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Past Decline Versus Current eGFR and Subsequent Mortality Risk

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ABSTRACT

A single determination of eGFR associates with subsequent mortality risk. Prior decline in eGFR indicates loss of kidney function, but the 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 CKD and 22 other cohorts within the CKD Prognosis Consortium. Over a 3-year antecedent period, 12% of participants in the CKD cohorts and 11% in the other cohorts had an eGFR slope <-5 ml/min per 1.73 m^2 per year, whereas 7% and 4% had a slope >5 ml/min per 1.73 m^2 per year, respectively. Compared with a slope of 0 ml/min per 1.73 m^2 per year, a slope of -6 ml/min per 1.73 m^2 per year associated with adjusted hazard ratios for all-cause mortality of 1.25 (95% confidence interval [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 of 3.2 years. A slope of +6 ml/min per 1.73 m^2 per year also associated with higher all–cause mortality risk, with adjusted hazard ratios of 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 and noncardiovascular causes of death and stronger for longer antecedent periods (3 versus <3 years). We conclude that prior decline or rise in eGFR associates with an increased risk of mortality, independent of current eGFR.

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CKD affects 10%–16% of the global population.[1,2] Numerous studies have reported the significant association of low eGFR at a single time point with mortality,[3–9] a more frequent occurrence than ESRD, 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 along with 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, because they were on the basis of data from single centers[13,14] and/or cohorts with mean baseline eGFR values of $\geq$50 ml/min per 1.73 m^2.[11–16] Improvement in eGFR in a CKD population might show different

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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 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 eGFR Slope

Over a 3-year antecedent period, median (interquartile range [IQR]) numbers of creatinine measurements were 7 (IQR, 7–7) in the CKD and 5 (IQR, 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 per 1.73 m^2 per year, whereas 7% and 4% experienced an eGFR slope $>+5$ ml/min per 1.73 m^2 per year during the antecedent period, respectively. There were no consistent differences in the age or sex distribution between subjects with antecedent slopes of <-5, ≥-5 to $\leq+5$, and $>+5$ ml/min per 1.73 m^2 year; however, black subjects tended to be in the <-5 ml/min per 1.73 m^2 category (Supplemental Table 1, Table 1). Subjects with annual slopes <-5 ml/min per 1.73 m^2 per year had a higher prevalence of elevated albuminuria, were more often diabetic, and were more likely to have a history of cardiovascular disease (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 in the other cohorts) were associated with antecedent slope <-5 ml/min per 1.73 m^2 per year (Supplemental Table 3). Factors associated with an eGFR slope $>+5$ ml/min per 1.73 m^2 per year included higher current (last) eGFR, women, 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 (Supplemental Table 4, Table 1). Among 12 CKD cohorts, 57,269 of 249,977 subjects died (23%), whereas among 22 other cohorts, 45,208 of 1,027,240 subjects died (4%). After antecedent intervals of 1 and 2 years, 223,979 of 1,765,589 (13%) and 158,617 of 1,597,849 (10%) subjects died, respectively (Supplemental Table 5).

Table 1. Cohort characteristics and outcomes: characteristics of the CKD (*n*=12) and other (general population and high cardiovascular risk; *n*=22) cohorts that could provide data for a 3-year antecedent period

Variable	Total Sample	CKD Cohorts	Other Cohorts
N	1,277,217	249,977	1,027,240
Median no. SCre (IQR)	5 (4–5)	7 (7–7)	5 (4–5)
Slope <-5 ml/yr			
N, %	11	12	11
Age (SD), yr	58 (17)	73 (11)	54 (17)
Women, %	49	9	60
Black, %	4	15	1
Slope ≥-5 to ≤5 ml/yr			
N, %	84	80	85
Age (SD), yr	59 (17)	76 (10)	55 (16)
Women, %	48	9	56
Black, %	2	9	0
Slope >5 ml/yr			
N, %	5	7	4
Age (SD), yr	57 (19)	73 (10)	50 (17)
Women, %	48	11	63
Black, %	3	10	1
Mean (SD) follow-up,[a] yr	3.2 (4.0)	3 (1)	3 (4)
ACM events	102,477	57,269	45,208
CVM events[b]	8231	340	7891

Slope <-5 ml/yr is the declining eGFR group with an annualized eGFR slope of <-5 ml/min per 1.73 m^2 per year. *N*, % is the proportion of the cohort belonging to a given slope category. Slope ≥-5 to ≤5 ml/yr is the stable eGFR group with an annualized GFR between ≥-5 and ≤5 ml/min per 1.73 m^2 per year. Slope >5 ml/yr is the increasing eGFR group with an annualized eGFR slope of >5 ml/min per 1.73 m^2 per year. SCre, serum creatinine measurements available during the antecedent period; CVM, cardiovascular mortality.

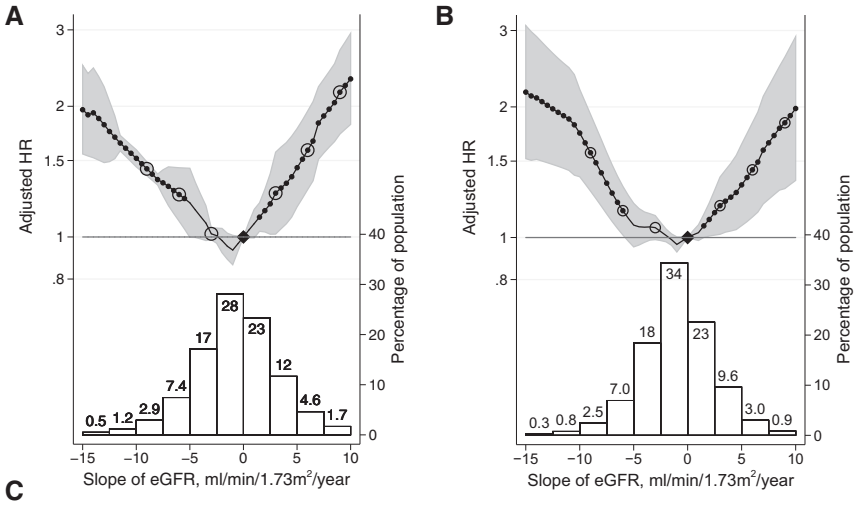
[a]Follow-up time refers to the at-risk period subsequent to the 3-year antecedent interval.

[b]Not all cohorts could provide data with respect to CVM (Supplemental Table 2).

Risk of All-Cause Mortality Associated with a Decline in eGFR

Compared with subjects with no change in eGFR over the antecedent 3-year period, a slope of -6 ml/min per 1.73 m^2 per year was associated with hazard ratios (HRs) for all-cause mortality (ACM) of 1.25 (95% confidence interval [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, 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



C

	Slope change in eGFR (ml/min/1.73m²/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. HRs of ACM and change in eGFR. Analyses are shown for (A) CKD cohorts and (B) other (general population and high cardiovascular risk) cohorts. C depicts the adjusted HRs for the open circles in A and B. The upper panels of A and B depict meta-analyzed HRs for ACM associated with various annualized rates of eGFR. The reference group for calculation of HRs was patients with stable eGFR values (*i.e.*, slope =0 ml/min per 1.73 m^2 per year). Black circles indicate statistical significance compared with the reference (diamonds). The HR for eGFR slope was adjusted for age, sex, race (black versus nonblack), systolic BP, total cholesterol, diabetes, history of CVD, and current (last) eGFR. The lower panels of A and B illustrate histograms of the distribution of eGFR slopes among members of the CKD and other cohorts.

of interaction between current albuminuria and antecedent eGFR decline (P for interaction =0.67 [moderately increased albuminuria] and 0.45 [severely increased albuminuria] for CKD cohorts and P for interaction =0.44 [moderately increased albuminuria] and 0.14 [severely increased albuminuria] for other cohorts) (Supplemental Figure 2).

The risk associated with an eGFR slope of −6 ml/min/ per 1.73 m^2 per year over the 3-year antecedent period showed heterogeneity (Figure 3). Among CKD cohorts, metaregression suggested that differences in follow-up time (with higher HRs associated with shorter follow-up) and median age (with higher HRs associated with older age) may have accounted for some heterogeneity (Supplemental Figure 3), whereas for the other cohorts, heterogeneity was not explained by metaregression (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 ACM 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 with subjects with no change in eGFR over the antecedent 3-year period, a slope of +6 ml/min per 1.73 m^2 per year was associated with HRs 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, Supplemental Table 6). The risk associated with an eGFR slope of +6 ml/min per 1.73 m^2 per year over the 3-year antecedent period showed 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 being 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 noncardiovascular 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 the 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 >2.0 kg was associated with increased odds of eGFR rise, excluding subjects who lost >2.0 kg during the antecedent 3 years did not alter the U-shaped relationship between antecedent eGFR slope and ACM (Supplemental Figure 7). Excluding patients with diabetes 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. Because a given absolute change in eGFR represents a higher percentage change for persons with lower current eGFR values and because 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% reduction in eGFR over 3 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 with 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

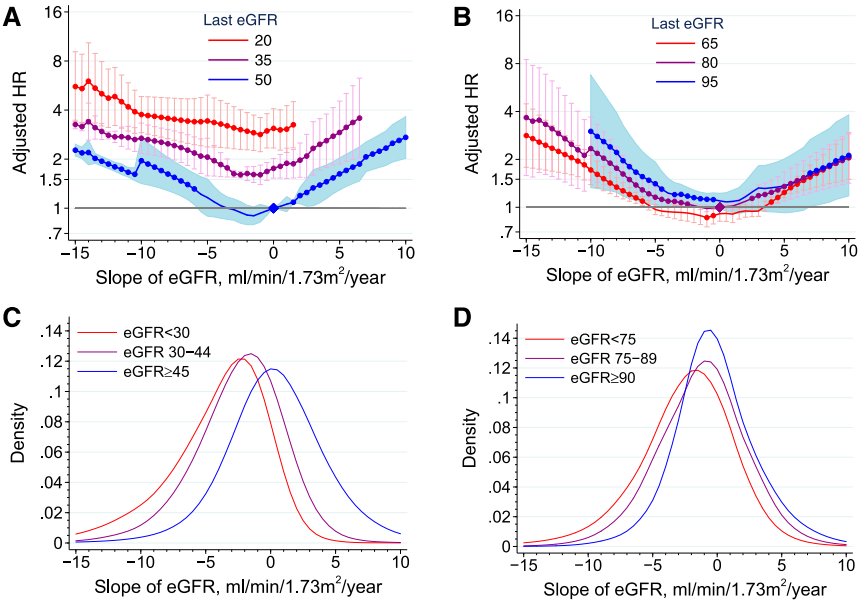


Figure 2. Interaction of eGFR slope and current value of eGFR. Analyses are shown for the CKD cohorts (A and C) and the other (B and D; general population and high cardiovascular risk) cohorts. In A and B, meta–analyzed adjusted HRs for ACM associated with various annualized rates of eGFR within strata of current eGFR are depicted. For CKD and other cohorts, the current eGFR strata were set at 20, 35, and 50 ml/min per 1.73 m^2 and 65, 80, and 95 ml/min per 1.73 m^2, respectively. The reference group for calculation of HRs was patients with stable eGFR values (*i.e.*, a slope =0 ml/min per 1.73 m^2 per year). The HR for eGFR slope was adjusted for age, sex, race (black versus nonblack), systolic BP, total cholesterol, diabetes, history of CVD, and current (last) eGFR. C and D illustrate kernel density plots of the distribution of eGFR slopes with current eGFR strata among members of the cohorts.

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 this analysis of >1.2 million subjects and >100,000 deaths, we found that antecedent eGFR slope over a 3-year period, whether positive or negative, exhibited a statistically significant association with ACM, cardiovascular mortality, and noncardiovascular 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 unusual (11% for <−5 ml/min per 1.73 m^2 per year and 5% for >5 ml/min per 1.73 m^2 per year), but associated with the highest risk of mortality, whereas lesser changes were more common, but associated with smaller risks. Antecedent improvement in eGFR was associated with a mortality risk similar in magnitude to antecedent decline. This association persisted in numerous sensitivity analyses, suggesting that rapid change in creatinine-based eGFR—whether for the worse or 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, whereas the other subject's eGFR either falls or rises.[20] In contrast, adjustment for last eGFR during the antecedent period, as per this 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 investigations are hampered by different indices of renal function change, different antecedent periods, and the use of rates, in some studies, rather than HRs to quantify mortality risk. However, Turin *et al.*[12] found adjusted HRs for ACM of 1.14 and 1.68 for 4-ml/min per 1.73 m^2 per year declining and increasing slopes, respectively, compared with 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 this analysis. The small quantitative difference may be caused by differences in the set of adjustment factors used in the two studies. Note that data from the latter cohort were included in this 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—caused by progression or remission of CKD or onset or recovery from acute kidney disease—or change in nonfiltration 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,

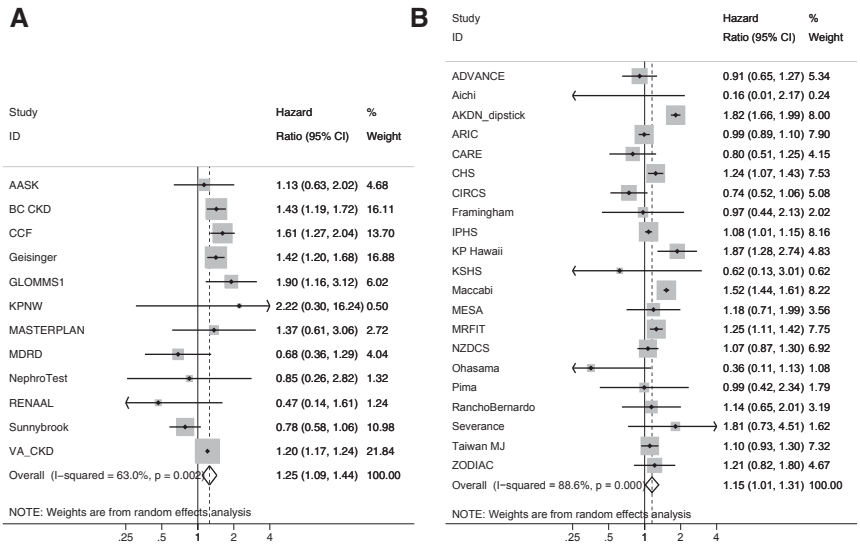


Figure 3. Forest plot of HRs associated with a 6 ml/min per 1.73 m^2 per year decline in eGFR (an eGFR slope of −6 ml/min per 1.73 m^2 per year) over a 3-year antecedent period. Analyses are shown for (A) CKD cohorts and (B) other (general population and high cardiovascular risk) cohorts. Adjusted HRs within each cohort for ACM associated with an annualized decline of the eGFR of 6 ml/min per 1.73 m^2 per year are depicted. The reference group for calculation of HRs was patients with stable eGFR values (*i.e.*, a slope =0 ml/min per 1.73 m^2 per year). The HR for eGFR slope was adjusted for age, sex, race (black versus nonblack), systolic BP, total cholesterol, diabetes, history of CVD, and current (last) eGFR. AASK, African American Study of Kidney Disease and Hypertension; ADVANCE, The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation Trial; Aichi, Aichi Workers' Cohort; AKDN_dipstick, Alberta Kidney Disease Network; ARIC, Atherosclerosis Risk in Communities Study; BC CKD, British Columbia CKD Study; CARE, The Cholesterol and Recurrent Events Trial; CCF, Cleveland Clinic CKD Registry Study; CHS, Cardiovascular Health Study; CIRCS, Circulatory Risk in Communities Study; Framingham, Framingham Heart Study; Geisinger, Geisinger CKD Study; GLOMMS 1, Grampian Laboratory Outcomes, Morbidity and Mortality Studies 1; IPHS, Ibaraki Prefectural Health Study; KP Hawaii, Kaiser Permanente Hawaii Cohort; KPNW, Kaiser Permanente Northwest; KSHS, Kangbuk Samsung Health Study; MASTERPLAN, Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of a Nurse Practitioner; MDRD, Modification of Diet in Renal Disease Study; MESA, Multi-Ethnic Study of Atherosclerosis; MRFIT, Multiple Risk Factor Intervention Trial; NephroTest, NephroTest Study; NZDCS, New Zealand Diabetes Cohort Study; Ohasama, Ohasama Study; Pima, Pima Indian Study; RanchoBernardo, Rancho Bernardo Study; RENAAL, Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan; Severance, Severance Cohort Study; Sunnybrook, Sunnybrook Cohort; Taiwan MJ, Taiwan MJ Cohort Study; VA CKD, Veterans Administration CKD Study; ZODIAC, Zwolle Outpatient Diabetes Project Integrating Available Care.

in this 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 subjects with diabetes, 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] However, we observed similar associations of antecedent eGFR decline with non-CVD mortality as we did with CVD mortality (albeit in the limited cohorts with these data). Previous investigations have suggested that variability in the eGFR itself may be associated with higher ACM risk.[25] However, in this 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 positive eGFR slope using cystatin C as a filtration marker, although 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 caused by 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 it is not generally hypothesized to be associated with mortality. Because single-nephron GFR cannot be measured in humans, this mechanism remains speculative.

The strengths of this 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 used in the clinical setting, the annualized eGFR slope, and in sensitivity analyses, the percentage change in eGFR. We estimated ACM risks with a uniform meta–analytic approach using individual-level data across collaborating

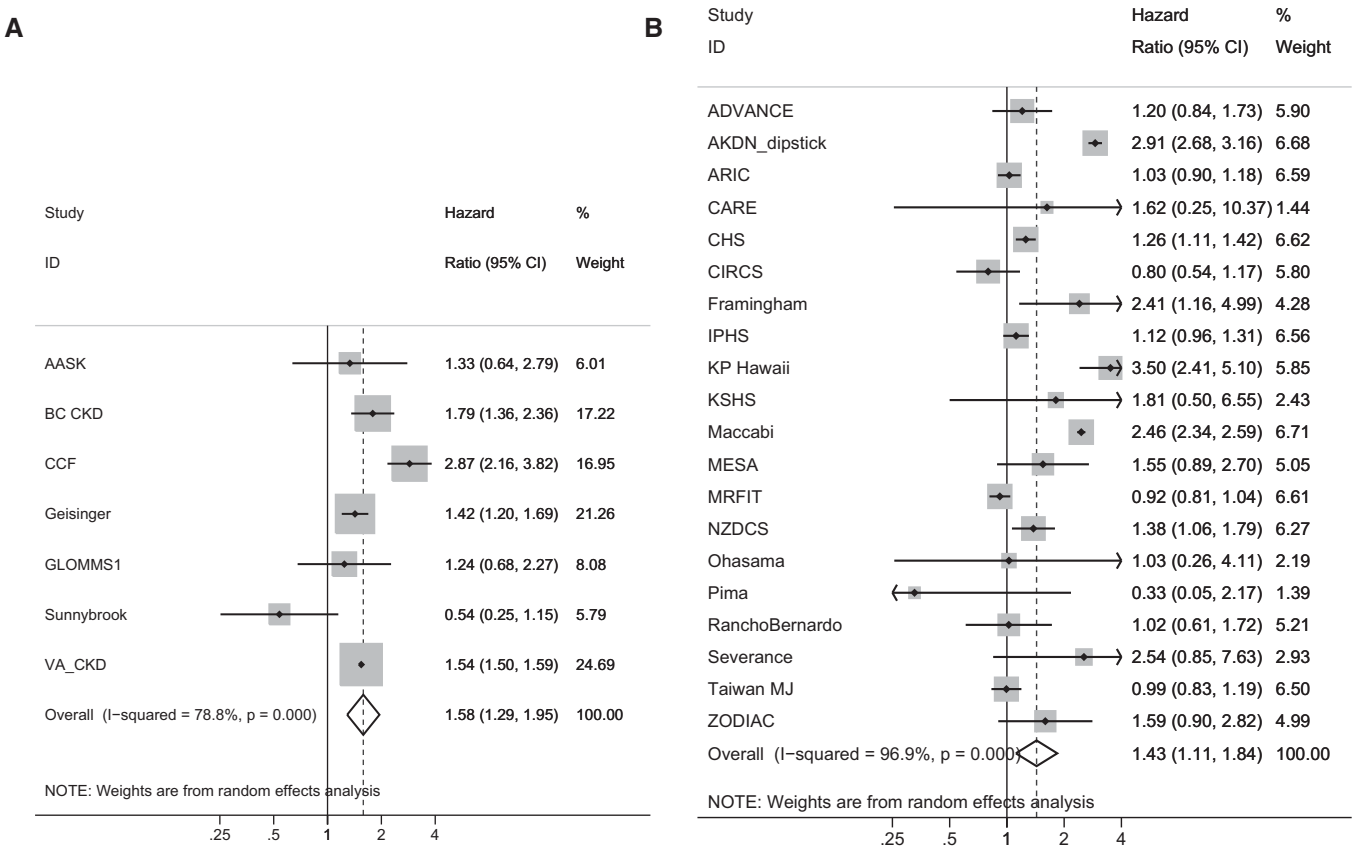


Figure 4. Forest plot of HRs associated with a 6 ml/min per 1.73 m^2 per year increase in eGFR (an eGFR slope of +6 ml/min per 1.73 m^2 per year) over a 3-year antecedent period. Analyses are shown for (A) CKD cohorts and (B) other (general population and high cardiovascular risk) cohorts. Adjusted HRs within each cohort for ACM associated with an annualized increase of the eGFR of 6 ml/min per 1.73 m^2 per year are depicted. The reference group for calculation of HRs was patients with stable eGFR values (*i.e.*, slope =0 ml/min per 1.73 m^2 per year). The HR for eGFR slope was adjusted for age, sex, race (black versus nonblack), systolic BP, total cholesterol, diabetes, history of CVD, and current (last) eGFR. AASK, African American Study of Kidney Disease and Hypertension; ADVANCE, The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation Trial; AKDN_dipstick, Alberta Kidney Disease Network; ARIC, Atherosclerosis Risk in Communities Study; BC CKD, British Columbia CKD Study; CARE, The Cholesterol and Recurrent Events Trial; CCF, Cleveland Clinic CKD Registry Study; CHS, Cardiovascular Health Study; CIRCS, Circulatory Risk in Communities Study; Framingham, Framingham Heart Study; Geisinger, Geisinger CKD Study; GLOMMS 1, Grampian Laboratory Outcomes, Morbidity and Mortality Studies 1; IPHS, Ibaraki Prefectural Health Study; KP Hawaii, Kaiser Permanente Hawaii Cohort; KSHS, Kangbuk Samsung Health Study; MESA, Multi-Ethnic Study of Atherosclerosis; MRFIT, Multiple Risk Factor Intervention Trial; NZDCS, New Zealand Diabetes Cohort Study; Ohasama, Ohasama Study; Pima, Pima Indian Study; RanchoBernardo, Rancho Bernardo Study; Severance, Severance Cohort Study; Sunnybrook, Sunnybrook Cohort; Taiwan MJ, Taiwan MJ Cohort Study; VA CKD, Veterans Administration CKD Study; ZODIAC, Zwolle Outpatient Diabetes Project Integrating Available Care.

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 toward the robustness of our findings. Finally, *P* values close to the nominal level of significance may be prone to type 1 error given the number of statistical tests involved in our analyses.

In conclusion, compared with 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 3 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

Table 2. Adjusted HRs for cardiovascular mortality and noncardiovascular mortality subsequent to an eGFR slope during a 3-year antecedent period for the other (general/high risk) cohorts (among 14 cohorts with available data)

Outcome	Slope Change in eGFR (ml/min per 1.73 m^2 per yr) during the 3-yr Antecedent Period						
	−9	−6	−3	Stable	3	6	9
CV mortality							
Other cohorts	1.33 (1.17 to 1.52)	1.10 (0.98 to 1.22)	1.08 (0.97 to 1.21)	Reference	1.12 (1.02 to 1.22)	1.27 (1.10 to 1.46)	1.46 (1.16 to 1.84)
Non-CV mortality							
Other cohorts	1.29 (1.17 to 1.43)	1.09 (1.03 to 1.15)	1.03 (0.95 to 1.13)	Reference	1.02 (0.95 to 1.09)	1.08 (0.95 to 1.23)	1.31 (1.00 to 1.73)

Data are presented as adjusted HR (95% CI). CV, cardiovascular. The HR for eGFR slope was adjusted for age, sex, race (black versus nonblack), systolic BP, total cholesterol, diabetes, history of CVD, and current (last) eGFR.

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 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–CVD risk cohorts; *i.e.*, other cohorts).[3–5,8,18] This study involved 35 cohorts (13 CKD and 22 other) and included subjects ≥18 years of age who had repeated serum creatinine measurements during antecedent intervals from 1 to 3 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.

Antecedent Change in eGFR

eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration 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 (milliliters per minute per 1.73 m^2 per year) was derived from ordinary least squares[10] regression using all eGFR measurements available during the antecedent period. This 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 Material). Rapidly declining, stable, and rapidly increasing eGFR slope were defined as antecedent slopes of <-5, -5 to $+5$, and $>+5$ ml/min per 1.73 m^2 per year, 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 before the last eGFR measurement during the antecedent period. Diabetes was defined as fasting glucose ≥7.0 mmol/L (126 mg/dl), nonfasting glucose ≥11.1 mmol/L (200 mg/dl), hemoglobin A1c ≥6.5%, use of antiglycemic 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, or severely increased.[29]

Assessment of Outcomes

The primary study outcome was ACM occurring subsequent to the antecedent time period, with time at risk starting at the last measurement of eGFR (current). In Supplemental Material, we analyzed cardiovascular and noncardiovascular 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 (Supplemental 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. Because 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 HRs of ACM according to GFR slope with piecewise linear splines (knots at -10, -5, -3, -1, $+1$, and $+3$ ml/min per 1.73 m^2 per year). Cox models were adjusted for age, sex, race (black versus nonblack), systolic BP, total cholesterol, diabetes, history of CVD, and current eGFR. Adjustment for albuminuria was done only in secondary analyses, because 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 per 1.73 m^2 per year 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 (Supplemental 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 per 1.73 m^2 per year 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 caused by myocardial infarction, heart failure, stroke, or sudden cardiac death) and noncardiovascular (all other etiologies) mortality. Second, we assessed the effect of individual residual eGFR variability. We used the RMSE as an indicator of the variation of an individual's eGFR values around his or her ordinary least squares regression line. The RMSE was included as a covariate and then, 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 >2 kg 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. Fifth, analyses were repeated according to whether individuals had ever been exposed to renin-angiotensin-system blocking medications in the antecedent interval as a covariate in the Cox model and then, a stratifying variable. Analyses were performed using Stata/SE 13 software (StataCorp., College Station, TX; www.stata.com). P values <0.05 were considered statistically significant.

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REFERENCES

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group: KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl* 3: 1–150, 2013

2. Levey AS, Atkins R, Coresh J, Cohen EP, Collins AJ, Eckardt KU, Nahas ME, Jaber BL, Jadoul M, Levin A, Powe NR, Rossert J, Wheeler DC, Lameire N, Eknoyan G: Chronic kidney disease as a global public health problem: Approaches and initiatives - a position statement from Kidney Disease Improving Global Outcomes. *Kidney Int* 72: 247–259, 2007
3. van der Velde M, Matsushita K, Coresh J, Astor BC, Woodward M, Levey A, de Jong P, Gansevoort RT, van der Velde M, Matsushita K, Coresh J, Astor BC, Woodward M, Levey AS, de Jong PE, Gansevoort RT, Levey A, El-Nahas M, Eckardt KU, Kasiske BL, Ninomiya T, Chalmers J, Macmahon S, Tonelli M, Hemmelgarn B, Sacks F, Curhan G, Collins AJ, Li S, Chen SC, Hawaii Cohort KP, Lee BJ, Ishani A, Neaton J, Svendsen K, Mann JF, Yusuf S, Teo KK, Gao P, Nelson RG, Knowler WC, Bilo HJ, Joosten H, Kleefstra N, Groenier KH, Auguste P, Veldhuis K, Wang Y, Camarata L, Thomas B, Manley T; Chronic Kidney Disease Prognosis Consortium: Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. *Kidney Int* 79: 1341–1352, 2011
4. Gansevoort RT, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J; Chronic Kidney Disease Prognosis Consortium: Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. *Kidney Int* 80: 93–104, 2011
5. Astor BC, Matsushita K, Gansevoort RT, van der Velde M, Woodward M, Levey AS, Jong PE, Coresh J, Astor BC, Matsushita K, Gansevoort RT, van der Velde M, Woodward M, Levey AS, de Jong PE, Coresh J, El-Nahas M, Eckardt KU, Kasiske BL, Wright J, Appel L, Greene T, Levin A, Djurdjev O, Wheeler DC, Landray MJ, Townend JN, Emberson J, Clark LE, Macleod A, Marks A, Ali T, Fluck N, Prescott G, Smith DH, Weinstein JR, Johnson ES, Thorp ML, Wetzels JF, Blankestijn PJ, van Zuilen AD, Menon V, Sarnak M, Beck G, Kronenberg F, Kollerits B, Froissart M, Stengel B, Metzger M, Remuzzi G, Ruggenenti P, Perna A, Heerspink HJ, Brenner B, de Zeeuw D, Rossing P, Parving HH, Auguste P, Veldhuis K, Wang Y, Camarata L, Thomas B, Manley T; Chronic Kidney Disease Prognosis Consortium: Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. *Kidney Int* 79: 1331–1340, 2011
6. Cheng TY, Wen SF, Astor BC, Tao XG, Samet JM, Wen CP: Mortality risks for all causes and cardiovascular diseases and reduced GFR in a middle-aged working population in Taiwan. *Am J Kidney Dis* 52: 1051–1060, 2008
7. Foley RN, Murray AM, Li S, Herzog CA, McBean AM, Eggers PW, Collins AJ: Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. *J Am Soc Nephrol* 16: 489–495, 2005
8. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT; Chronic Kidney Disease Prognosis Consortium: Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: A collaborative meta-analysis. *Lancet* 375: 2073–2081, 2010
9. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW; American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention: Kidney disease as a risk factor for development of cardiovascular disease: A statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 108: 2154–2169, 2003
10. Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH: Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med* 164: 659–663, 2004
11. Turin TC, Coresh J, Tonelli M, Stevens PE, de Jong PE, Farmer CK, Matsushita K, Hemmelgarn BR: One-year change in kidney function is associated with an increased mortality risk. *Am J Nephrol* 36: 41–49, 2012
12. Turin TC, Coresh J, Tonelli M, Stevens PE, de Jong PE, Farmer CK, Matsushita K, Hemmelgarn BR: Change in the estimated glomerular filtration rate over time and risk of all-cause mortality. *Kidney Int* 83: 684–691, 2013
13. Al-Aly Z, Zeringue A, Fu J, Rauchman MI, McDonald JR, El-Achkar TM, Balasubramanian S, Nurutdinova D, Xian H, Stroupe K, Abbott KC, Eisen S: Rate of kidney function decline associates with mortality. *J Am Soc Nephrol* 21: 1961–1969, 2010
14. Perkins RM, Bucaloiu ID, Kirchner HL, Ashouian N, Hartle JE, Yahya T: GFR decline and mortality risk among patients with chronic kidney disease. *Clin J Am Soc Nephrol* 6: 1879–1886, 2011
15. Matsushita K, Selvin E, Bash LD, Franceschini N, Astor BC, Coresh J: Change in estimated GFR associates with coronary heart disease and mortality. *J Am Soc Nephrol* 20: 2617–2624, 2009
16. Rifkin DE, Shlipak MG, Katz R, Fried LF, Siscovick D, Chonchol M, Newman AB, Sarnak MJ: Rapid kidney function decline and mortality risk in older adults. *Arch Intern Med* 168: 2212–2218, 2008
17. Fox CS, Matsushita K, Woodward M, Bilo HJG, Chalmers J, Heerspink HJL, Lee BJ, Perkins RM, Rossing P, Sairenchi T, Tonelli M, Vassalotti JA, Yamagishi K, Coresh J, de Jong PE, Wen C-P, Nelson RG; Chronic Kidney Disease Prognosis Consortium: Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: A meta-analysis. *Lancet* 380: 1662–1673, 2012
18. Matsushita K, Mahmoodi BK, Woodward M, Emberson JR, Jafar TH, Jee SH, Polkinghorne KR, Shankar A, Smith DH, Tonelli M, Warnock DG, Wen CP, Coresh J, Gansevoort RT, Hemmelgarn BR, Levey AS; Chronic Kidney Disease Prognosis Consortium: Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. *JAMA* 307: 1941–1951, 2012
19. Shlipak MG, Matsushita K, Ärnlöv J, Inker LA, Katz R, Polkinghorne KR, Rothenbacher D, Sarnak MJ, Astor BC, Coresh J, Levey AS, Gansevoort RT; CKD Prognosis Consortium: Cystatin C versus creatinine in determining risk based on kidney function. *N Engl J Med* 369: 932–943, 2013
20. Coresh J, Turin TC, Matsushita K, Sang Y, Ballew SH, Appel LJ, Arima H, Chadban SJ, Cirillo M, Djurdjev O, Green JA, Heine GH, Inker LA, Irie F, Ishani A, Ix JH, Kovesdy CP, Marks A, Ohkubo T, Shalev V, Shankar A, Wen CP, de Jong PE, Iseki K, Stengel B, Gansevoort RT, Levey AS; CKD Prognosis Consortium: Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. *JAMA* 311: 2518–2531, 2014
21. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352: 837–853, 1998
22. de Boer IH, Sun W, Cleary PA, Lachin JM, Molitch ME, Steffes MW, Zinman B; DCCT/EDIC Research Group: Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. *N Engl J Med* 365: 2366–2376, 2011
23. Sud M, Tangri N, Pintilie M, Levey AS, Naimark DM: ESRD and death after heart failure in CKD. *J Am Soc Nephrol* 26: 715–722, 2015
24. Sud M, Tangri N, Pintilie M, Levey AS, Naimark D: Risk of end-stage renal disease and death after cardiovascular events in chronic kidney disease. *Circulation* 130: 458–465, 2014
25. Perkins RM, Tang X, Bengier AC, Kirchner HL, Bucaloiu ID: Variability in estimated glomerular filtration rate is an independent risk factor for death among patients with stage 3 chronic kidney disease. *Kidney Int* 82: 1332–1338, 2012
26. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration): A new equation to estimate glomerular filtration rate. *Ann Intern Med* 150: 604–612, 2009

27. Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, Van Lente F; Chronic Kidney Disease Epidemiology Collaboration: Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem* 53: 766–772, 2007
28. Kidney Disease Improving Global Outcomes (KDIGO) Work Group: KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Chapter 2: Definition, identification, and prediction of CKD progression. *Kidney Int Suppl* 3: 63–72, 2013
29. Miller WG, Bruns DE, Hortin GL, Sandberg S, Aakre KM, McQueen MJ, Itoh Y, Lieske JC, Seccombe DW, Jones G, Bunk DM, Curhan GC, Narva AS; National Kidney Disease Education Program-IFCC Working Group on Standardization of Albumin in Urine: Current issues in measurement and reporting of urinary albumin excretion. *Clin Chem* 55: 24–38, 2009

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

AASK:	African American Study of Kidney Disease and Hypertension[1]
ADVANCE:	The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial[2]
Aichi:	Aichi Workers' Cohort[3]
AKDN:	Alberta Kidney Disease Network[4]
ARIC:	Atherosclerosis Risk in Communities Study[5]
BC CKD	British Columbia CKD Study[6]
CARE:	The Cholesterol and Recurrent Events (CARE) Trial[7]
CCF:	Cleveland Clinic CKD Registry Study[8]
CHS:	Cardiovascular Health Study[9]
CIRCS:	Circulatory Risk in Communities Study[10]
CRIB:	Chronic Renal Impairment in Birmingham[11]
Framingham:	Framingham Heart Study[12]
Geisinger:	Geisinger CKD Study[13]
GLOMMS-1:	Grampian Laboratory Outcomes, Morbidity and Mortality Studies – 1[14]
IPHS:	Ibaraki Prefectural Health Study[15]
KP Hawaii:	Kaiser Permanente Hawaii Cohort[16]
KPNW:	Kaiser Permanente Northwest[17]
KSHS:	Kangbuk Samsung Health Study
Maccabi:	Maccabi[18]
MASTERPLAN:	Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of a Nurse Practitioner[19]
MDRD:	Modification of Diet in Renal Disease Study[20]
MESA:	Multi-Ethnic Study of Atherosclerosis[21]
MRFIT:	Multiple Risk Factor Intervention Trial[22]
Nephro Test:	NephroTest Study[23]
NZDCS:	New Zealand Diabetes Cohort Study[24]
Ohasama:	Ohasama Study[25]
Pima:	Pima Indian Study[26]
PREVEND:	Prevention of Renal and Vascular End-stage Disease Study[27]
Rancho Bernardo:	Rancho Bernardo Study[28]
RENAAL:	Reduction of Endpoints in Non-insulin Dependent Diabetes Mellitus withthe Angiotensin II Antagonist Losartan[29]
Severance:	Severance Cohort Study[30]
Sunnybrook:	Sunnybrook Cohort[31]
Taiwan:	Taiwan MJ Cohort Study[32]
VA CKD:	Veterans Administration CKD Study[33]
ZODIAC:	Zwolle Outpatient Diabetes project Integrating Available Care[34]

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

Overview:

As previously reported,[35, 36] participating studies were asked to prepare a dataset with approximately 20 variables (event variables and dates and several predictors including age, sex, race, and repeated laboratory and vital data including serum creatinine measurement to estimate change in eGFR over the baseline period). Because the analysis used the CKD-EPI formula, the race variable only distinguished between black and non-black, under the assumption that this formula performs reasonably well in other ethnic groups. To minimize heterogeneity, we circulated guidelines for definitions of variables (e.g. hypertension, diabetes, smoking) and dataset preparation.

Prevalent cardiovascular disease (CVD) was defined as history of myocardial infarction, coronary revascularization, heart failure or stroke. Hypertension was defined as a blood pressure ≥ 140/90 mmHg or taking anti-hypertensive medication. Diabetes mellitus was defined as hemoglobin A1c ≥6.5%, fasting blood glucose ≥7.0 mmol/l, non-fasting glucose ≥11.1 mmol/l, or taking glucose lowering drugs.

Analyses were restricted to subjects aged 18 years or older. We instructed studies not to impute the two key kidney measures, eGFR (i.e., age, gender, race, and serum creatinine) and albuminuria. Zero values of ACR were treated as 0.1 for log transformation. For other variables in the models with missing values we imputed with the mean value of the covariate. Values of covariates, e.g., systolic blood pressure <50 or >300 mmHg were excluded from the analysis.

Out of 43 studies with repeated serum creatinine, 8 studies (AusDiab, Beaver Dam, CARE FOR HOMe, ESTHER, Gubbio, HUNT, Okinawa, ULSAM) did not have enough data within antecedent periods of interest for the present study. For 24 of the 35 studies in the present study, analysis was done at the Data Coordination Center at Johns Hopkins University; for the remainder the standard code was run in-house at individual study centers, with the output returned to the Data Coordinating Center. The code was written in STATA by the Data Coordinating Center. The standard code was designed to automatically save all output needed for the meta-analysis. The Data Coordinating Center then pooled the estimates across studies using STATA. Studies with outcomes fewer than 10 in any strata for particular analysis were excluded.

Studies were instructed to standardize and calibrate their serum creatinine to their best ability and report the method of standardization. The reported creatinine calibration allows grouping studies into studies that reported using an IDMS traceable method or conducted some serum creatinine calibration to IDMS traceable methods (AKDN, CCF, Geisinger, GLOMMS-1, KPNW, Maccabi, NephroTest, Rancho Bernardo) and studies where the creatinine standardization was not done (AASK, ADVANCE, Aichi, ARIC, British Columbia CKD, CARE, CHS, CIRCS, CRIB, Framingham, IPHS, KP Hawaii, KSHS, MASTERPLAN, MDRD, MESA, MRFIT, Ohasama, Pima, PREVEND, RENAAL, Severance, Sunnybrook, Taiwan, ZODIAC). Retrospective assessment of creatinine calibration without direct collection of laboratory data is limited since substantial creatinine calibration differences have been documented even within a single laboratory using the same method over time.

Piecewise-linear splines were used to allow for non-linear association in a manner that still allows for a simple interpretation of the association within each segment and transparently shows changes in slope at clinically interpretable points. Estimates and standard errors for each point are the combination of all terms between that point and the reference point with covariances used for standard error estimates. For points in the same linear segment as the reference points statistical significance compared to the reference point is only dependent on the statistical significance of the slope for that segment. If the slope is statistically significant, all points on the segment will be statistically significant since smaller effect sizes near the reference point have proportionately small standard errors and the same statistical significance test.

Adjusted weighted average absolute risk was calculated using the weighted average baseline risk and meta-analyzed hazard ratios. Baseline risk (the risk when all the covariates are zero) was calculated in each cohort for the following combination of covariates after centering the continuous covariates: age at 60 year, non-black, male, 0% change in eGFR, a first eGFR of 50 ml/min/1.73 m^2, a systolic blood pressure of 130 mmHg, a total cholesterol of 5 mmol/L, no history of diabetes or CVD. These baseline risks for 1-y follow-up after baseline across cohorts were averaged with weights based on square root of the number of events. Successive follow-up periods multiply by the ratio of that time and the previous time (e.g., 3 year risk vs. 1 year risk) to obtain consistent estimates despite fewer cohorts having longer follow-up.

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

Notes for individual studies:

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

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

AKDN: Although this study has not collected information on race, the proportion of blacks in the province of Alberta is considered <1%.[4] Other variables that were not collected in this study are systolic blood pressure, total cholesterol concentration, and smoking. Restricted analyses to those with at least 3 repeated serum creatinine measurement.

ARIC: Serum creatinine was repeated three years apart and thus this cohort could contribute to 3-y antecedent period analysis only. Albuminuria was not available in this time frame.

BC CKD: Includes patients referred to nephrologists and maintained in follow-up practice or with eGFR <60 ml/min/1.73m^2 at enrollment.

CARE: This study is an intervention study in which all patients had a previous myocardial infarction.

CCF: Includes patients who had at least one face-to-face outpatient encounter with a Cleveland Clinic health care provider and had two eGFR < 60 ml/min/1.73m^2 90 days apart. Albuminuria was available in 35% of participants.

CHS: This study consists of participants only aged 65 or older. Serum creatinine was repeated three years apart and thus this cohort could contribute to 3-y antecedent period analysis only.

CRIB: This study includes hospital nephrology outpatients with creatinine >130 µmol/L. Serum creatinine was repeated two years apart and this this cohort could contribute to 2-y antecedent period analysis only.

Geisinger: This study includes all Geisinger primary care recipients, 18 years or older as of index date, and who have CKD, defined as two or more outpatient eGFR values < 60 by CKD-EPI equation. Covariates obtained most closely to index date within a past year were included in models. Albuminuria was available in 13% of participants.

GLOMMS-1: This study included adult patients that resided in Grampian with abnormal renal function tests measured from January to June 2003 (creatinine >150 µmol/L for men and 130 µmol/L for women). This study did not collect data on use of anti-diabetic or anti-hypertensive medication, total cholesterol, systolic or diastolic blood pressure. Diabetes and hypertension status were coded based on hospital physician or general practitioner diagnosis recorded in case notes. Albuminuria was available in 57% of participants. The ethnicity of the Grampian population is relatively homogenous with overall 98.3% of males and 98.4% of females being white. Indians account for 0.2% of the population, Pakistani and other South Asian individuals account for 0.3%, Chinese 0.3% and 0.8% are recorded as other. [37]

KP Hawaii: This study measured ACR and/or PCR.

KPNW: This study included patients that were HMO members with CKD stage 3 or 4 without a history of renal replacement therapy. This study defined diabetes using their own clinical tool that includes diagnosis codes, treatment codes, and laboratory values. This study has not collected use of anti-diabetic medications.

Maccabi: Albuminuria available in 11% of participants.

MASTERPLAN: This study measured ACR in patients with albuminuria in the low range, PCR in patients with overt proteinuria.

MDRD: This clinical trial has not collected use of anti-diabetic or anti-hypertensive medications.

MESA: Serum creatinine was repeated three years apart and thus this cohort could contribute to 3-y antecedent period analysis only.

MRFIT: This study is an intervention study which includes men at above risk (study specified) for coronary heart disease based on higher levels of blood pressure, serum cholesterol, and

cigarette use. Men were excluded if their serum creatinine was > 2.0 mg/dl. The study only included men.

NephroTest: This study includes nephrologist referred patients with diagnosed CKD stages 1-5.

NZDCS: All participants had a diagnosis of diabetes according to primary care provider.

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

Pima: This study consists entirely of Pima and the closely-related Tohono O'odham Indians. ACR was measured in a spot urine specimen.

PREVEND: Serum creatinine was repeated at two years and three years apart and thus this cohort could contribute to 2-y and 3-y antecedent period analyses only.

Rancho Bernardo: Serum creatinine was repeated three years apart and thus this cohort could contribute to 3-y antecedent period analysis only.

RENAAL: This was a clinical trial comparing the effect of angiotensin receptor blocker vs. placebo regarding the prevention of CKD progression in those with diabetic nephropathy. All participants had diabetes.

Sunnybrook: This cohort includes patients seen in the nephrology clinics at Sunnybrook Hospital in Toronto, Ontario, Canada with CKD stage 3-5 or proteinuric CKD stage 1-2. Albuminuria was available in 27% of participants.

VA CKD: Includes all United States veterans with stable CKD stage 1-5 but not on dialysis. Albuminuria was available in 15% of participants.

ZODIAC: This study includes only individuals with type 2 diabetes.

Covariate availability by cohort:

Study	Total N	Total Chol	Systolic BP	% DM	% Hx of CVD
AASK	831	3%	0%	0%	0%
ADVANCE	9402	38%	0%	0%	0%
Aichi	1500	0%	0%	0%	0%
AKDN	230489	100%	100%	0%	0%
ARIC	13833	0.2%	0.1%	0.08%	1%
BC CKD	6276	27%	63%	0%	0%
CARE	3527	0.03%	100%	0%	0%
CCF	10564	29%	3%	0%	0%
CHS	4012	0.07%	0.02%	0%	0%
CIRCS	6768	0%	0.06%	0%	0%
CRIB*	190	10%	5%	0%	0%
Framingham	746	0%	0%	0%	0%
Geisinger	11593	21%	4%	0%	0%
GLOMMS 1	580	100%	100%	0%	0%
IPHS	57344	0%	0.003%	0%	0%
KP Hawaii	13357	23%	5%	0%	1%
KPNW*	522	11%	1%	0%	0%
KSHS	26674	0%	0.22%	0%	0%
Maccabi	560464	7%	30%	0%	0%
MASTERPLAN	538	18%	20%	0%	0%
MDRD	316	0%	1%	0%	0%
MESA	4942	0.04%	0.04%	0%	0%
MRFIT	11527	0.04%	0.09%	0%	0%
NephroTest	414	1%	3%	0%	1%
NZDCS	4388	1%	0.2%	0%	0%
Ohasama	996	0%	0%	0%	0%
Pima	786	0%	0.4%	0%	0%
PREVEND*	4740	0%	0.3%	0.4%	3%
Rancho Bernardo	477	0%	0%	0%	0%
RENAAL	885	13%	0%	0%	0%
Severance	3477	0%	0.2%	0%	0%
Sunnybrook	1889	30%	18%	0%	0%
Taiwan MJ	71000	0%	0.04%	0.07%	0.01%
VA CKD	216046	18%	40%	0.005%	0.005%
ZODIAC	784	4%	15%	0%	0%

* Data from 2 year. Otherwise from 3 year.							
<0.2% missing	0.2-1% missing	1-5% missing	5-20% missing	20-50% missing	>50% missing		Non-IPD study

Appendix 3. Acknowledgements and funding for collaborating cohorts

Study	List of sponsors
AASK	NIDDK
ADVANCE	National Health and Medical Research Council of Australia program grant 571281; Servier
Aichi	KAKENHI (09470112, 13470087, 17390185, 18590594, 20590641, 20790438, 22390133, 26293153)
AKDN	Canadian Institutes of Health Research; Alberta Innovates - Health Solutions; Kidney Foundation of Canada
ARIC	The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C). The authors thank the staff and participants of the ARIC study for their important contributions.
BC Cohort	BC Provincial Renal Agency, an Agency of the Provincial Health Services Authority in collaboration with University of British Columbia.
CARE	Alberta Heritage Foundation for Medical Research/Alberta Innovates Health Solutions Interdisciplinary Team Grants Program
CCF	Supported by an unrestricted educational grant from Amgen to the Department of Nephrology and Hypertension.
CHS	This research was supported by contracts HHSN268201200036C, HHSN268200800007C, N01 HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, and grant HL080295 from the National Heart, Lung, and Blood Institute (NHLBI), with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided by AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org.
CIRCS	N/A
CRIB	British Renal Society Project Grant Award British Heart Foundation Project Grant Award.
Framingham	NHLBI Framingham Heart Study (N01-HC-25195).
Geisinger	Geisinger Clinic
GLOMMS-1	Chief Scientist Office CZH/4/656
IPHS	N/A
KP Hawaii	N/A
KPNW	Amgen
KSHS	

Maccabi	
MASTERPLAN	The MASTERPLAN study is a clinical trial with trial registration ISRCTN registry: 73187232. Sources of funding: The MASTERPLAN Study was supported by grants from the Dutch Kidney Foundation (Nierstichting Nederland, number PV 01), and the Netherlands Heart Foundation (Nederlandse Hartstichting, number 2003 B261). Unrestricted grants were provided by Amgen, Genzyme, Pfizer and Sanofi-Aventis.
MDRD	NIDDK UO1 DK35073 and K23 DK67303, K23 DK02904
MESA	This research was supported by contracts N01-HC-95159 through N01-HC-95169 from the National Heart, Lung, and Blood Institute and by grants UL1-RR-024156 and UL1-RR-025005 from NCRR. The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.
MRFIT	The Multiple Risk Factor Intervention Trial was contracted by the National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH), Bethesda, Md. Follow-up after the end of the trial was supported with NIH/NHLBI grants R01-HL-43232 and R01-HL-68140. The principal investigators and senior staff of the clinical centers, coordinating center, other support centers and key committees are listed in a previous report (JAMA 1982; 248: 1465-1477).
NephroTest	The NephroTest CKD cohort study is supported by grants from: Inserm GIS-IReSP AO 8113LS TGIR; French Ministry of Health AOM 09114 and AOM 10245; Inserm AO 8022LS; Agence de la Biomédecine R0 8156LL, AURA, and Roche 2009-152-447G. The Nephrotest initiative was also sponsored by unrestricted grants from F.Hoffman-La Roche Ltd. The authors thank the collaborators and the staff of the NephroTest Study: François Vrtovsnik, Eric Daugas, Martin Flamant, Emmanuelle Vidal-Petiot (Bichat Hospital); Christian Jacquot, Alexandre Karras, Eric Thervet, Christian d'Auzac, P. Houillier, M. Courbebaisse, D. Eladari et G. Maruani (European Georges Pompidou Hospital); Jean-Jacques Boffa, Pierre Ronco, H. Fessi, Eric Rondeau, Emmanuel Letavernier, Jean Philippe Haymann, P. Urena-Torres (Tenon Hospital)
NZDCS	The New Zealand Diabetes Cohort study was supported by the New Zealand Health Research Council and Auckland Medical Research Foundation and the New Zealand Society for the Study of Diabetes.
Ohasama	Grant-in-Aid(H20-22Junkankitou[Seishuu]-Ippan-009, 013 and H23-Junkankitou [Senshuu]-Ippan-005) from the Ministry of Health, Labor and Welfare, Health and Labor Sciences Research Grants, Japan; Japan Atherosclerosis Prevention Fund.
Pima	This work was supported by the Intramural Research Program of the National Institute of Diabetes and Digestive and Kidney Diseases.
PREVEND	The PREVEND study is supported by several grants from the Dutch Kidney Foundation, and grants from the Dutch Heart Foundation, the Dutch Government (NWO), the US National Institutes of Health (NIH) and the University Medical Center Groningen, The Netherlands (UMCG). Dade

	Behring, Marburg, Germany supplied equipment and reagents for nephelometric measurement of urinary albumin.
Rancho Bernardo	NIA AG07181 and AG028507 NIDDK DK31801
RENAAL	The RENAAL trial was supported by Merck and Company.
Severance	Seoul city R&BD program (10526), Korea, The National R&D Program for Cancer Control, Ministry for Health, Welfare and Family affairs, Republic of Korea (1220180), and The National Research Foundation of Korea(NRF) grant funded by the Korea government(MEST) (2011-0029348).
Sunnybrook	
Taiwan	This study was supported by Taiwan Department of Health Clinical Trial and Research Centre of Excellence (DOH 101-TD-B-111-004)
VA CKD	This study was supported by resources from the US Department of Veterans Affairs. Opinions expressed in this paper are those of the authors' and do not represent the official opinion of the US Department of Veterans Affairs.
ZODIAC	N/A

Supplemental Table 1. Cohort demographic characteristics by estimated glomerular filtration rate (eGFR) slope category

	Slope <-5ml/y				Slope ≥-5ml/y to ≤5ml/y				Slope >5ml/y			
Study	**%N**	**Age**	**%Female**	**%Black**	**%N**	**Age**	**%Female**	**%Black**	**%N**	**Age**	**%Female**	**%Black**
CKD cohorts												
AASK	14	55 (11)	43	100	82	58 (10)	38	100	4	55 (11)	43	100
BC CKD	13	65 (15)	40	0.4	84	73 (13)	47	0.4	3	67 (15)	52	1
CCF	10	73 (12)	54	18	85	75 (11)	54	12	6	72 (13)	65	14
Geisinger	12	72 (10)	59	2	77	73 (9)	60	1	11	70 (10)	61	1
GLOMMS 1	6	64 (18)	54	0	88	73 (12)	49	0	6	74 (9)	42	0
KPNW	53	69 (10)	54	0	45	72 (10)	50	0	2	60 (na)	0	0
MASTERPLAN	8	60 (14)	30	0	91	64 (12)	31	0	1	54 (15)	50	0
MDRD	20	49 (12)	42	6	79	56 (12)	38	4	1	53 (23)	100	0
NephroTest	11	58 (16)	30	14	85	61 (14)	29	11	4	56 (15)	39	11
RENAAL	42	62 (7)	31	18	58	64 (7)	38	13	0.1	70 (na)	100	0
Sunnybrook	22	61 (17)	40	0	74	65 (17)	43	0	3	57 (19)	52	0
VA_CKD	12	74 (10)	2	15	80	76 (9)	3	9	7	74 (10)	4	11
Sub-Total	**12**	**73 (11)**	**9**	**15**	**80**	**76 (10)**	**9**	**9**	**7**	**73 (10)**	**11**	**10**
Other (General Population and High Risk cohorts)												
ADVANCE	20	69 (6)	48	0.3	72	69 (6)	39	0.4	9	69 (6)	57	0.2
Aichi	16	51 (7)	18	0	73	51 (6)	16	0	11	50 (6)	18	0
AKDN	11	59 (17)	65	0	84	60 (15)	59	0	4	56 (17)	61	0
ARIC	20	57 (6)	64	35	78	58 (6)	53	20	3	57 (6)	55	31
CARE	30	61 (9)	18	3	69	62 (9)	11	3	0.3	56 (11)	0	0
CHS	6	76 (6)	71	6	86	75 (5)	56	4	8	75 (5)	58	4
CIRCS	9	58 (9)	66	0	87	58 (9)	64	0	4	56 (8)	75	0
Framingham	11	63 (10)	51	0	84	61 (10)	54	0	5	61 (9)	57	0
IPHS	11	61 (10)	72	0	87	62 (10)	67	0	1	62 (10)	80	0
KP Hawaii	13	63 (13)	52	0	81	65 (13)	49	0	5	62 (14)	52	0
KSHS	8	43 (7)	52	0	90	44 (7)	31	0	3	42 (6)	33	0
Maccabi	9	53 (17)	59	0	87	53 (16)	58	0	4	47 (17)	70	0
MESA	8	66 (10)	55	44	90	65 (10)	52	27	2	64 (10)	38	45
MRFIT	6	50 (6)	0	11	89	50 (6)	0	7	5	49 (6)	0	9
NZDCS	26	64 (13)	51	0	69	65 (13)	50	0	4	63 (14)	58	0
Ohasama	8	67 (8)	68	0	89	67 (8)	67	0	3	65 (10)	84	0

Pima	8	40 (14)	73	0	89	34 (13)	60	0	3	31 (12)	77	0
PREVEND	18	53 (10)	49	1	80	56 (11)	46	1	1	55 (7)	46	0
RanchoBernardo	11	77 (10)	62	0	80	77 (10)	61	0	9	80 (10)	77	0
Severance	34	47 (9)	39	0	61	49 (9)	31	0	4	48 (9)	59	0
Taiwan MJ	17	42 (12)	60	0	76	44 (13)	49	0	7	41 (12)	50	0
ZODIAC	12	71 (9)	56	0	85	70 (11)	57	0	3	68 (12)	73	0
Sub-Total	**11**	**54 (17)**	**60**	**1**	**85**	**55 (16)**	**56**	**0**	**4**	**50 (17)**	**63**	**1**
Total	**11**	**58 (17)**	**49**	**4**	**84**	**59 (17)**	**48**	**2**	**5**	**57 (19)**	**48**	**3**

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 antecedent period. %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.

Supplemental Table 2. Additional cohort characteristics by eGFR slope category for cohorts able to contribute data for a 3-year antecedent period.

	Slope <-5ml/y					Slope ≥-5ml/y to ≤5ml/y					Slope >5ml/y				
Study	**eGFR 1st**	**eGFR Last**	**% Alb**	**% DM**	**% CVD**	**eGFR 1st**	**eGFR Last**	**% Alb**	**% DM**	**% CVD**	**eGFR 1st**	**eGFR Last**	**% Alb**	**% DM**	**% CVD**
CKD cohorts															
AASK	49 (15)	27 (15)	79	0	50	47 (14)	46 (17)	65	0	50	49 (11)	70 (14)	72	0	57
BC CKD	52 (20)	28 (16)	85	65	14	35 (14)	32 (15)	71	53	16	39 (17)	59 (18)	64	55	23
CCF	49 (9)	33 (11)	45	44	32	46 (10)	46 (13)	29	32	30	46 (10)	68 (14)	28	34	29
Geisinger	53 (6)	38 (12)	86	57	44	52 (7)	54 (11)	78	38	27	50 (9)	72 (12)	68	40	30
GLOMMS 1	42 (13)	20 (9)	89	74	40	34 (8)	33 (11)	78	61	48	33 (7)	54 (9)	60	52	51
KPNW	71 (14)	43 (7)	14	54	64	59 (7)	48 (8)	4	63	54	47 (na)	59 (na)	0	0	100
MASTERPLAN	44 (14)	24 (11)	61	30	33	40 (15)	38 (17)	38	27	30	41 (16)	65 (19)	25	25	25
MDRD	40 (11)	19 (9)	95	6	9	36 (14)	31 (15)	86	4	12	46 (14)	56 (7)	50	0	50
NephroTest	57 (20)	34 (21)	95	36	16	41 (18)	39 (19)	96	26	22	49 (12)	69 (13)	83	22	17
RENAAL	46 (13)	23 (12)	98	100	44	41 (13)	34 (15)	96	100	46	34 (na)	69 (na)	100	100	0
Sunnybrook	71 (27)	46 (25)	86	49	54	60 (31)	57 (31)	78	41	52	59 (28)	81 (28)	80	37	43
VA_CKD	62 (18)	42 (18)	50	61	45	54 (15)	54 (16)	33	45	42	54 (12)	73 (14)	0	44	42
Sub-Total	**61 (18)**	**41 (18)**	**53**	**60**	**44**	**53 (15)**	**53 (17)**	**35**	**44**	**40**	**53 (12)**	**73 (14)**	**6**	**44**	**40**
Other (General Population and High Risk cohorts)															
ADVANCE	85 (16)	59 (15)	33	100	30	78 (17)	76 (17)	30	100	28	66 (13)	88 (11)	30	100	28
Aichi	99 (11)	76 (12)	na	13	2	93 (14)	92 (12)	na	11	1	79 (10)	105 (22)	na	7	2
AKDN	90 (20)	68 (21)	na	12	7	84 (20)	82 (20)	na	8	5	71 (18)	92 (17)	na	8	7
ARIC	100 (14)	78 (15)	6	18	12	95 (14)	91 (14)	5	15	11	76 (12)	97 (12)	4	22	12
CARE	87 (13)	65 (13)	14	16	100	71 (14)	66 (13)	11	12	100	64 (13)	82 (16)	18	18	100
CHS	77 (13)	57 (14)	na	25	70	68 (15)	69 (15)	na	16	63	61 (11)	80 (10)	na	16	64
CIRCS	91 (12)	72 (12)	4	10	3	83 (13)	81 (13)	3	7	2	72 (9)	91 (10)	3	8	1
Framingham	97 (19)	70 (17)	na	17	12	91 (16)	89 (15)	na	9	4	73 (10)	93 (9)	na	11	5
IPHS	91 (12)	70 (12)	3	9	11	86 (13)	82 (13)	2	9	9	71 (10)	91 (10)	1	12	10
KP Hawaii	80 (22)	58 (24)	67	84	24	76 (23)	75 (24)	49	72	22	67 (19)	86 (18)	47	65	23
KSHS	101 (10)	82 (10)	3	6	0	88 (11)	86 (10)	2	6	1	79 (9)	98 (9)	2	9	1
Maccabi	100 (21)	79 (22)	22	17	4	96 (20)	94 (20)	10	15	3	85 (17)	104 (18)	13	10	3
MESA	87 (17)	65 (17)	7	30	6	83 (16)	81 (16)	5	14	2	69 (15)	91 (14)	3	26	4
MRFIT	94 (12)	74 (13)	28	10	8	88 (13)	88 (13)	17	10	4	78 (9)	97 (9)	17	15	4
NZDCS	86 (22)	59 (22)	15	100	17	76 (21)	73 (21)	8	100	11	66 (20)	87 (19)	7	100	11
Ohasama	87 (9)	69 (10)	4	8	3	83 (11)	82 (11)	4	8	2	70 (8)	89 (10)	0	13	3

Pima	115 (28)	87 (34)	15	54	0	123 (15)	121 (15)	14	32	0	110 (19)	132 (20)	0	31	0
PREVEND	91 (12)	72 (12)	57	8	6	80 (14)	76 (14)	20	9	6	70 (14)	91 (13)	12	46	8
Rancho Bernardo	77 (15)	54 (17)	19	21	19	72 (16)	70 (17)	16	14	19	60 (12)	82 (10)	31	20	27
Severance	99 (12)	75 (11)	3	2	1	82 (14)	80 (14)	3	4	2	73 (11)	94 (12)	1	7	3
Taiwan MJ	106 (14)	84 (14)	2	3	2	93 (16)	92 (16)	1	3	2	83 (12)	105 (15)	1	3	2
ZODIAC	75 (17)	51 (17)	16	100	42	68 (16)	65 (17)	5	100	31	58 (12)	79 (12)	9	100	14
Sub-Total	**96 (20)**	**75 (21)**	**21**	**17**	**7**	**92 (20)**	**90 (20)**	**14**	**14**	**5**	**80 (18)**	**100 (18)**	**14**	**12**	**5**
Total	**88 (25)**	**67 (25)**	**29**	**27**	**15**	**84 (24)**	**83 (24)**	**18**	**19**	**11**	**72 (20)**	**92 (21)**	**11**	**21**	**15**

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; eGFR 1st – mean (std. deviation, SD) eGFR at beginning of antecedent period in ml/min/1.73m^2; eGFR Last – mean (SD) eGFR at end of antecedent period in ml/min/1.73m^2; %Alb – proportion of participants with urine albumin-to-creatinine ratio ≥30 mg/g or urine protein-to-creatinine ratio ≥50 mg/g or dipstick protein ≥1+; %DM – percentage of subjects with diabetes. %CVD – percentage of subjects with prior cardiovascular disease.

Supplemental Table 3. Multiple logistic regression analysis for the adjusted odds ratios associated with given baseline factors for an antecedent eGFR slope less than – 5 or greater than +5 ml/min/1.73m^2/yr for both CKD and other cohorts.

	slope <-5ml/y vs. slope ≥-5ml/y to ≤5ml/y		slope >5ml/y vs. slope ≥-5ml/y to ≤5ml/y	
Variables	CKD Cohorts	Other (General/high-risk Cohorts)	CKD Cohorts	Other (General/high-risk cohorts)
eGFR per ml at the range <60	0.93 (0.91, 0.94)	0.97 (0.97, 0.98)	1.16 (1.14, 1.17)	1.10 (1.09, 1.11)
eGFR per ml at the range ≥60	0.94 (0.93, 0.96)	0.91 (0.91, 0.92)	1.05 (1.01, 1.09)	1.07 (1.06, 1.08)
Age, per 10y	0.67 (0.62, 0.72)	0.48 (0.45, 0.51)	1.00 (0.85, 1.18)	1.43 (1.36, 1.49)
Female gender	0.86 (0.80, 0.92)	1.29 (1.20, 1.39)	1.33 (1.14, 1.56)	1.33 (1.17, 1.51)
Black	1.38 (1.25, 1.51)	1.87 (1.34, 2.61)	1.02 (0.90, 1.15)	0.97 (0.70, 1.35)
Systolic BP, per 5 mmHg	1.03 (1.02, 1.03)	0.99 (0.98, 1.01)	1.03 (1.02, 1.04)	1.00 (0.99, 1.01)
Diabetes	1.61 (1.49, 1.74)	1.41 (1.36, 1.47)	0.91 (0.74, 1.12)	1.20 (1.03, 1.40)
Total cholesterol, per mmol/L	1.02 (1.01, 1.04)	1.02 (1.00, 1.03)	0.94 (0.90, 0.98)	1.02 (1.01, 1.02)
History of CVD	1.07 (0.94, 1.21)	1.16 (1.09, 1.23)	1.40 (1.29, 1.52)	1.39 (1.30, 1.49)
logACR	1.13 (1.04, 1.23)	1.09 (1.05, 1.13)	0.96 (0.88, 1.04)	1.04 (1.00, 1.07)
ACR 30-300 vs. ACR<30	0.87 (0.80, 0.95)	1.13 (1.04, 1.22)	1.47 (1.25, 1.72)	1.07 (1.01, 1.14)
ACR 300+ vs ACR<30	1.38 (1.07, 1.780)	1.25 (1.13, 1.40)	1.20 (0.76, 1.89)	1.28 (1.19, 1.38)
Current smoker	1.10 (0.95, 1.29)	1.25 (1.16, 1.35)	1.04 (0.93, 1.15)	1.03 (0.97, 1.09)
BMI	1.00 (1.00, 1.01)	0.99 (0.99, 0.99)	0.99 (0.98, 1.00)	1.01 (1.00, 1.01)

Values in the table represent the exponentiation of the adjusted log odds ratio (95% confidence interval) associated with a one unit increase in the given baseline factor. CKD – chronic kidney disease cohorts; Other - general population and CV high-risk cohorts; slope <-5ml/yr vs slope >= -5 to <5ml/yr – represents an analysis where the event to be predicted is an estimated glomerular filtration rate (eGFR) slope of less than -5 ml/min/1.73m^2/year from among subjects with a declining or stable eGFR slope {i.e. those with a slope <= + 5 ml/min/1.73m^2/year); Slope >5ml/yr vs slope >= -5 to <5ml/yr – represents an analysis where the event to be predicted is an eGFR slope of more than +5 ml/min/1.73m^2/year from among subjects with an increasing or stable eGFR slope {i.e. those with a slope >= -5 ml/min/1.73m^2/year); y – year; BP – blood pressure; CVD - cardiovascular disease; logACR – natural logarithm of the urine albumin to creatinine ratio (in mg/g); BMI – body mass index.

Supplemental Table 4. Cohort characteristics and outcomes for a 3-year antecedent period

	During 3y Antecedent Period		After 3y Antecedent Period		
Cohorts (n=34)	**N**	**Median # Scre (IQR)**	**ACM events**	**CVM events**	**Mean (SD) Follow-up, years**
CKD cohorts					
AASK	831	9 (9-8)	115	n/a	6 (3)
BC CKD	6276	15 (11-20)	1,176	n/a	2 (1)
CCF	10564	8 (6-12)	666	n/a	1 (0.4)
Geisinger	11593	9 (6-13)	1,652	n/a	3 (2)
GLOMMS 1	572	12 (8-17)	201	65	3 (1)
KPNW	53	13 (7-20)	26	n/a	4 (2)
MASTERPLAN	538	11 (9-12)	67	25	3 (1)
MDRD	316	11 (10-11)	146	66	12 (4)
NephroTest	414	4 (3-4)	44	n/a	3 (2)
RENAAL	885	14 (13-14)	61	29	0.5 (0.4)
Sunnybrook	1889	10 (7-15)	361	155	5 (2)
VA_CKD	216046	7 (5-11)	52,754	n/a	3 (1)
Sub-Total	**249,977**	**7 (7-7)**	**57,269**	**340**	**3 (1)**
Other (General Population and High Risk cohorts)					
ADVANCE	9402	5 (5-5)	374	185	2 (0.4)
Aichi	1500	3 (2-4)	17	n/a	6 (1)
AKDN	230489	4 (3-6)	5,174	n/a	1 (0.5)
ARIC	13833	2 (2-2)	3,875	936	16 (4)
CARE	3527	4 (4-4)	141	84	2 (1)
CHS	4012	2 (2-2)	2,857	1,083	11 (5)
CIRCS	6768	3 (2-4)	840	n/a	16 (4)
Framingham	746	2 (2-2)	79	20	6 (1)
IPHS	57344	4 (3-4)	9,384	2,746	12 (2)
KP Hawaii	13357	8 (6-11)	302	n/a	1 (0.4)
KSHS	26674	3 (3-4)	77	n/a	2 (1)
Maccabi	560464	5 (3-7)	15,171	n/a	2 (1)
MESA	4942	2 (2-2)	192	40	4 (1)
MRFIT	11306	4 (4-4)	3,835	2266	22 (7)
NZDCS	4388	4 (3-7)	879	109	6 (2)
Ohasama	996	4 (3-4)	58	13	6 (1)
Pima	786	2 (2-2)	120	24	11 (7)
PREVEND	968	n/a	11	n/a	n/a
RanchoBernardo	477	2 (2-2)	133	50	7 (3)
Severance	3477	3 (2, 4)	62	n/a	11 (2)
Taiwan MJ	71000	3 (2-4)	1,381	241	7 (4)
ZODIAC	784	4 (4-4)	246	94	6 (2)
Sub-Total	**1,027,240**	**5 (4-5)**	**45,208**	**7,891**	**3 (4)**
Total	**1,277,217**	**5 (4-5)**	**102,477**	**8,231**	**3.2 (4.0)**

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. ACM – all-cause mortality; CVM – cardiovascular mortality; SD – standard deviation; #Scre – number of serum creatinine measurements available during antecedent period; IQR – inter-quartile range.

Supplemental Table 5. Cohort characteristics and outcomes for 1- and 2-year antecedent periods

	During 1y Baseline Period		After 1y Baseline Period			During 2y Baseline Period		After 2y Baseline Period		
Cohorts (n=35)	**N**	**Median # Scre (IQR)**	**ACM events**	**CVM events**	**Mean (SD) Follow-up, years**	**N**	**Median # Scre (IQR)**	**ACM events**	**CVM events**	**Mean (SD) Follow-up, years**
CKD cohorts										
AASK	1005	5 (4-5)	153	n/a	7 (3)	913	7 (6-7)	136	n/a	6 (3)
BC CKD	10444	6 (4-8)	2457	n/a	3 (1)	8,644	10 (8-14)	1,797	n/a	3 (1)
CCF	25165	3 (2-5)	3592	n/a	2 (1)	17,140	6 (4-9)	1,749	n/a	1 (1)
CRIB	n/a	n/a	n/a	n/a	n/a	190	2 (2-2)	45	25	5 (2)
Geisinger	18325	4 (3-5)	3071	n/a	4 (2)	14,876	6 (4-9)	2,291	n/a	3 (2)
GLOMMS 1	781	5 (3-7)	391	143	4 (2)	665	8 (6-12)	284	90	3 (1)
KPNW	1192	4 (3-7)	554	n/a	5 (2)	522	7 (4-12)	240	n/a	5 (2)
MASTERPLAN	605	5 (4-5)	99	40	4 (1)	576	8 (7-9)	83	31	4 (1)
MDRD	750	5 (5-5)	334	154	13 (5)	618	8 (7-8)	275	123	13 (4)
NephroTest	579	2 (2-2)	77	11	4 (3)	553	3 (2-3)	62	12	4 (2)
RENAAL	1425	6 (6-6)	265	139	2 (1)	1,201	10 (9-10)	154	77	1 (1)
Sunnybrook	3846	4 (3-6)	757	337	6 (3)	2,657	7 (5-11)	527	227	5 (3)
VA_CKD	457402	3 (2-4)	146278	n/a	4 (2)	350,456	5 (4-7)	98,889	n/a	3 (1)
Sub-Total	**521,519**	**3 (3-3)**	**158,028**	**824**	**4 (2)**	**399,011**	**5 (5-5)**	**106,532**	**585**	**3 (2)**
Other (General Population and High Risk cohorts)										
ADVANCE	10361	3 (3-3)	762	375	4 (1)	9,999	4 (4-4)	557	268	3 (0.5)
Aichi	1805	2 (2-2)	28	n/a	8 (2)	1,812	2 (2-3)	16	n/a	7 (2)
AKDN	309367	2 (2-3)	14250	n/a	2 (1)	293,254	3 (3-4)	9,657	n/a	2 (1)
ARIC	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
CARE	3806	2 (2-2)	279	156	4 (1)	3,681	3 (3-3)	212	125	3 (1)
CHS	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
CIRCS	4638	2 (2-2)	675	n/a	19 (4)	4,461	3 (2-3)	617	n/a	17 (4)
Framingham	n/a	n/a	n/a	n/a	n/a	698	2 (2-2)	71	20	6 (1)
IPHS	64686	2 (2-2)	12138	3,637	13 (3)	62,466	3 (3-3)	11,002	3,249	12 (3)
KP Hawaii	27584	3 (2-4)	1121	n/a	2 (1)	20,629	5 (4-8)	693	n/a	1 (1)
KSHS	32955	2 (2-2)	158	22	3 (2)	63,027	3 (3-5)	174	23	3 (1)
Maccabi	642015	2 (2-3)	25818	n/a	4 (1)	604,670	8 (7-9)	20,241	n/a	4 (1)
MESA	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
MRFIT	11757	2 (2-2)	4125	2,419	24 (8)	11,527	3 (3-3)	3,986	2,344	23 (8)
NZDCS	15748	2 (2-3)	3182	415	6 (2)	9,006	3 (3-5)	1,809	221	6 (2)

Ohasama	1174	2 (2-2)	90	20	7 (2)	1,077	3 (3-3)	65	13	7 (1)
Pima	n/a	n/a	n/a	n/a	n/a	1,606	2 (2-2)	353	67	13 (8)
PREVEND	n/a	n/a	n/a	n/a	n/a	4,740	2 (2-2)	132	32	4 (1)
RanchoBernardo	n/a	n/a	n/a	n/a	n/a	207	2 (2-2)	26	n/a	7 (1)
Severance	5680	2 (2, 2)	120	12	12 (3)	6,263	2 (2, 3)	127	13	12 (2)
Taiwan MJ	111702	2 (2-2)	2895	542	8 (4)	98,845	2 (2-3)	2,041	401	7 (4)
ZODIAC	792	2 (2-2)	310	126	7 (3)	870	3 (3-3)	306	122	7 (3)
Sub-Total	**1,244,070**	**2 (2-2)**	**65,951**	**7,724**	**5 (4)**	**1,198,838**	**3 (3-3)**	**52,085**	**6,898**	**4 (4)**
Total	**1,765,589**	**2 (2-3)**	**223,979**	**8,548**	**4.4 (3.6)**	**1,597,849**	**3 (3-5)**	**158,617**	**7,483**	**3.7 (3.6)**

Characteristics of the chronic kidney disease (CKD, n = 13) and other (general population and high cardiovascular risk, n = 22) and cohorts using 1- and 2-year antecedent periods are shown. ACM – all-cause mortality; CVM – cardiovascular mortality; SD – standard deviation; #Scre – number of serum creatinine measurements available during antecedent period; ICR – inter-quartile range.

Supplemental Table 6. Hazard ratios of all-cause mortality and change in estimated glomerular filtration rate.

Slope change in eGFR (ml/min/1.73m^2/year) during the 3-year baseline period	CKD cohorts	Other (General/high-risk cohorts)
-15 ml	1.96 (1.55, 2.49)	2.16 (1.52, 3.08)
-14 ml	1.93 (1.52, 2.45)	2.10 (1.51, 2.91)
-13 ml	1.81 (1.48, 2.22)	2.02 (1.49, 2.74)
-12 ml	1.70 (1.51, 1.90)	1.94 (1.46, 2.59)
-11 ml	1.60 (1.54, 1.67)	1.88 (1.43, 2.46)
-10 ml	1.52 (1.45, 1.59)	1.74 (1.38, 2.20)
-9 ml	1.43 (1.38, 1.49)	1.57 (1.28, 1.92)
-8 ml	1.36 (1.32, 1.40)	1.41 (1.18, 1.68)
-7 ml	1.31 (1.18, 1.45)	1.27 (1.09, 1.47)
-6 ml	1.25 (1.09, 1.44)	1.15 (1.01, 1.31)
-5 ml	1.20 (1.00, 1.44)	1.07 (0.95, 1.20)
-4 ml	1.11 (0.99, 1.25)	1.06 (0.97, 1.15)
-3 ml	1.02 (0.98, 1.05)	1.05 (0.99, 1.12)
-2 ml	0.98 (0.92, 1.05)	1.01 (0.98, 1.05)
-1 ml	0.93 (0.86, 1.01)	0.96 (0.93, 1.00)
Stable	ref	ref
1 ml	1.07 (0.99, 1.16)	1.03 (0.98, 1.07)
2 ml	1.15 (1.03, 1.29)	1.10 (1.01, 1.20)
3 ml	1.26 (1.02, 1.57)	1.18 (1.02, 1.38)
4 ml	1.33 (1.07, 1.65)	1.24 (1.04, 1.48)
5 ml	1.44 (1.17, 1.78)	1.32 (1.06, 1.64)
6 ml	1.58 (1.29, 1.95)	1.43 (1.11, 1.84)
7 ml	1.83 (1.51, 2.22)	1.59 (1.19, 2.12)
8 ml	1.97 (1.61, 2.41)	1.72 (1.26, 2.35)
9 ml	2.16 (1.73, 2.70)	1.84 (1.30, 2.61)
10 ml	2.31 (1.82, 2.95)	1.98 (1.35, 2.90)

The reference group for calculation of hazard ratios (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 baseline (last) eGFR.

Supplemental Table 7. Absolute risks of all-cause mortality

Follow-up time	Last eGFR	6ml decline	4ml decline	2ml decline	Stable	2ml increase	4ml increase	6ml increase
	CKD cohorts							
1 year	20	4.6%	4.1%	3.7%	3.9%			
	35	2.9%	2.6%	2.3%	2.4%	2.7%	3.1%	3.6%
	50	1.8%	1.6%	1.4%	1.5%	1.7%	2.0%	2.3%
3 year	20	14%	13%	12%	12%	13%	15%	17%
	35	9.3%	8.3%	7.3%	7.6%	8.5%	9.7%	11%
	50	5.9%	5.3%	4.7%	4.8%	5.5%	6.3%	7.4%
5 year	20	28%	25%	23%	24%	26%	29%	33%
	35	18%	17%	15%	15%	17%	19%	22%
	50	12%	11%	9.5%	9.7%	11%	13%	15%
10 year	20	64%	60%	56%	57%	61%	66%	72%
	35	47%	44%	40%	41%	44%	49%	55%
	50	33%	30%	27%	28%	31%	35%	40%
	Other (General Population and High Risk cohorts)							
1 year	65	0.44%	0.39%	0.37%	0.37%	0.39%	0.45%	0.52%
	80	0.47%	0.43%	0.41%	0.41%	0.45%	0.50%	0.58%
	95	0.51%	0.46%	0.45%	0.44%	0.50%	0.57%	0.65%
3 year	65	1.7%	1.5%	1.5%	1.5%	1.6%	1.8%	2.1%
	80	1.9%	1.7%	1.6%	1.6%	1.8%	2.0%	2.3%
	95	2.0%	1.8%	1.8%	1.8%	2.0%	2.3%	2.6%
5 year	65	3.3%	2.9%	2.8%	2.8%	3.0%	3.4%	3.9%
	80	3.5%	3.2%	3.1%	3.0%	3.3%	3.7%	4.3%
	95	3.8%	3.5%	3.4%	3.3%	3.8%	4.3%	4.9%
10 year	65	9.3%	8.3%	7.9%	7.9%	8.5%	9.6%	11%
	80	9.9%	9.1%	8.8%	8.7%	9.5%	11%	12%
	95	11%	10%	10%	9.4%	11%	12%	14%

Absolute, all-cause mortality (ACM) risk at 1, 3, 5, and 10 years after the 3-year baseline period are depicted for the general population and high cardiovascular risk (GH) and chronic kidney disease (CKD) cohorts. Absolute risks were calculated using the adjusted HR for eGFR slopes of -6, -4, -2, 0, 2, 4, and 6 ml/min/1.73m^2/yr calculated from a 3-year baseline periods and the base-case hazard associated with the cohort. The base-case cumulative hazard of ACM at one year past the baseline period was calculated for the following set of covariates: a 60 year-old non-black man with no change in eGFR, a last eGFR of 50 ml/min/1.73m^2, a systolic blood pressure of 130 mm Hg, a total cholesterol of 5 mmol/L, and no history of diabetes or CV disease.

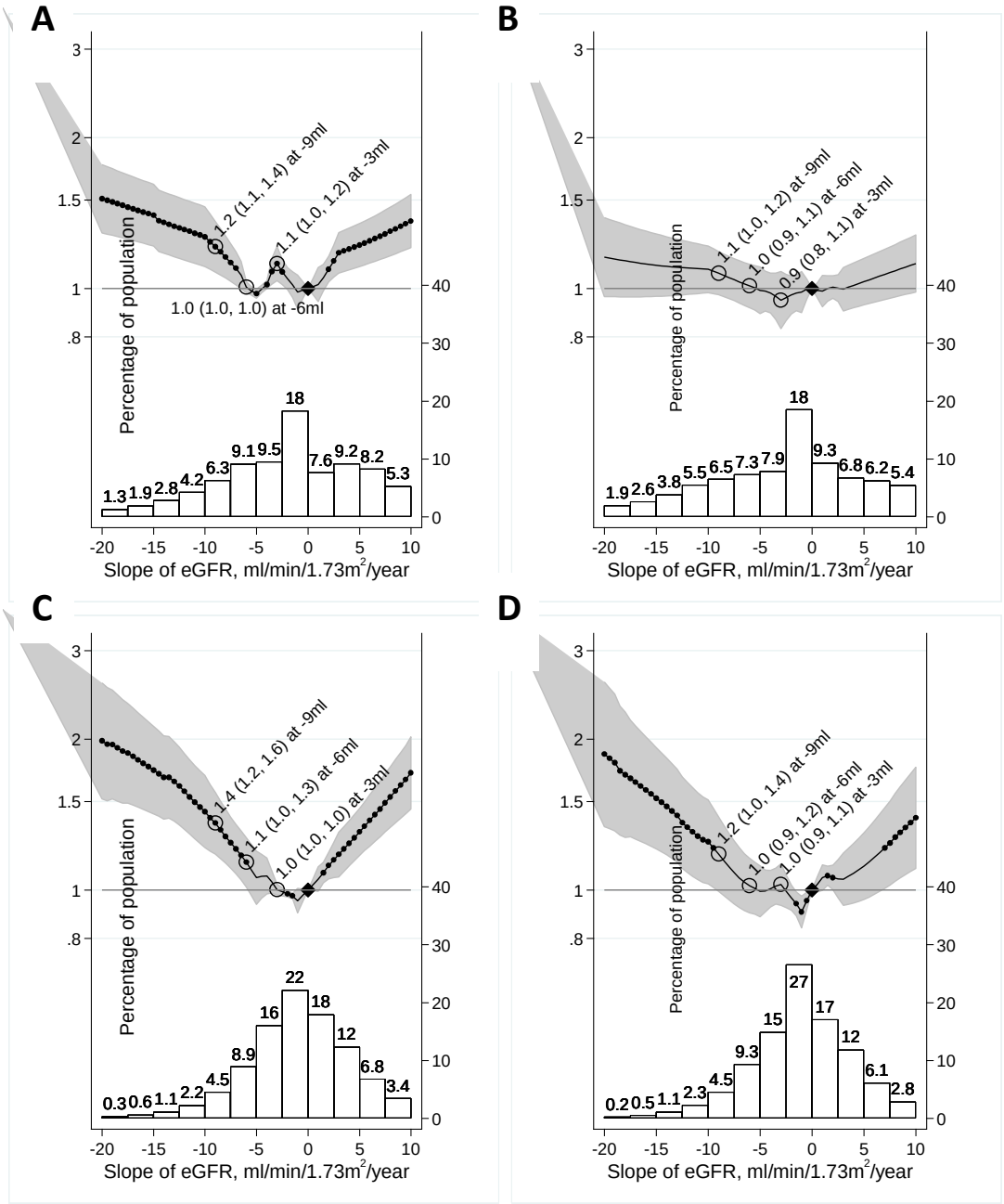
Supplemental Table 8. Change in concordance statistics after including estimated glomerular filtration rate (eGFR) slope in the model

Study	Delta c-stat.	95% confidence interval		% Weight
CKD cohorts				
AASK	0.006	-0.010	0.021	4.08
BC CKD	0.005	0.001	0.008	12.37
CCF	0.019	0.007	0.031	5.89
Geisinger	0.003	0.000	0.006	12.75
GLOMMS1	0.006	-0.002	0.014	8.30
KPNW	0.001	-0.019	0.021	2.78
MASTERPLAN	0.001	-0.012	0.014	5.19
MDRD	-0.005	-0.010	-0.001	11.88
NephroTest	0.008	-0.017	0.033	1.91
RENAAL	-0.003	-0.013	0.006	7.56
Sunnybrook	-0.001	-0.002	0.001	13.50
VA_CKD	0.007	0.007	0.008	13.77
Pooled estimate	0.003	-0.001	0.007	100.00
Other (General Population/High Risk cohorts)				
ADVANCE	0.002	-0.003	0.008	4.36
Aichi	-0.005	-0.023	0.014	0.59
ARIC	0.000	0.000	0.001	9.40
CARE	0.001	-0.010	0.012	1.54
CHS	0.002	0.000	0.003	8.57
CIRCS	0.000	-0.001	0.001	9.15
Framingham	0.012	-0.011	0.036	0.39
IPHS	0.000	0.000	0.000	9.49
KP Hawaii	0.023	0.011	0.034	1.42
KSHS	-0.005	-0.029	0.019	0.37
Maccabi	0.008	0.008	0.009	9.23
MESA	0.003	-0.002	0.008	4.51
MRFIT	0.001	0.000	0.002	9.01
NZDCS	0.001	-0.003	0.005	5.39
Ohasama	0.009	-0.006	0.024	0.91
Pima	-0.001	-0.012	0.009	1.71
PREVEND	0.002	-0.014	0.017	0.81
RanchoBernardo	0.002	0.000	0.003	8.18
Severance	0.009	-0.005	0.023	0.97
Taiwan MJ	0.001	0.000	0.002	9.13
ZODIAC	0.002	-0.003	0.007	4.86
Pooled estimate	0.002	0.001	0.004	100.00

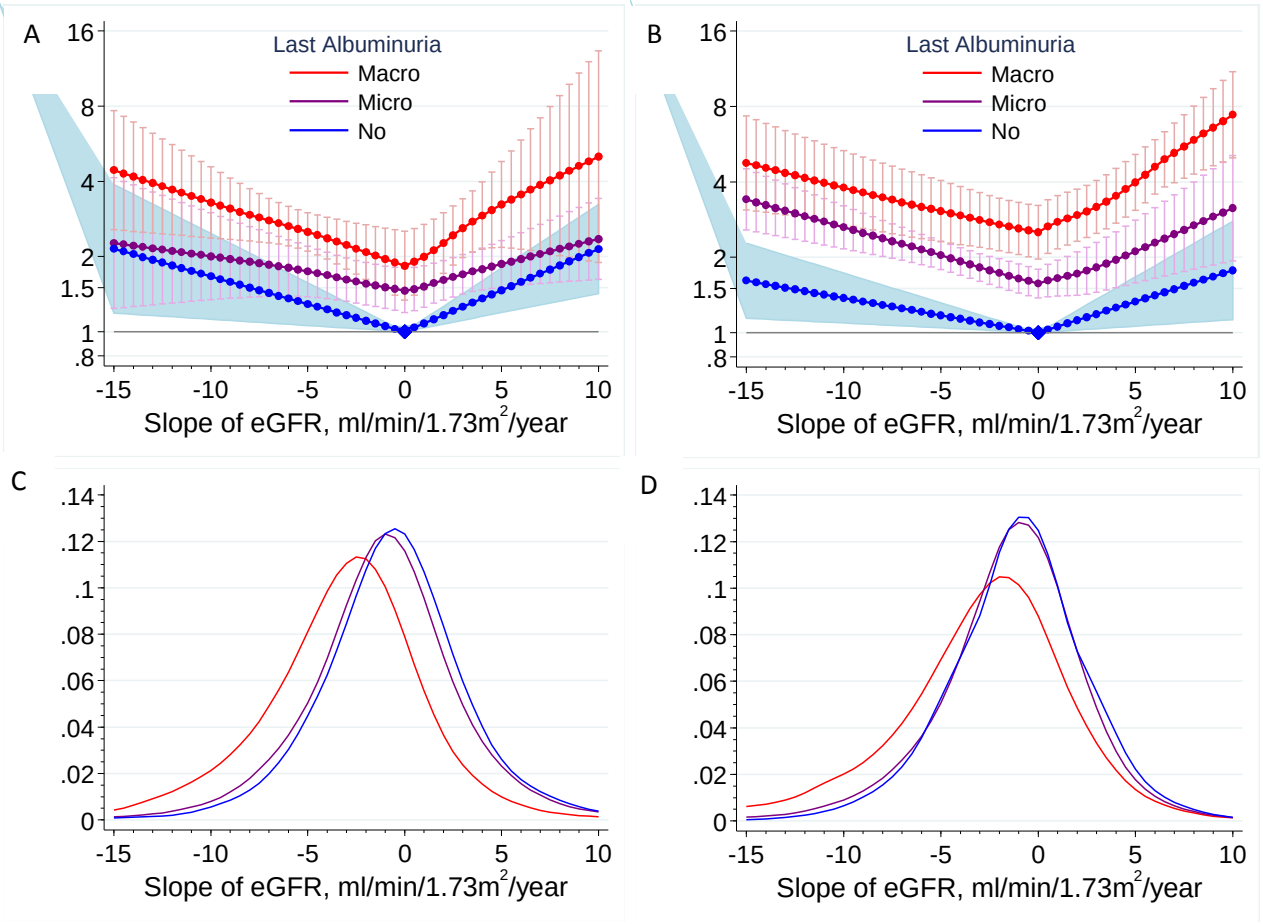
Values in the table represent the change in the proportion of concordant among all possible evaluable pairs of subjects (delta c-stat.) for a Cox regression model adjusted for age, sex, race (blacks vs. non-blacks), systolic blood pressure, total cholesterol, diabetes, history of CVD, and baseline (last) eGFR compared to a model with the same adjustment factors but which also included prior eGFR slope observed within a 3-year antecedent period. Pooled estimates across chronic kidney disease (CKD) and other (general population/high risk) cohorts were obtained using the random effects, DerSimonian and Laird, method.

For the CKD cohorts, Heterogeneity chi-squared = 131.44 (d.f. = 11) p = 0.000, I-squared (variation in delta c-stat. attributable to heterogeneity) = 91.6; Estimate of between-study variance Tau-squared = 0.0000; Test of delta c-stat.=0 : z= 1.77 p = 0.077. For the other cohorts, Heterogeneity chi-squared = 401.13 (d.f. = 20) p = 0.000; I-squared (variation in delta c-stat attributable to heterogeneity) = 95.0%; Estimate of between-study variance Tau-squared = 0.0000; Test of delta c-stat =0 : z= 2.79 p = 0.005.

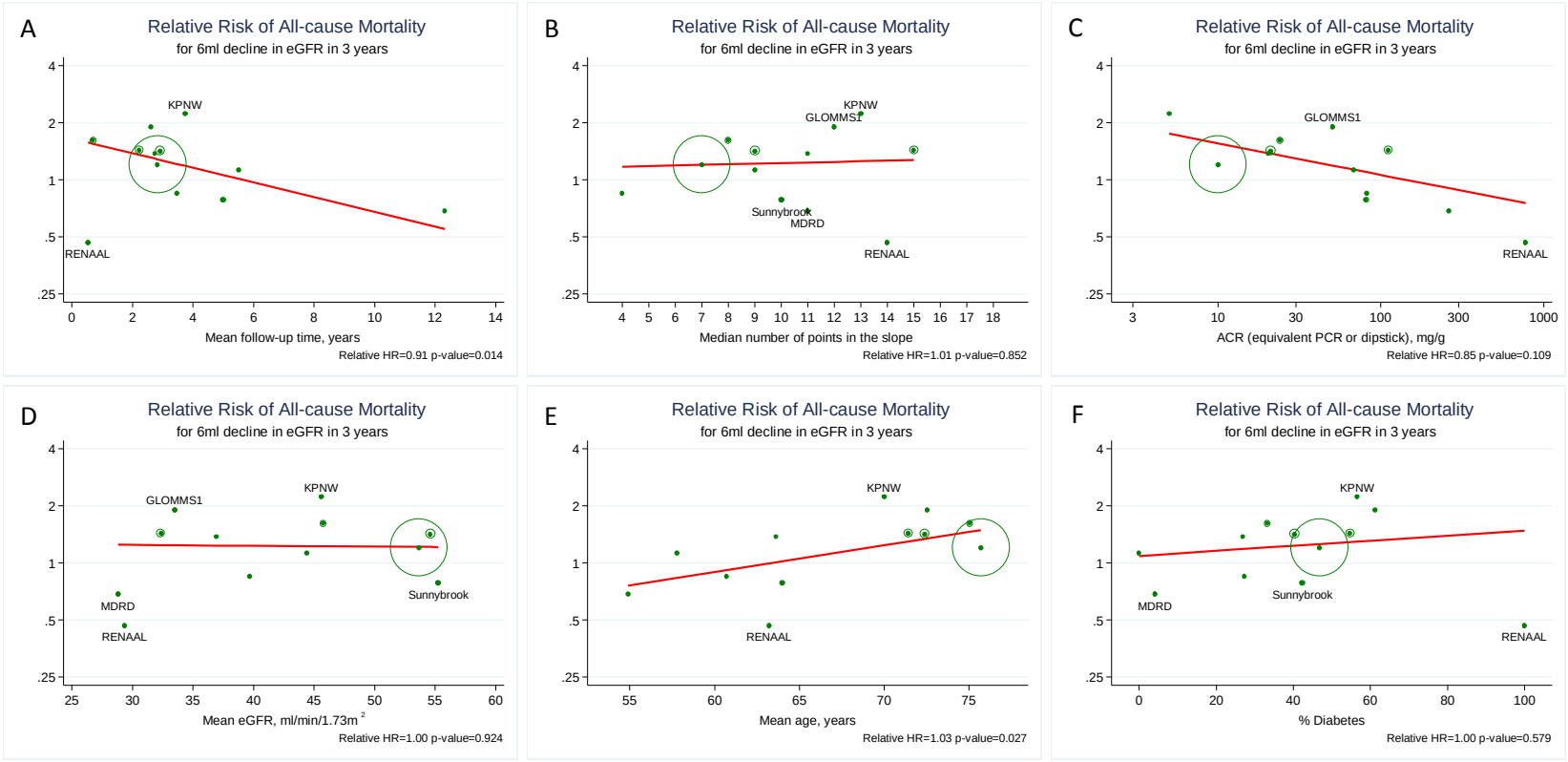
Supplemental Figure 1. Adjusted hazard ratios (HR) for all-cause mortality (ACM) by annualized estimated glomerular filtration rate (eGFR) slope subsequent to 1- and 2-year antecedent periods. Results for analyses using one (A, B) and two-year (C, D) antecedent periods are shown in panels A, B and C, D, respectively, for CKD (A, C) and other (B, D) cohorts: other - general population and CV high-risk cohorts; CKD – chronic kidney disease cohorts. Histograms underneath the risk curves indicate that distribution of the cohorts within each eGFR slope category. HRs for ACM were adjusted for age, sex, race (blacks *vs*. non-blacks), systolic blood pressure, total cholesterol, diabetes, history of CVD, and last eGFR



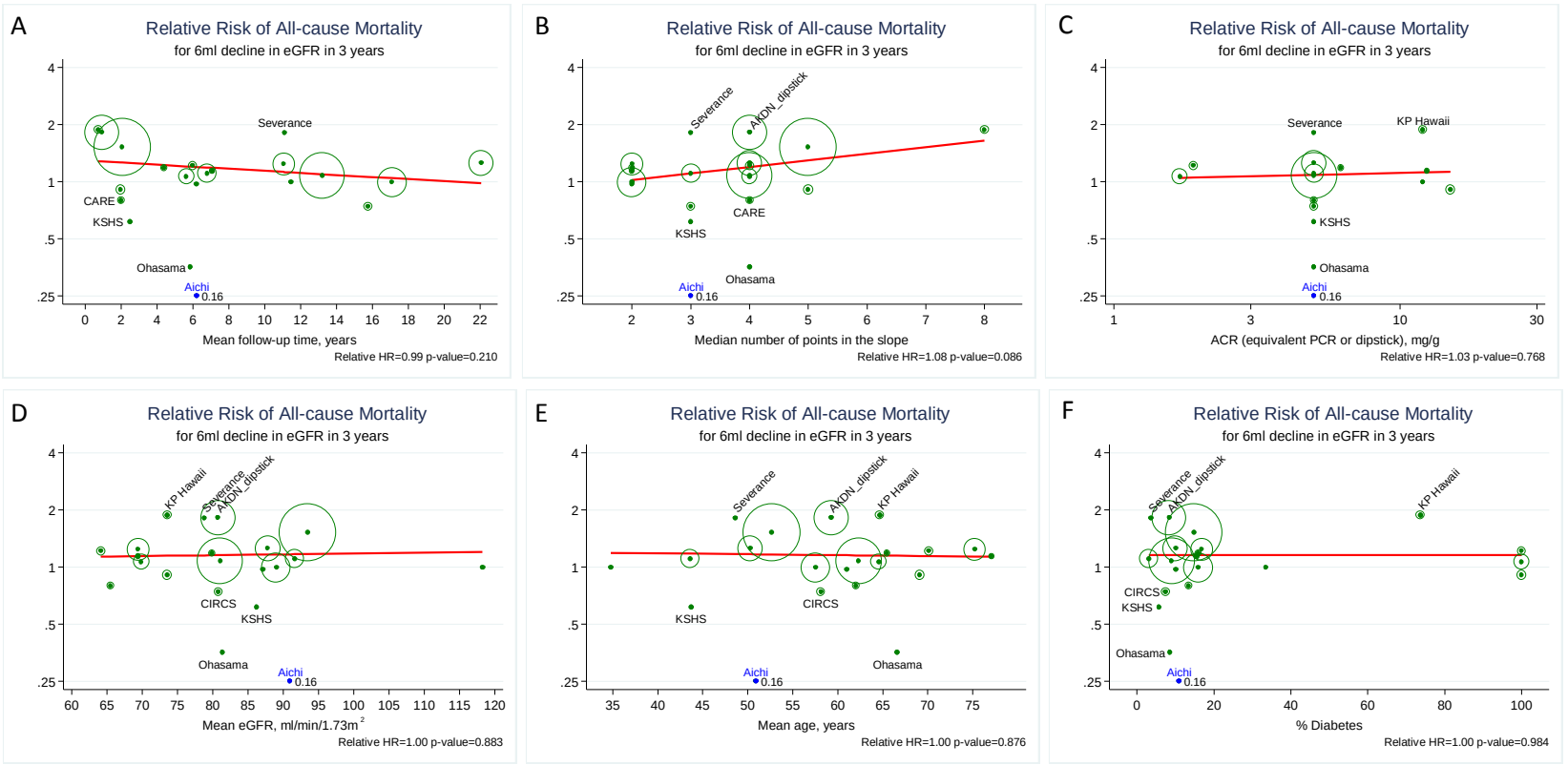
Supplemental Figure 2. Interaction model for albuminuria and eGFR slope for both other (general/high risk) and CKD cohorts. Adjusted hazard ratios (HR) for all-cause mortality (ACM) by annualized estimated glomerular filtration rate (eGFR) slope during a 3-year antecedent period are shown for three different albuminuria strata (macro- [severely increased], micro- [moderately increased], and no albuminuria) for both CKD (A) and other (B) cohorts: general/high risk - general population and CV high-risk cohorts; CKD – chronic kidney disease cohorts. HRs for ACM were adjusted for age, sex, race (blacks *vs*. non-blacks), systolic blood pressure, total cholesterol, diabetes, history of CVD, and last eGFR. Kernel density plots indicate the distribution by eGFR slope and albuminuria strata for both CKD (C) and other (D) cohorts.



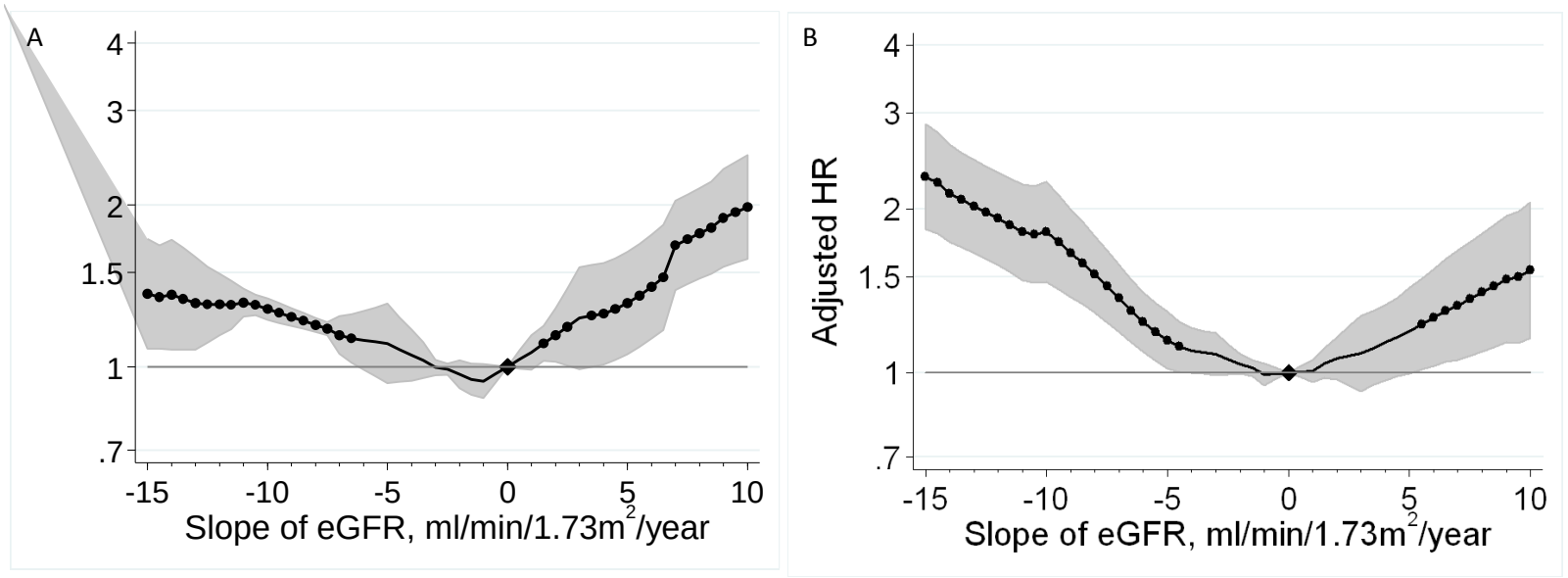
Supplemental Figure 3. Meta-regression among CKD cohorts – **A.** mean follow-up time, **B.** median number of creatinine measurements, **C.** median ACR, **D**. Baseline eGFR, **E.** mean age, **F.** percent with diabetes. adjusted hazard ratios (HR) for all-cause mortality (ACM) subsequent to an estimated glomerular filtration rate (eGFR) slope of -6ml/min/1.73m^2/yr during a 3-year antecedent period are shown. HRs for ACM were adjusted for age, sex, race (blacks *vs*. non-blacks), systolic blood pressure, total cholesterol, diabetes, history of CVD, and last eGFR. ACR – urine albumin to creatinine ratio in mg/g. Sizes of green circles are proportional to the inverse of the variance of the log hazard ratio. Cohort names listed when the distance is more than 30% from the regression line.



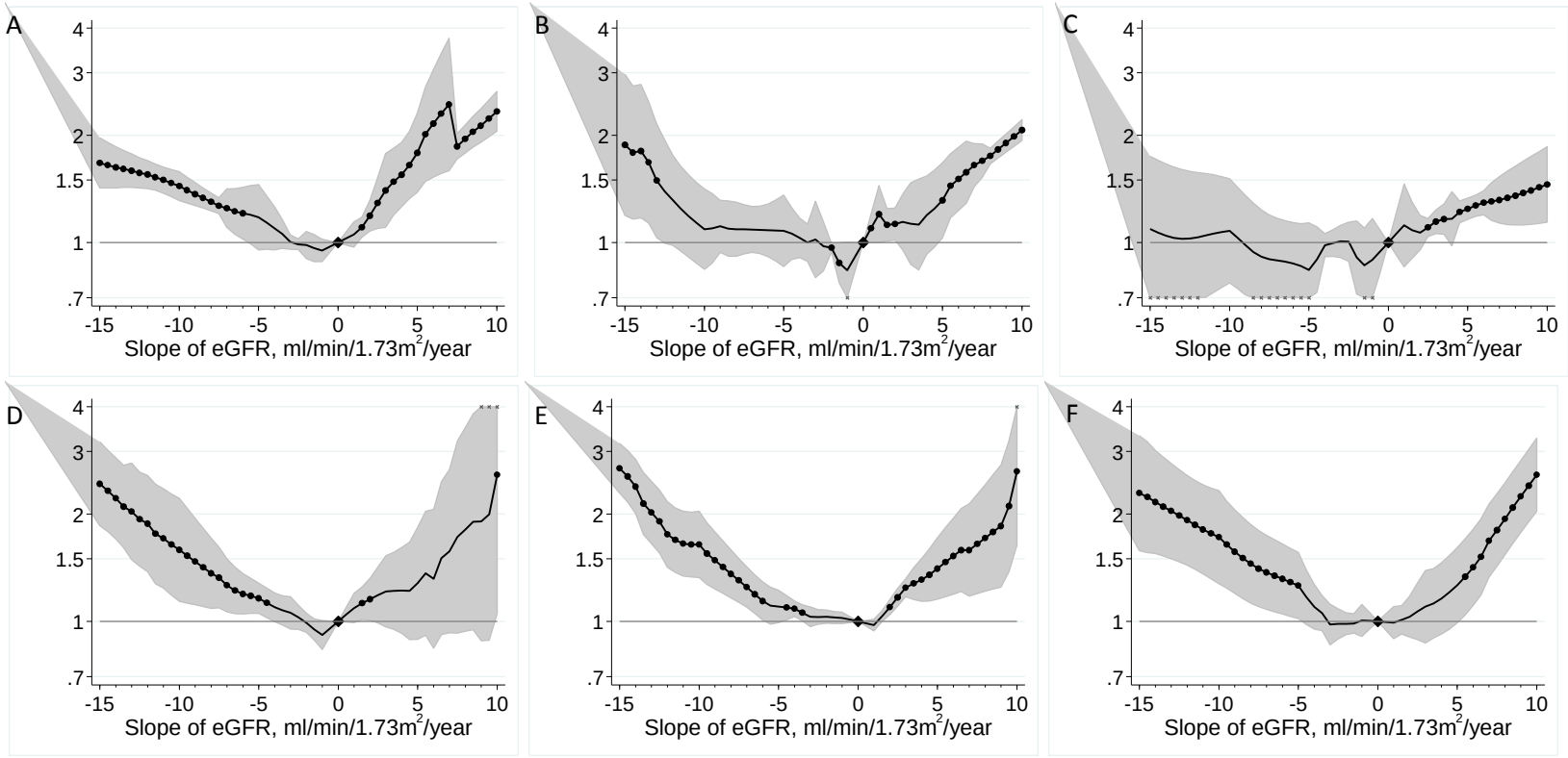
Supplemental Figure 4. Meta-regression among other (general population/high risk) cohorts – **A.** mean follow-up time, **B.** median number of creatinine measurements, **C.** median ACR, **D**. Baseline eGFR, **E.** mean age, **F.** percent with diabetes. Adjusted hazard ratios (HR) for all-cause mortality (ACM) subsequent to an estimated glomerular filtration rate (eGFR) slope of -6ml/min/1.73m^2/yr during a 3-year antecedent period are shown. HRs for ACM were adjusted for age, sex, race (blacks *vs*. non-blacks), systolic blood pressure, total cholesterol, diabetes, history of CVD, and last eGFR. ACR – urine albumin to creatinine ratio in mg/g. Sizes of green circles are proportional to the inverse of the variance of the log hazard ratio. Cohort names listed when the distance is more than 30% from the regression line. Effect size out of the range of y-axis listed as blue text.



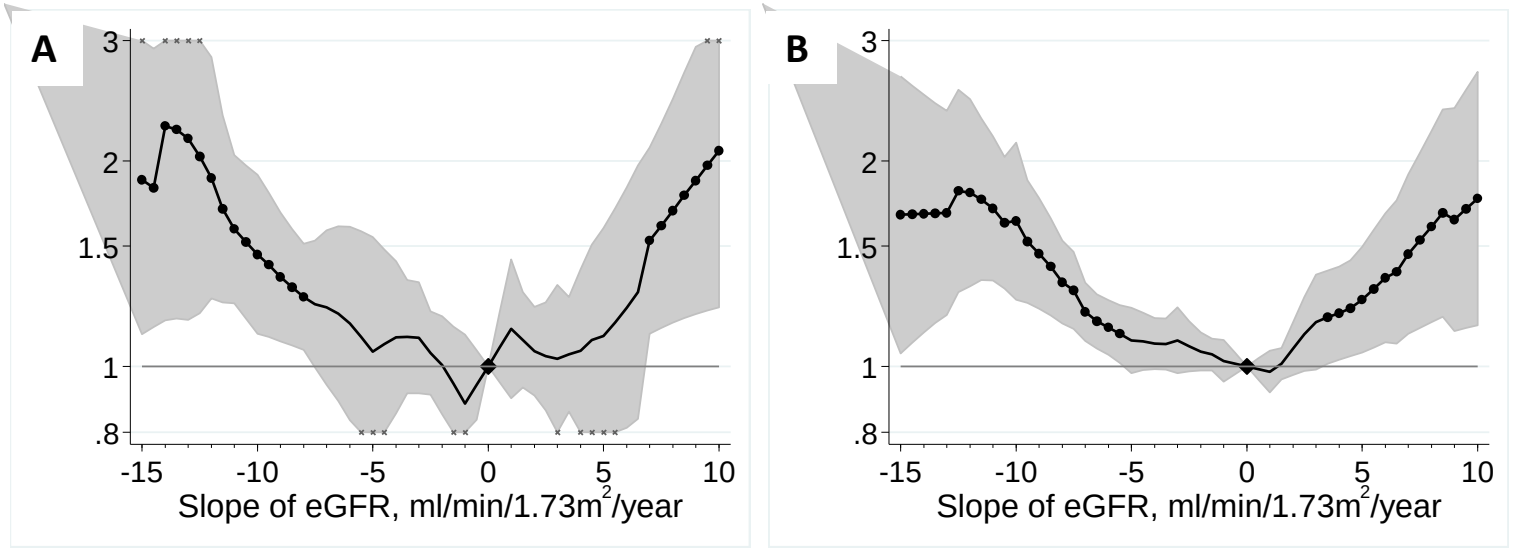
Supplemental Figure 5. Adjusted hazard ratios (HR) for all-cause mortality (ACM) subsequent to an estimated glomerular filtration (eGFR) slope during a 3-year antecedent period including root mean squared error (RMSE) as a covariate and by cohort type (CKD, A vs. other - general/high risk, B) – The HRs associated with eGFR slope for ACM were adjusted for age, sex, race (blacks vs. non-blacks), systolic blood pressure, total cholesterol, diabetes, history of CVD, RMSE and baseline (last) eGFR. general/high risk - general population and high cardiovascular risk cohorts; CKD - chronic kidney disease cohorts.



Supplemental Figure 6. Adjusted hazard ratios (HR) for all-cause mortality (ACM) subsequent to an estimated glomerular filtration (eGFR) slope during a 3-year antecedent period stratified by root mean squared error (RMSE) (RMSE<5, A, D; RMSE 5-10, B, E; RMSE>10, C, F) and by cohort type (CKD, A-C vs. other - general/high risk, D-E) – The HRs associated with eGFR slope for ACM were adjusted for age, sex, race (blacks *vs*. non-blacks), systolic blood pressure, total cholesterol, diabetes, history of CVD, and baseline (last) eGFR. general/high risk - general population and high cardiovascular risk cohorts; CKD - chronic kidney disease cohorts.



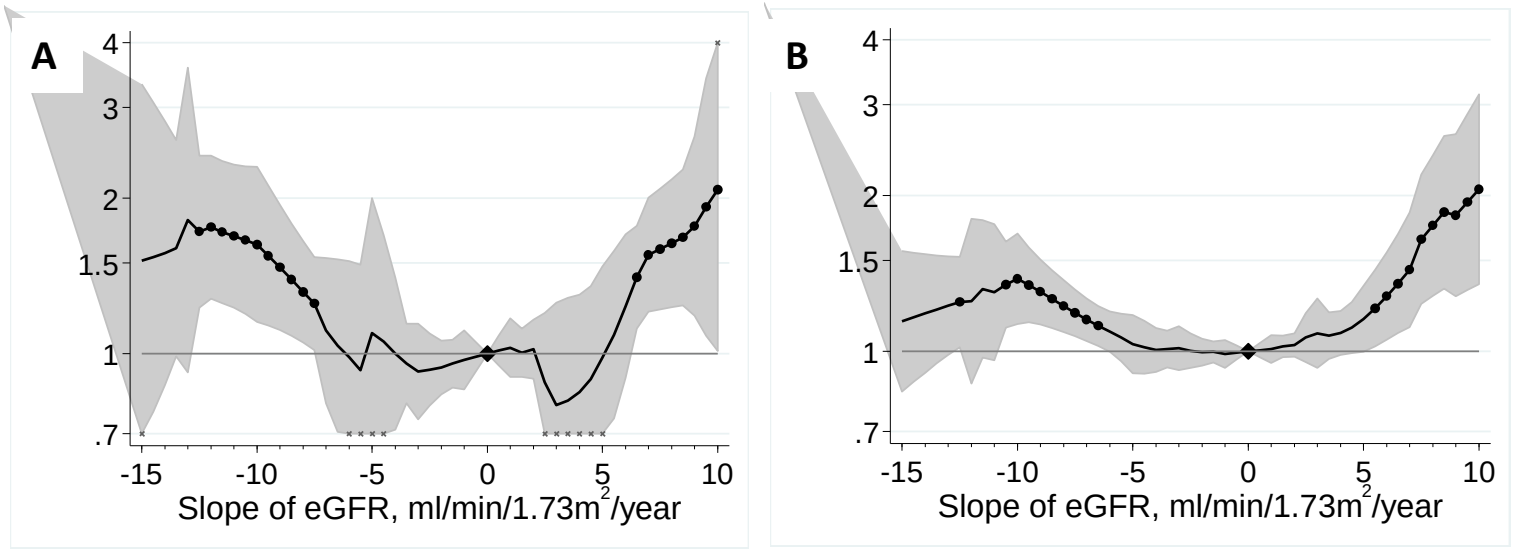
Supplemental Figure 7. Effect of weight loss on the analytical results – Adjusted hazard ratios (HR) for all-cause mortality (ACM) subsequent to an estimated glomerular filtration rate (eGFR) slope during a 3-year antecedent period are shown after exclusion of subjects with a weight loss of >= 2.0 kg over the antecedent period for both CKD or (**A)** or other - general/high risk (**B**) cohorts. Multiple logistic regression analysis for the adjusted odds-ratios associated with weight changes over the antecedent period for either an eGFR slope less than – 5 or greater than +5 ml/min/1.73m^2/yr is shown in Panel **C**. **–** The HRs associated with eGFR slope for ACM were adjusted for age, sex, race (blacks *vs*. non-blacks), systolic blood pressure, total cholesterol, diabetes, history of CVD, and baseline (last) eGFR. CKD - chronic kidney disease cohorts; Other - general population and high cardiovascular risk cohorts;.



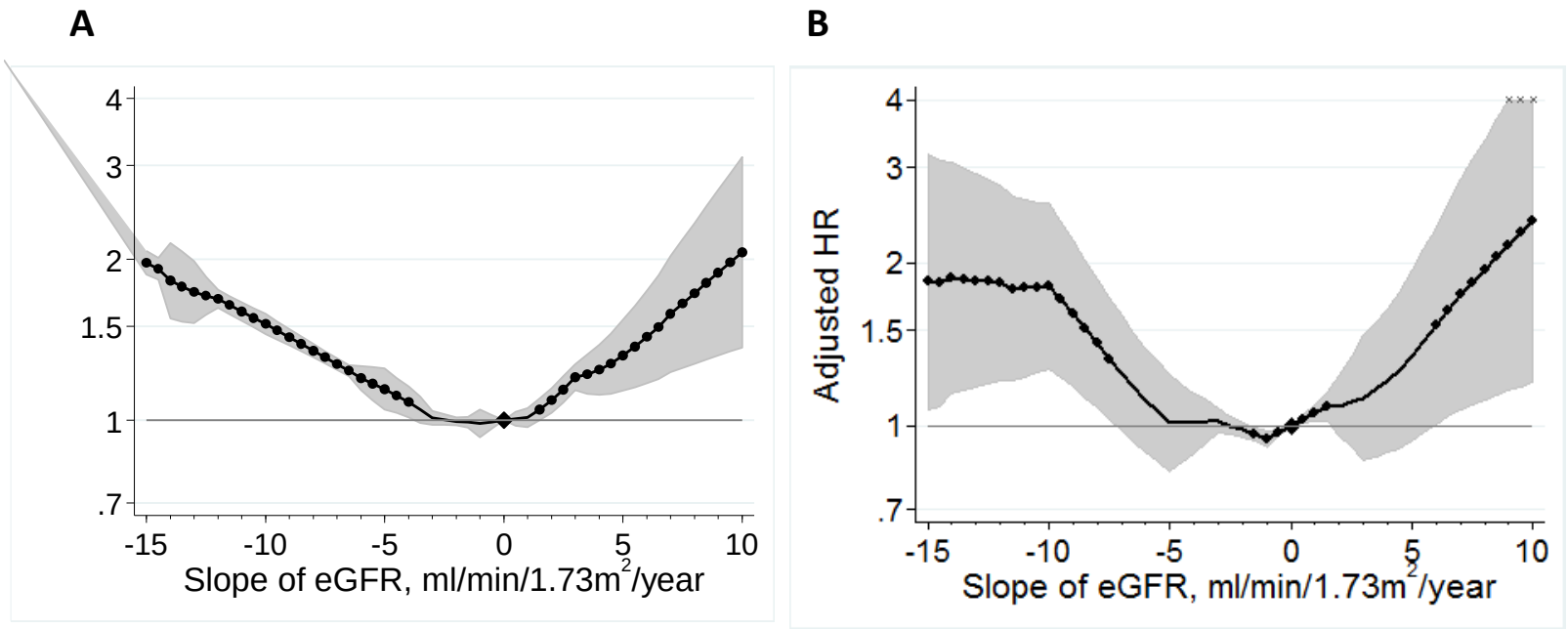
C

Variables	slope <-5ml/y vs. slope ≥-5ml/y to ≤5ml/y		slope >5ml/y vs. slope ≥-5ml/y to ≤5ml/y	
	CKD Cohorts	Other - general/high risk Cohorts	CKD Cohorts	Other - general/high risk cohorts
Body weight loss >2 kg	2.00 (1.84, 2.18)	1.12 (0.76, 1.67)	15.99 (14.48, 17.66)	1.97 (1.04, 3.72)
Body weight gain >2 kg	2.12 (0.27, 16.80)	1.91 (1.30, 2.80)	7.46 (6.61, 8.42)	1.00 (0.65, 1.54)

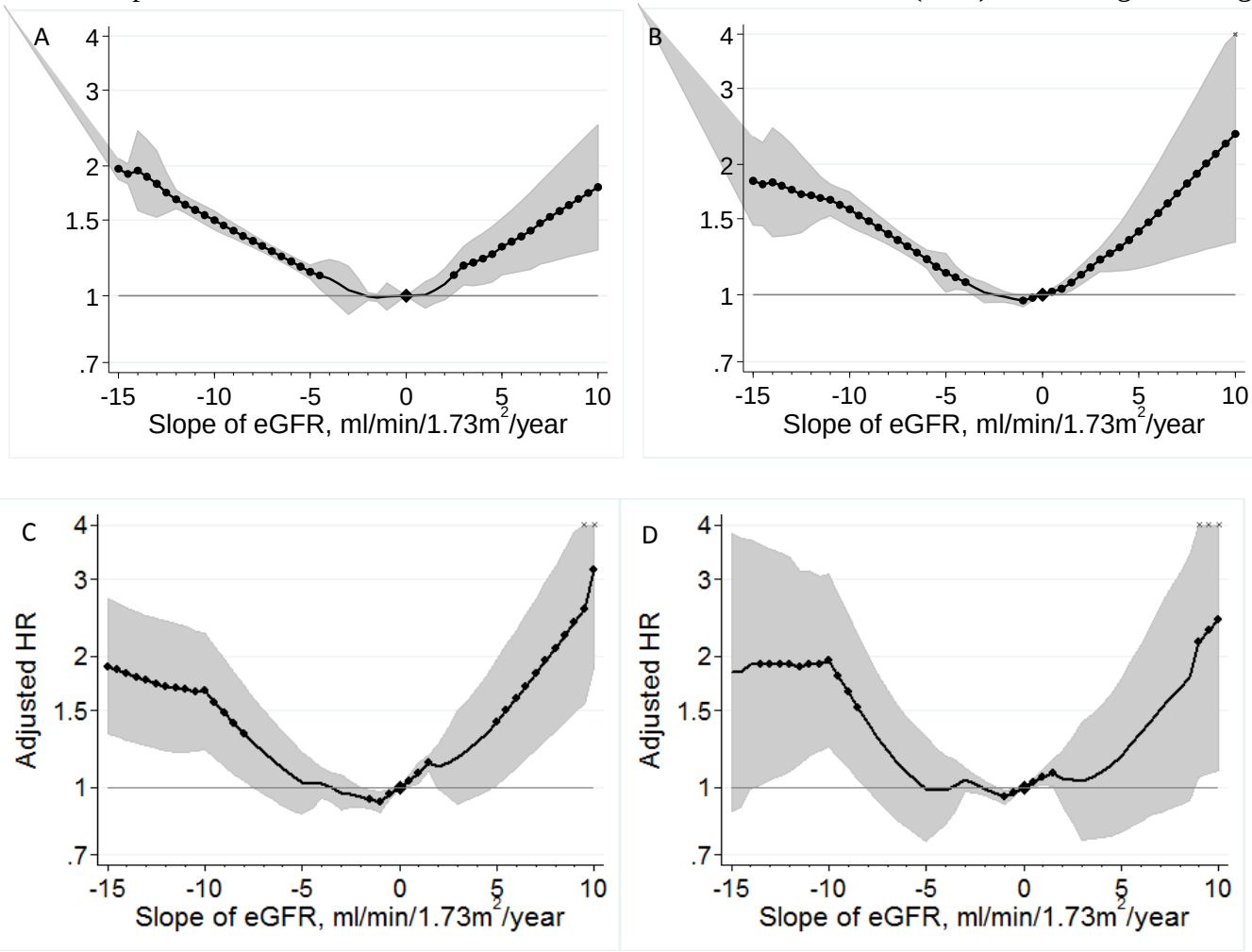
Supplemental Figure 8. Effect of diabetes status on the analytical results – Adjusted hazard ratios (HR) for all-cause mortality (ACM) subsequent to an estimated glomerular filtration rate (eGFR) slope during a 3-year antecedent period are shown after exclusion of subjects with diabetes for both CKD (**A)** or other - general/high risk (**B**) cohorts (among the 14 cohorts with available data). The HRs associated with eGFR slope for ACM were adjusted for age, sex, race (blacks *vs*. non-blacks), systolic blood pressure, total cholesterol, history of CVD, and baseline (last) eGFR. general/high risk - general population and high cardiovascular risk cohorts; CKD - chronic kidney disease cohorts.



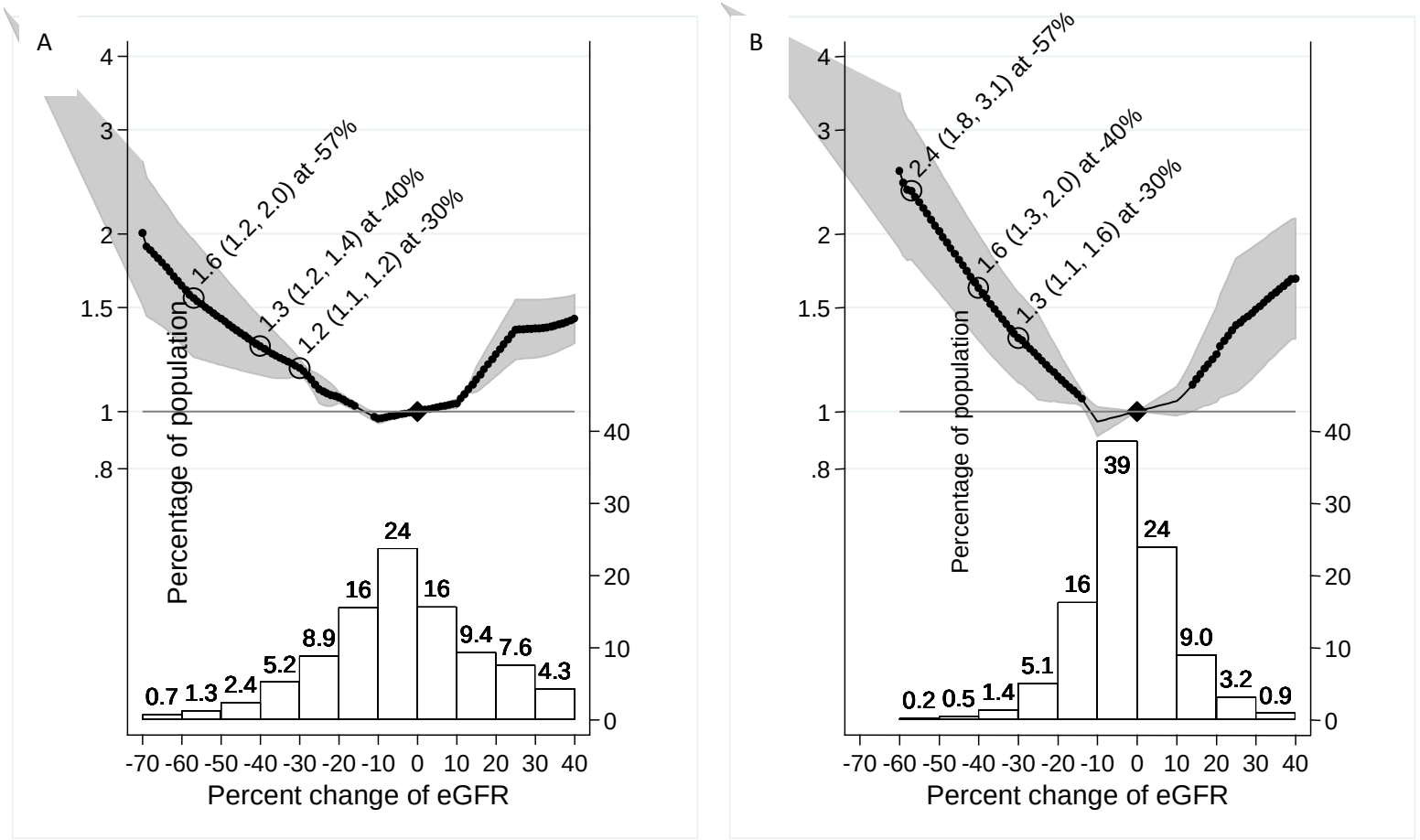
Supplemental Figure 9. Effect of renin-angiotensin system blockade inhibitor (RASi) use on the analytical results (adjustment) – Adjusted hazard ratios (HR) for all-cause mortality (ACM) subsequent to an estimated glomerular filtration rate (eGFR) slope during a 3-year antecedent period are shown after inclusion of RASi exposure within the antecedent period as a covariate in the Cox model are shown for both CKD (**A)** or other - general/high risk (**B**) cohorts.



Supplemental Figure 10. Effect of renin-angiotensin system blockade inhibitor (RASi) use on the analytical results (stratification) – Adjusted hazard ratios (HR) for all-cause mortality (ACM) subsequent to an estimated glomerular filtration rate (eGFR) slope during a 3-year antecedent period are shown for persons with **(A, C)** and without **(B, D)** RASi exposure within the antecedent period as a covariate in the Cox model are shown for both CKD (**A, B)** or other - general/high risk (**C, D**) cohorts



Supplemental Figure 11. Adjusted hazard ratios (HR) for all-cause mortality (ACM) by percent change in estimated glomerular filtration rate (eGFR) subsequent to 3-year antecedent periods. Results for CKD **(A)** and other – general population/high risk **(B)** cohorts: general/high risk - general population and CV high-risk cohorts; CKD – chronic kidney disease cohorts. Histograms underneath the risk curves indicate that distribution of the cohorts within each percent change in eGFR category. HRs for ACM were adjusted for age, sex, race (blacks *vs*. non-blacks), systolic blood pressure, total cholesterol, diabetes, history of CVD, and last eGFR



References

1. Wright, JT, Jr., Bakris, G, Greene, T, Agodoa, LY, Appel, LJ, Charleston, J, Cheek, D, Douglas-Baltimore, JG, Gassman, J, Glassock, R, Hebert, L, Jamerson, K, Lewis, J, Phillips, RA, Toto, RD, Middleton, JP, Rostand, SG: Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA,* 288**:** 2421-2431, 2002.
2. Patel, A, MacMahon, S, Chalmers, J, Neal, B, Woodward, M, Billot, L, Harrap, S, Poulter, N, Marre, M, Cooper, M, Glasziou, P, Grobbee, DE, Hamet, P, Heller, S, Liu, LS, Mancia, G, Mogensen, CE, Pan, CY, Rodgers, A, Williams, B: Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet,* 370**:** 829-840, 2007.
3. Mitsuhashi, H, Yatsuya, H, Matsushita, K, Zhang, H, Otsuka, R, Muramatsu, T, Takefuji, S, Hotta, Y, Kondo, T, Murohara, T, Toyoshima, H, Tamakoshi, K: Uric acid and left ventricular hypertrophy in Japanese men. *Circ J,* 73**:** 667-672, 2009.
4. Hemmelgarn, BR, Clement, F, Manns, BJ, Klarenbach, S, James, MT, Ravani, P, Pannu, N, Ahmed, SB, MacRae, J, Scott-Douglas, N, Jindal, K, Quinn, R, Culleton, BF, Wiebe, N, Krause, R, Thorlacius, L, Tonelli, M: Overview of the Alberta Kidney Disease Network. *BMC Nephrol,* 10**:** 30, 2009.
5. Matsushita, K, Selvin, E, Bash, LD, Franceschini, N, Astor, BC, Coresh, J: Change in estimated GFR associates with coronary heart disease and mortality. *J Am Soc Nephrol,* 20**:** 2617-2624, 2009.
6. Levin, A, Djurdjev, O, Beaulieu, M, Er, L: Variability and risk factors for kidney disease progression and death following attainment of stage 4 CKD in a referred cohort. *Am J Kidney Dis,* 52**:** 661-671, 2008.
7. Tonelli, M, Jose, P, Curhan, G, Sacks, F, Braunwald, E, Pfeffer, M: Proteinuria, impaired kidney function, and adverse outcomes in people with coronary disease: analysis of a previously conducted randomised trial. *BMJ,* 332**:** 1426, 2006.
8. Schold, JD, Navaneethan, SD, Jolly, SE, Poggio, ED, Arrigain, S, Saupe, W, Jain, A, Sharp, JW, Simon, JF, Schreiber, MJ, Jr., Nally, JV, Jr.: Implications of the CKD-EPI GFR estimation equation in clinical practice. *Clin J Am Soc Nephrol,* 6**:** 497-504, 2011.
9. Shlipak, MG, Katz, R, Kestenbaum, B, Fried, LF, Newman, AB, Siscovick, DS, Stevens, L, Sarnak, MJ: Rate of kidney function decline in older adults: a comparison using creatinine and cystatin C. *Am J Nephrol,* 30**:** 171-178, 2009.
10. Shimizu, Y, Maeda, K, Imano, H, Ohira, T, Kitamura, A, Kiyama, M, Okada, T, Ishikawa, Y, Shimamoto, T, Yamagishi, K, Tanigawa, T, Iso, H: Chronic kidney disease and drinking status in relation to risks of stroke and its subtypes: the Circulatory Risk in Communities Study (CIRCS). *Stroke,* 42**:** 2531-2537, 2011.
11. Landray, MJ, Thambyrajah, J, McGlynn, FJ, Jones, HJ, Baigent, C, Kendall, MJ, Townend, JN, Wheeler, DC: Epidemiological evaluation of known and suspected cardiovascular risk factors in chronic renal impairment. *Am J Kidney Dis,* 38**:** 537-546, 2001.
12. Parikh, NI, Hwang, S-J, Larson, MG, Levy, D, Fox, CS: Chronic Kidney Disease as a Predictor of Cardiovascular Disease (from the Framingham Heart Study). *Am J Cardiol,* 102**:** 47-53, 2008.
13. Perkins, RM, Bucaloiu, ID, Kirchner, HL, Ashouian, N, Hartle, JE, Yahya, T: GFR decline and mortality risk among patients with chronic kidney disease. *Clin J Am Soc Nephrol,* 6**:** 1879-1886, 2011.
14. Marks, A, Black, C, Fluck, N, Smith, WC, Prescott, GJ, Clark, LE, Ali, TZ, Simpson, WG, MacLeod, AM: Translating chronic kidney disease epidemiology into patient care--the individual/public health risk paradox. *Nephrol Dial Transplant,* 27 Suppl 3**:** iii65-72, 2012.

15. Noda, H, Iso, H, Irie, F, Sairenchi, T, Ohtaka, E, Doi, M, Izumi, Y, Ohta, H: Low-density lipoprotein cholesterol concentrations and death due to intraparenchymal hemorrhage: the Ibaraki Prefectural Health Study. *Circulation,* 119**:** 2136-2145, 2009.
16. Lee, BJ, Forbes, K: The role of specialists in managing the health of populations with chronic illness: the example of chronic kidney disease. *BMJ,* 339**:** b2395, 2009.
17. Keith, DS, Nichols, GA, Gullion, CM, Brown, JB, Smith, DH: Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med,* 164**:** 659-663, 2004.
18. Shalev, V, Chodick, G, Goren, I, Silber, H, Kokia, E, Heymann, AD: The use of an automated patient registry to manage and monitor cardiovascular conditions and related outcomes in a large health organization. *Int J Cardiol,* 152**:** 345-349, 2011.
19. van Zuilen, AD, Bots, ML, Dulger, A, van der Tweel, I, van Buren, M, Ten Dam, MA, Kaasjager, KA, Ligtenberg, G, Sijpkens, YW, Sluiter, HE, van de Ven, PJ, Vervoort, G, Vleming, LJ, Blankestijn, PJ, Wetzels, JF: Multifactorial intervention with nurse practitioners does not change cardiovascular outcomes in patients with chronic kidney disease. *Kidney Int,* 82**:** 710-717, 2012.
20. Klahr, S, Levey, AS, Beck, GJ, Caggiula, AW, Hunsicker, L, Kusek, JW, Striker, G: The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl J Med,* 330**:** 877-884, 1994.
21. Bild, DE, Bluemke, DA, Burke, GL, Detrano, R, Diez Roux, AV, Folsom, AR, Greenland, P, Jacob, DR, Jr., Kronmal, R, Liu, K, Nelson, JC, O'Leary, D, Saad, MF, Shea, S, Szklo, M, Tracy, RP: Multi-ethnic study of atherosclerosis: objectives and design. *Am J Epidemiol,* 156**:** 871-881, 2002.
22. Ishani, A, Grandits, GA, Grimm, RH, Svendsen, KH, Collins, AJ, Prineas, RJ, Neaton, JD: Association of single measurements of dipstick proteinuria, estimated glomerular filtration rate, and hematocrit with 25-year incidence of end-stage renal disease in the multiple risk factor intervention trial. *J Am Soc Nephrol,* 17**:** 1444-1452, 2006.
23. Moranne, O, Froissart, M, Rossert, J, Gauci, C, Boffa, JJ, Haymann, JP, M'Rad M, B, Jacquot, C, Houillier, P, Stengel, B, Fouqueray, B: Timing of onset of CKD-related metabolic complications. *J Am Soc Nephrol,* 20**:** 164-171, 2009.
24. Elley, CR, Kenealy, T, Robinson, E, Drury, PL: Glycated haemoglobin and cardiovascular outcomes in people with Type 2 diabetes: a large prospective cohort study. *Diabet Med,* 25**:** 1295-1301, 2008.
25. Nakayama, M, Metoki, H, Terawaki, H, Ohkubo, T, Kikuya, M, Sato, T, Nakayama, K, Asayama, K, Inoue, R, Hashimoto, J, Totsune, K, Hoshi, H, Ito, S, Imai, Y: Kidney dysfunction as a risk factor for first symptomatic stroke events in a general Japanese population--the Ohasama study. *Nephrol Dial Transplant,* 22**:** 1910-1915, 2007.
26. Pavkov, ME, Knowler, WC, Hanson, RL, Bennett, PH, Nelson, RG: Predictive power of sequential measures of albuminuria for progression to ESRD or death in Pima Indians with type 2 diabetes. *Am J Kidney Dis,* 51**:** 759-766, 2008.
27. Hillege, HL, Fidler, V, Diercks, GF, van Gilst, WH, de Zeeuw, D, van Veldhuisen, DJ, Gans, RO, Janssen, WM, Grobbee, DE, de Jong, PE: Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation,* 106**:** 1777-1782, 2002.
28. Jassal, SK, Kritz-Silverstein, D, Barrett-Connor, E: A Prospective Study of Albuminuria and Cognitive Function in Older Adults: The Rancho Bernardo Study. *Am J Epidemiol,* 171**:** 277-286, 2010.
29. Brenner, BM, Cooper, ME, de Zeeuw, D, Keane, WF, Mitch, WE, Parving, HH, Remuzzi, G, Snapinn, SM, Zhang, Z, Shahinfar, S: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med,* 345**:** 861-869, 2001.
30. Kimm, H, Yun, JE, Jo, J, Jee, SH: Low Serum Bilirubin Level as an Independent Predictor of Stroke Incidence: A Prospective Study in Korean Men and Women. *Stroke,* 40**:** 3422-3427, 2009.

31. Tangri, N, Stevens, LA, Griffith, J, Tighiouart, H, Djurdjev, O, Naimark, D, Levin, A, Levey, AS: A predictive model for progression of chronic kidney disease to kidney failure. *JAMA,* 305**:** 1553-1559, 2011.
32. Wen, CP, Cheng, TY, Tsai, MK, Chang, YC, Chan, HT, Tsai, SP, Chiang, PH, Hsu, CC, Sung, PK, Hsu, YH, Wen, SF: All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462 293 adults in Taiwan. *Lancet,* 371**:** 2173-2182, 2008.
33. Kovesdy, CP, Lott, EH, Lu, JL, Malakauskas, SM, Ma, JZ, Molnar, MZ, Kalantar-Zadeh, K: Hyponatremia, hypernatremia, and mortality in patients with chronic kidney disease with and without congestive heart failure. *Circulation,* 125**:** 677-684, 2012.
34. Bilo, HJ, Logtenberg, SJ, Joosten, H, Groenier, KH, Ubink-Veltmaat, LJ, Kleefstra, N: Modification of diet in renal disease and Cockcroft-Gault formulas do not predict mortality (ZODIAC-6). *Diabet Med,* 26**:** 478-482, 2009.
35. Matsushita, K, van der Velde, M, Astor, BC, Woodward, M, Levey, AS, de Jong, PE, Coresh, J, Gansevoort, RT: Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet,* 375**:** 2073-2081, 2010.
36. Matsushita, K, Mahmoodi, BK, Woodward, M, Emberson, JR, Jafar, TH, Jee, SH, Polkinghorne, KR, Shankar, A, Smith, DH, Tonelli, M, Warnock, DG, Wen, CP, Coresh, J, Gansevoort, RT, Hemmelgarn, BR, Levey, AS: Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. *JAMA,* 307**:** 1941-1951, 2012.
37. S201 sex and age by ethnic group, all people, geographic level: Health board - Grampian 2001 census [Internet]. General Register Office for Scotland, 2009.