (0.13, 3.01) 0.62
Maccabi 1.52 (1.44, 1.61) 8.22
MESA 1.18 (0.71, 1.99) 3.56
MRFIT 1.25 (1.11, 1.42) 7.75
NZDCS 1.07 (0.87, 1.30) 6.92
Ohasama 0.36 (0.11, 1.13) 1.08
Pima 0.99 (0.42, 2.34) 1.79
RanchoBernardo 1.14 (0.65, 2.01) 3.19
Severance 1.81 (0.73, 4.51) 1.62
Taiwan MJ 1.10 (0.93, 1.30) 7.32
ZODIAC 1.21 (0.82, 1.80) 4.67
Overall (I-squared = 88.6%, p = 0.000) 1.15 (1.01, 1.31) 100.00
NOTE: Weights are from random effects analysis
.25
.5
1
2
4

Figure 3.

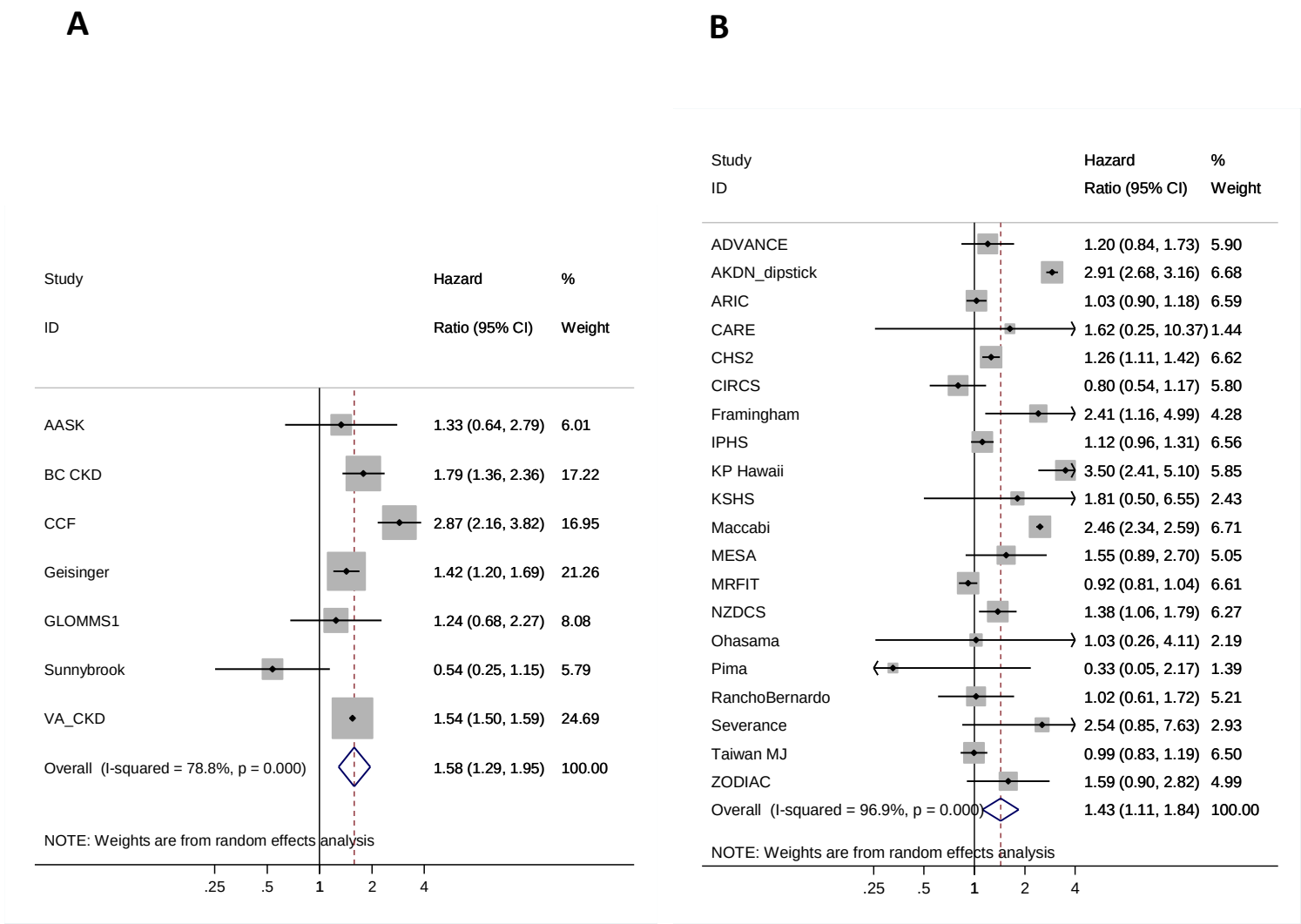

A
Study
ID
Hazard
Ratio (95% CI)
%
Weight
AASK
1.33 (0.64, 2.79)
6.01
BC CKD
1.79 (1.36, 2.36)
17.22
CCF
2.87 (2.16, 3.82)
16.95
Geisinger
1.42 (1.20, 1.69)
21.26
GLOMMS1
1.24 (0.68, 2.27)
8.08
Sunnybrook
0.54 (0.25, 1.15)
5.79
VA_CKD
1.54 (1.50, 1.59)
24.69
Overall (I-squared = 78.8%, p = 0.000)
1.58 (1.29, 1.95)
100.00
NOTE: Weights are from random effects analysis
.25
.5
1
2
4
B
Study
ID
Hazard
Ratio (95% CI)
%
Weight
ADVANCE
1.20 (0.84, 1.73)
5.90
AKDN_dipstick
2.91 (2.68, 3.16)
6.68
ARIC
1.03 (0.90, 1.18)
6.59
CARE
1.62 (0.25, 10.37)
1.44
CHS2
1.26 (1.11, 1.42)
6.62
CIRCS
0.80 (0.54, 1.17)
5.80
Framingham
2.41 (1.16, 4.99)
4.28
IPHS
1.12 (0.96, 1.31)
6.56
KP Hawaii
3.50 (2.41, 5.10)
5.85
KSHS
1.81 (0.50, 6.55)
2.43
Maccabi
2.46 (2.34, 2.59)
6.71
MESA
1.55 (0.89, 2.70)
5.05
MRFIT
0.92 (0.81, 1.04)
6.61
NZDCS
1.38 (1.06, 1.79)
6.27
Ohasama
1.03 (0.26, 4.11)
2.19
Pima
0.33 (0.05, 2.17)
1.39
RanchoBernardo
1.02 (0.61, 1.72)
5.21
Severance
2.54 (0.85, 7.63)
2.93
Taiwan MJ
0.99 (0.83, 1.19)
6.50
ZODIAC
1.59 (0.90, 2.82)
4.99
Overall (I-squared = 96.9%, p = 0.000)
1.43 (1.11, 1.84)
100.00
NOTE: Weights are from random effects analysis
.25
.5
1
2
4

Figure 4.