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Past Decline Versus Current eGFR and Subsequent ESRD Risk

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ABSTRACT

eGFR is a robust predictor of ESRD risk. However, the prognostic information gained from the past trajectory (slope) beyond that of the current eGFR is unclear. We examined 22 cohorts to determine the association of past slopes and current eGFR level with subsequent ESRD. We modeled hazard ratios as a spline function of slopes, adjusting for demographic variables, eGFR, and comorbidities. We used random effects meta–analyses to combine results across studies stratified by cohort type. We calculated the absolute risk of ESRD at 5 years after the last eGFR using the weighted average baseline risk. Overall, 1,080,223 participants experienced 5163 ESRD events during a mean follow-up of 2.0 years. In CKD cohorts, a slope of −6 versus 0 ml/min per 1.73 m^2 per year over the previous 3 years (a decline of 18 ml/min per 1.73 m^2 versus no decline) associated with an adjusted hazard ratio of ESRD of 2.28 (95% confidence interval, 1.88 to 2.76). In contrast, a current eGFR of 30 versus 50 ml/min per 1.73 m^2 (a difference of 20 ml/min per 1.73 m^2) associated with an adjusted hazard ratio of 19.9 (95% confidence interval, 13.6 to 29.1). Past decline contributed more to the absolute risk of ESRD at lower than higher levels of current eGFR. In conclusion, during a follow-up of 2 years, current eGFR associates more strongly with future ESRD risk than the magnitude of past eGFR decline, but both contribute substantially to the risk of ESRD, especially at eGFR<30 ml/min per 1.73 m^2.

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CKD is characterized by poor outcomes and high costs, and its increasing worldwide prevalence represents a significant public health challenge.[1] Although the vast majority of patients with CKD have early-stage disease,[2–4] patients with late-stage disease and especially, those with ESRD suffer from an especially high burden of comorbid conditions, have extremely poor outcomes, and consume a disproportionate amount of health care resources.[5] It

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is, thus, important to focus interventions, such as efforts to slow kidney progression and preparation for the transition to ESRD, on patients who are most prone to experience a progressive disease course. Recent studies have emphasized the importance of eGFR and albuminuria as measures of kidney disease severity, which can be assessed at the point of clinical contact, used to classify patients into various stages of CKD and form the basis of clinical interventions.[2] However, many other factors influence the rate of progression, including age,[6,7] comorbid conditions, such as diabetes mellitus or hypertension,[7–9] race-ethnicity,[10] and genetic mutations.[11] Nonetheless, these factors do not account for the observed variability in kidney disease progression.[12]

A seminal study almost 40 years ago proposed that the trajectory of kidney disease progression could be predicted from the past rate of decline in kidney function.[13] Current clinical practice guidelines continue to recommend assessing the future risk of kidney disease progression from the past slope of eGFR over time.[2] Despite the widespread acceptance of this practice, relatively few studies have evaluated the past eGFR decline as a predictor of ESRD after taking into account the current level of eGFR.[14] In clinical practice, both the level of eGFR at the point of assessment and its past trajectory over time are readily available for assessment, but the relative contribution of each to the risk of subsequent ESRD is not clear. We, thus, examined the magnitudes of associations of past decline in eGFR over 3 years versus current level of eGFR at the end of the slope evaluation period with subsequent progression to ESRD in 22 large and diverse cohort studies from across the globe to investigate the usefulness of both measures as predictors of CKD progression in clinical practice.

RESULTS

We primarily provide results on the 3-year slope evaluation period and the absolute risk of ESRD at 5 years of follow-up in the CKD cohorts, and we present results for other baseline (1- and 2-year slopes) and follow-up periods (1, 3, and 10 years) and the other (general population and high risk) cohorts in the Supplemental Material. Twenty of 22 participating cohorts (11 CKD and nine other cohorts) provided data on change in eGFR for a slope evaluation period of 3 years. Among 1,080,223 participants (232,250 in CKD cohorts and 847,973 in other cohorts), approximately 10% and 5% had rapid decline (slope <-5 ml/min per 1.73 m^2 per year) or rapid increase (slope >5 ml/min per 1.73 m^2 per year), respectively, with the remaining 85% having less rapid changes (slope ≥ -5 to ≤ 5 ml/min per 1.73 m^2 per year) (Supplemental Table 1, Table 1). Individuals with rapid decline tended to have a poorer risk profile (higher prevalence of albuminuria, diabetes, and history of CVD) compared with those with rapid increase and less rapid changes, regardless of cohort types (Supplemental Tables 1–5, Table 1).

Table 1. Three-year baseline period characteristics by slope category in CKD cohorts

Study	Total *N*	Slope <-5 ml/yr						Slope ≥ -5 to ≤ 5 ml/yr						Slope >5 ml/yr					
		% *N*	% DM	% CVD	eGFR First	eGFR Last	% Alb[a]	% *N*	% DM	% CVD	eGFR First	eGFR Last	% Alb[a]	% *N*	% DM	% CVD	eGFR First	eGFR Last	% Alb[a]
AASK	831	14	0	50	49 (15)	27 (15)	79	82	0	50	47 (14)	46 (17)	65	4	0	57	49 (11)	70 (14)	72
BC CKD	6274	13	65	14	52 (20)	28 (16)	85	84	53	16	35 (14)	32 (15)	71	3	55	23	39 (17)	59 (18)	64
CCF	10,563	10	44	32	49 (9)	33 (11)	45	85	32	30	46 (10)	46 (13)	30	6	34	29	46 (10)	68 (14)	28
CRIB[b]	n/a																		
Geisinger	11,587	12	57	44	53 (6)	38 (12)	64	77	38	27	52 (7)	54 (11)	46	11	40	30	50 (9)	72 (12)	48
GLOMMS1	572	6	74	40	42 (13)	20 (9)	89	88	61	48	34 (8)	33 (11)	78	6	52	52	33 (7)	54 (9)	60
KPNW[b]	n/a																		
MASTERPLAN	546	8	28	33	44 (14)	23 (11)	60	90	26	30	40 (15)	37 (17)	38	1.5	25	25	41 (16)	65 (19)	25
MDRD	316	20	6	9	40 (11)	19 (9)	95	79	4	12	36 (14)	31 (15)	86	0.6	0	50	46 (14)	56 (7)	50
NephroTest	414	11	36	16	57 (20)	34 (21)	95	85	26	22	41 (18)	39 (19)	96	4	22	17	49 (12)	69 (13)	83
RENAAL	885	42	100	44	46 (13)	23 (12)	98	58	100	46	41 (13)	34 (15)	96	0.1	100	0	34 (n/a)	69 (n/a)	100
Sunnybrook	1888	22	49	54	71 (27)	46 (25)	86	74	41	52	60 (31)	57 (31)	78	3	37	43	59 (28)	81 (28)	80
VA CKD	198,374	12	62	46	63 (18)	43 (18)	50	81	46	43	54 (15)	54 (16)	33	8	44	42	54 (12)	73 (14)	0
Total	232,250	12	61	45	61 (18)	42 (18)	53	81	45	41	53 (15)	53 (17)	36	7	44	41	53 (12)	73 (14)	6

Slope <-5 ml/yr indicates declining eGFR group with an annualized eGFR slope of <-5 ml/min per 1.73 m^2 per year. Slope ≥ -5 to ≤ 5 ml/yr indicates stable eGFR group with an annualized eGFR ≥ -5 and ≤ 5 ml/min per 1.73 m^2 per year. Slope >5 ml/yr indicates increasing eGFR group with an annualized eGFR slope of >5 ml/min per 1.73 m^2 per year. DM, diabetes mellitus; Alb, albumin; AASK, African American Study of Kidney Disease and Hypertension; BC CKD, British Columbia CKD Study; CCF, Cleveland Clinic CKD Registry Study; CRIB, Chronic Renal Impairment in Birmingham; n/a, There is only 1 participant in the category thus the estimate is not available; Geisinger, Geisinger CKD Study; GLOMMS1, Grampian Laboratory Outcomes, Morbidity and Mortality Studies 1; KPNW, Kaiser Permanente Northwest; 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; NephroTest, NephroTest Study; RENAAL, Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan; Sunnybrook, Sunnybrook Cohort; VA CKD, Veterans Administration CKD Study.

[a]Proportion of participants with urine albumin-to-creatinine ratio ≥ 30 mg/g, urine protein-to-creatinine ratio ≥ 50 mg/g, or dipstick protein $\geq 1+$.

[b]Cohorts that did not have enough information in the 3-year baseline period to contribute to analyses, but are included in the 1-year or 2-year baseline period analyses in the supplement.

Table 2. Three-year baseline period events by slope category in CKD cohorts

Cohorts (*N*=13)	Slope <−5 ml/yr				Slope ≥−5 to ≤5 ml/yr				Slope >5 ml/yr			
	N	ESRD Events	Mean (SD) Follow-Up	Median Measurements of Serum Creatinine (IQR)	*N*	ESRD Events	Mean (SD) Follow-Up	Median Measurements of Serum Creatinine (IQR)	*N*	ESRD Events	Mean (SD) Follow-Up	Median Measurements of Serum Creatinine (IQR)
AASK	113	62	4 (3)	8 (8–9)	681	142	6 (2)	9 (8–9)	37	2	6 (2)	8 (7–9)
BC CKD	833	269	2 (2)	15 (10–20)	5244	567	2 (2)	15 (11–20)	197	3	2 (2)	15 (11–22)
CCF	1024	56	1 (0)	11 (7–17)	8943	54	1 (0)	8 (6–12)	596	1	1 (0)	9 (6–14)
CRIB[a]												
Geisinger	1348	107	2 (2)	12 (8–19)	8949	70	3 (2)	8 (6–12)	1290	2	3 (2)	9 (7–14)
GLOMMS1	35	14	2 (1)	14 (10–18)	504	28	3 (1)	12 (8–17)	33	0	3 (1)	12 (8–17)
KPNW[a]												
MASTERPLAN	46	22	2 (1)	11 (8–12)	492	72	3 (1)	11 (9–12)	8	0	3 (1)	10 (8–12)
MDRD	64	62	2 (3)	11 (10–11)	250	174	7 (5)	11 (10–11)	2	0	14 (1)	10 (9–11)
NephroTest	44	10	2 (2)	4 (3–4)	352	57	3 (2)	4 (3–4)	18	0	2 (2)	3 (2–3)
RENAAL	372	70	0 (0)	13 (12–14)	512	19	1 (0)	14 (13–14)	1	0	0 (n/a)	14 (14–14)
Sunnybrook	418	51	3 (2)	11 (7–16)	1405	62	3 (2)	10 (7–14)	65	2	3 (3)	11 (8–16)
VA CKD	23,239	568	1 (1)	9 (6–16)	160,076	702	1 (1)	7 (5–10)	15,059	8	1 (1)	7 (5–13)
Total	27,536	1291	1 (1)	5 (5–9)	187,408	1947	1 (1)	5 (5–5)	17,306	18	1 (1)	4 (4–7)

Slope <−5 ml/yr indicates declining eGFR group with an annualized eGFR slope of <−5 ml/min per 1.73 m^2 per year. Slope ≥−5 to ≤5 ml/yr indicates stable eGFR group with an annualized eGFR ≥−5 and ≤5 ml/min per 1.73 m^2 per year. Slope >5 ml/yr indicates increasing eGFR group with an annualized eGFR slope of >5 ml/min per 1.73 m^2 per year. IQR, interquartile range; AASK, African American Study of Kidney Disease and Hypertension; BC CKD, British Columbia CKD Study; CCF, Cleveland Clinic CKD Registry Study; CRIB, Chronic Renal Impairment in Birmingham; Geisinger, Geisinger CKD Study; GLOMMS1, Grampian Laboratory Outcomes, Morbidity and Mortality Studies 1; KPNW, Kaiser Permanente Northwest; 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; NephroTest, NephroTest Study; RENAAL, Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan; n/a, There is only 1 participant in the category thus the estimate is not available.; Sunnybrook, Sunnybrook Cohort; VA CKD, Veterans Administration CKD Study.

[a]Cohorts that did not have enough information in the 3-year baseline period to contribute to analyses, but are included in the 1-year or 2-year baseline period analyses in the supplement.

We observed a total of 5163 ESRD events (3256 in CKD cohorts and 1907 in other cohorts) during a mean subsequent follow-up period of 2.0 years after the 3-year baseline period (Supplemental Tables 2 and 6, Table 2). In CKD cohorts, the subsequent risk of ESRD showed overall higher adjusted hazard ratios (HRs) at both greater negative and positive slopes of eGFR compared with stable eGFR (slope of 0 ml/min per 1.73 m^2 per year) (Figure 1). This finding was most pronounced for 3-year slopes, being slightly weaker for slopes assessed over shorter (1 and 2 years) baseline periods (Supplemental Figure 1). Slopes of −6 and −3 ml/min per 1.73 m^2 per year over 3 years (−18 and −9 ml/min per 1.73 m^2 per year over 3 years) were associated with adjusted HRs of ESRD of 2.28 (95% confidence interval [95% CI], 1.88 to 2.76) and 1.73 (95% CI, 1.50 to 2.00), respectively. Other cohorts displayed similar trends (Supplemental Figure 2). Additional adjustment for albuminuria did not alter the results substantially (Supplemental Figures 3 and 4). Furthermore, results were largely consistent across individual cohorts (Figure 2, Supplemental Figure 5). Associations were similar in CKD cohorts for patients exposed to renin-angiotensin-aldosterone system (RAAS) inhibitors and those not exposed to such agents. In other cohorts, the association of slope with ESRD was significant in patients who received RAAS inhibitors but not in patients who were not exposed to such agents (Supplemental Figure 6). Participants with a rapid rise in eGFR also had an elevated ESRD risk, but the number of events in this group was small (n=18).

In analyses stratified by level of last eGFR, the risk of ESRD was always significantly associated with more rapid declines, but the magnitude of the excess risk was much less than that imparted by lower versus higher levels of last recorded eGFR (Figure 3A). The HRs of ESRD associated with eGFR levels of 20, 30, and 40 ml/min per 1.73 m^2 (compared with 50 ml/min per 1.73 m^2 and a slope of 0 ml/min per 1.73 m^2 per year) were 216.8 (95% CI, 124.8 to 376.7), 46.4 (95% CI, 31.9 to 67.6), and 9.99 (95% CI, 8.03 to 12.44) in those with a slope of −6 ml/min per 1.73 m^2 per year, respectively; 178.3 (95% CI, 92.9 to 342.2), 38.4 (95% CI, 23.8 to 61.9), and 8.11 (95% CI, 5.98 to 11.00) in participants with a slope of −3 ml/min per 1.73 m^2 per year, respectively; and 88.7 (95% CI, 50.0 to 157.3), 19.9 (95% CI, 13.6 to 29.1), and 4.46 (95% CI, 3.69 to 5.40) in participants with a slope of 0 ml/min per 1.73 m^2 per year, respectively (overall P for interaction between eGFR slope and last eGFR was 0.26). Consequently, both the slopes and the eGFR levels were independently associated with higher 5-year estimated absolute risk of ESRD (Figure 3B, Supplemental Table 7). The higher estimated absolute risk of ESRD associated with steeper declines in eGFR seemed to be more pronounced at lower levels of eGFR. Of note, at eGFR<30 ml/min per 1.73 m^2, the estimated absolute risk of ESRD was substantial, even at a slope of 0 ml/min per 1.73 m^2 per year. Results displayed similar trends when assessing 1- and 2-year slopes and when examining other cohorts (Supplemental Figures 7–11).

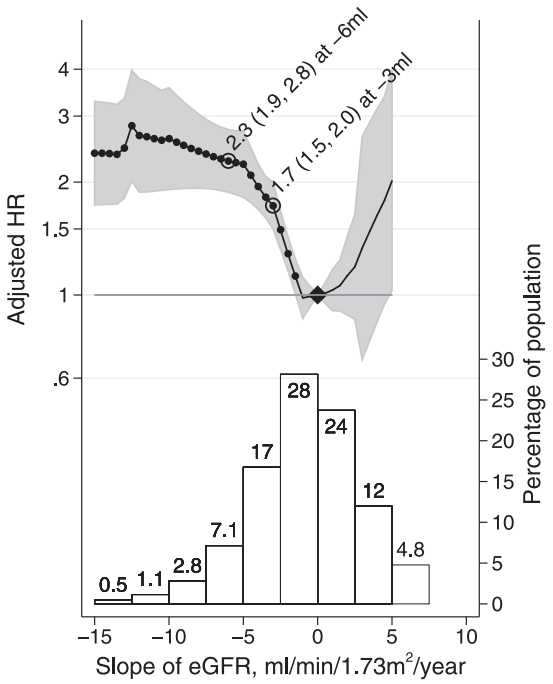

Figure 1. Adjusted HR of ESRD associated with slope of eGFR during a 3-year baseline period and a histogram of the slope of eGFR in CKD cohorts. Values were trimmed at a −15-ml slope (0.3%) and a 10-ml slope (1.1%). Black dots indicate statistical significance compared with the reference (diamond) slope of eGFR=0 ml/min per 1.73 m^2 per year. Open circles show slope of eGFR=−6 and −3 ml/min per 1.73 m^2 per year.

DISCUSSION

In this international meta-analysis of 1,080,223 participants in 22 diverse cohorts, approximately 10% of participants had experienced past rapid eGFR declines (slopes) of <-5 ml/min per 1.73 m^2 per year over 1–3 years before the current eGFR assessment. We observed a significant and independent association of both a lower current level of eGFR and a more rapid past decline in eGFR (slope) with higher subsequent risk of ESRD in CKD cohorts, especially when slopes were calculated from creatinine levels measured over 3 years. For example, a slope of −6- versus 0-ml/min per 1.73 m^2 per year change over 3 years (an 18-ml/min per 1.73 m^2 per year decline in total) was associated with adjusted HR of subsequent ESRD of 2.28 (95% CI, 1.88 to 2.76), whereas a current eGFR of 30 versus 50 ml/min per 1.73 m^2 (a 20-ml/min per 1.73 m^2 difference in final eGFR) was associated with an adjusted HR of subsequent ESRD of 19.9 (95% CI, 13.6 to 29.1) if the previous slope was 0 ml/min per 1.73 m^2. Other cohorts displayed similar trends but with substantially higher heterogeneity and lack of statistical significance, indicating that our conclusions primarily refer to patients with CKD. The current level of eGFR seemed to be associated with a larger risk of ESRD, especially at very low eGFR, where the ESRD risk was substantial, even with past slopes of 0 ml/min per 1.73 m^2 per year. However, more rapid past declines contributed substantially to significantly higher absolute risk of ESRD, especially in individuals with very low eGFR level. An additional finding in our study was that approximately 5% of participants had experienced a past rapid eGFR rise (>5 ml/min per 1.73 m^2 per year) and that a more rapid past rise in eGFR was associated significantly and independently with a higher ESRD risk. The results are consistent with the current body of evidence indicating that point estimates of eGFR are one of the most robust predictors of ESRD, but they also provide new evidence that the past trajectory of eGFR slopes could be used in addition to contemporarily evaluated other risk factors to assess future risk of ESRD.

The level of eGFR is a well established predictor of ESRD,[2] but the role of past eGFR trajectories (slopes) in the assessment of patients with kidney disease has been less clear. Most previous studies have evaluated the association between slopes of eGFR and mortality,[15–21] and a few assessed the role of future slopes (*i.e.*, after the point of assessment adjusted for the initial level of eGFR) in predicting ESRD.[22,23] The association of future slopes or percentage changes in eGFR with ESRD relates to their role as surrogate end points in clinical trials.[24] In contrast, past slopes of eGFR are helpful to clinicians, who need information readily available at the point of contact for clinical decision making and future projection, and their association with ESRD events has not been previously extensively evaluated. Past slopes of eGFR provide an empirical measure of the disease process for an individual, which represents the aggregate effect of all known and unknown predictors of kidney disease progression for each patient. A prior community–based study found that the association between past slopes of eGFR and ESRD was attenuated and became nonsignificant after adjusting for the level of the last eGFR.[14] Our study confirms the major association between eGFR level and the risk of ESRD but suggests that past slopes may also have an independent, albeit weaker association with this end point. Our study may have been better suited than the previous study for a detailed evaluation of the role of past eGFR trajectories because of the much higher statistical power imparted by the large number of outcomes, the availability of longer evaluation periods for slope estimations, and the diversity of patient populations with representation of higher–risk patient groups.

The finding of substantial risk of ESRD associated with very low eGFR in the absence of eGFR decline in the past 1–3 years suggests possible difficulty in accurate ascertainment of eGFR trajectory over a short interval, especially in patients with slowly progressive or nonlinear eGFR declines.[25] The much stronger relative risk of ESRD associated with lower levels of eGFR versus steeper slopes may also be related to the fact that the studied end point (ESRD) is directly dependent on a very low eGFR but less dependent on rapid eGFR decline; hence, during the relatively short follow-up period of our study, it is much more likely for ESRD to be observed in patients who start follow-up with lower eGFR levels, and it is possible that more rapid declines in eGFR could have been stronger predictors of ESRD if patients were followed for a longer period of time. Nevertheless, in clinical practice, prediction of ESRD is

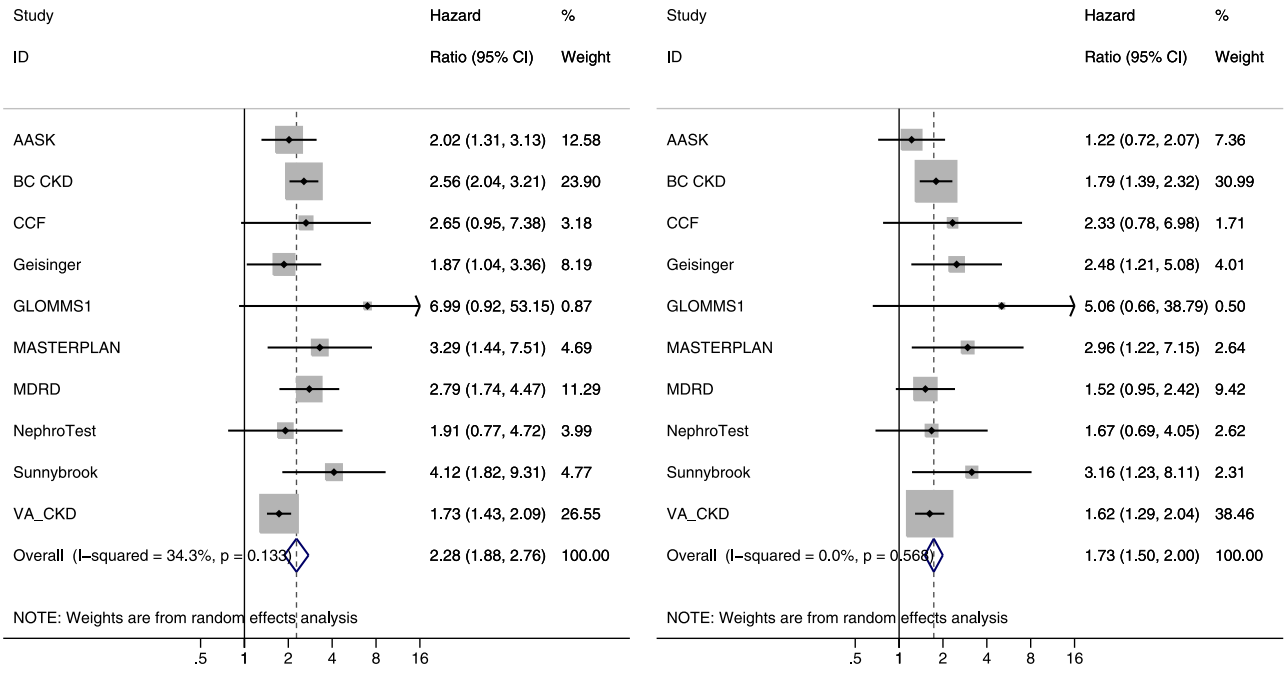

Figure 2. Adjusted relative HRs of ESRD for a 6-ml/min per 1.73 m^2 per year decline and a 3-ml/min per 1.73 m^2 per year decline in eGFR (compared with a decline of 0 ml/min per 1.73 m2 per year) during a 3-year baseline period in CKD cohorts. The left panel shows adjusted relative HRs for a 6-ml/min per 1.73 m^2 per year decline and the right panel shows adjusted relative HRs for a 3-ml/min per 1.73 m^2 per year decline. AASK, African American Study of Kidney Disease and Hypertension; BC CKD, British Columbia CKD Study; CCF, Cleveland Clinic CKD Registry Study; Geisinger, Geisinger CKD Study; GLOMMS1, Grampian Laboratory Outcomes, Morbidity and Mortality Studies 1; 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; NephroTest, NephroTest Study; Sunnybrook, Sunnybrook Cohort; VA CKD, Veterans Administration CKD Study.

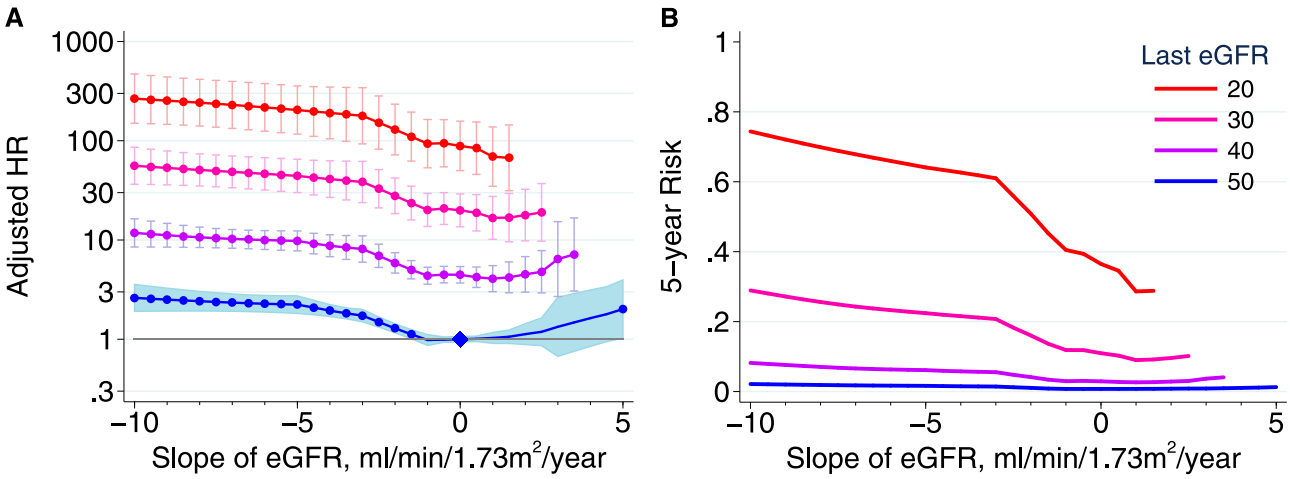

Figure 3. Adjusted HRs (95% CIs; reference: patients with eGFR=50 ml/min per 1.73 m^2 and slope of 0 ml/min per 1.73 m^2 per year) and absolute risks of ESRD associated with slope of eGFR and different levels of last eGFR during a 3-year baseline period in CKD cohorts. Panel A shows the adjusted HRs and panel B shows the absolute risks.

most important for the immediately foreseeable future, because clinicians need to implement preparations, such as vascular access planning and referral for transplantation, during the 6–12 months preceding ESRD. These results suggest that interventions that slow kidney disease progression and preparations for ESRD should be continuously implemented in patients with CKD stages 4 and 5, even in the absence of demonstrable eGFR decline in the past 1–3 years.

The finding that a more rapid past eGFR rise is associated with higher ESRD risk is reminiscent of associations between positive slopes and higher mortality in previous studies.[16,18] The explanation for these seemingly counterintuitive associations is unclear but could be because of confounding by loss of muscle mass, volume overload, presence of severe illness with an underlying heightened propensity for faster kidney disease progression, or recovery from previous AKI events. In our study, patients with positive slopes represented a minority of the study population (7% of patients) and experienced only a tiny fraction (n=18; 0.5%) of the total ESRD events, thereby limiting our ability to distinguish among these potential explanations. The demographic and comorbidity characteristics of those with positive eGFR slopes were similar to those seen in patients with stable eGFR, and significantly fewer of them had albuminuria, making it less likely that a heightened propensity for progressive CKD existed in this group. Recovery from a prior AKI might be associated with an increased risk for and subsequent development of ESRD, perhaps as a result of another AKI event. Many of our cohorts included unselected patients, and even the cohorts that included stable patients provided follow-up creatinine measurements during a subsequent time period when acute events could have occurred. We did not have detailed information about the cause of ESRD, characteristics, such as body composition and muscle mass, or other filtration markers, such as cystatin C, that would be necessary to evaluate these possibilities.

Our study is notable for its large size, international representation, and a diverse patient population. Despite its advantages, this study also has a number of limitations. Standardization of serum creatinine values may have varied across time and studies. The assumption that slopes of eGFR are uniform over time may be flawed. The least squares regression method for the calculation of slopes provides an average linear trajectory over the evaluation period but cannot account for nonlinear trajectories, and its results may be influenced by transient reversible changes in kidney function (*e.g.*, episodes of AKI). Variation in design across cohorts introduces heterogeneity, but the consistency of our results across cohorts, despite the marked variation in design and populations, inspires confidence in them. The added benefit of using slopes over longer durations than 3 years, more frequent serum creatinine measurements, or measurement of other filtration markers, such as cystatin C, was not studied.

In summary, although the last eGFR level seems to be a robust predictor of future ESRD, past trajectory of eGFR over time is also independently associated with ESRD and adds significantly to the information provided by the single last eGFR level, especially in patients with lower eGFR in whom risk of progression to ESRD in the near future is greatest. The ubiquity of electronic medical records makes the evaluation of both single eGFR levels and past slopes of eGFR readily available to increasing numbers of physicians, and their incorporation in everyday clinical practice could improve risk prediction and allow for better strategic resource allocation. The result could be the delivery of better care for later stages of CKD with potential downstream advantages, such as lower ESRD incidence or a more seamless transition to ESRD.

CONCISE METHODS

Study Selection Criteria

The Chronic Kidney Disease Prognosis Consortium (CKD-PC) has been described previously and is also described in Supplemental Appendices 1 and 2.[26–30] Briefly, the CKD-PC incorporates cohorts with at least 1000 participants (not applied to cohorts predominantly enrolling persons with CKD [CKD cohorts]) with data on serum creatinine, albuminuria, and ≥50 events of outcomes of interest (mortality or kidney outcomes).[26–30] This study included 22 cohorts (13 cohorts in which the presence of CKD was required for cohort entry [CKD cohorts] and nine cohorts in which entry was determined by factors other than CKD [general population and high–cardiovascular disease (CVD) risk cohorts; *i.e.*, other cohorts]) with repeated measures of serum creatinine during baseline evaluation periods of 0.5–3.5 years to determine change in eGFR and data on subsequent ESRD. Meta-analyses were restricted to cohorts with a minimum of 10 ESRD events and participants ages ≥18 years old. This study was approved by the Institutional Review Board at the Johns Hopkins Bloomberg School of Public Health.

Procedures

eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation.[31] In cohorts where the creatinine measurement was not standardized to isotope dilution mass spectrometry, creatinine concentrations were reduced by 5%.[32]

Our primary measure of change in eGFR was the annual change (slope), because this is the conventional approach to assess past trajectory in clinical practice. An average annual change in eGFR was estimated from a least squares regression model using all eGFR measurements during baseline periods of 1–3 years. For each baseline period, a 0.5 year of margin before and after the end of the period was allowed for determining the last available eGFR to calculate the change (*e.g.*, eGFR between 0.5 and 1.5 years after the first available eGFR could be used for the 1-year baseline period analysis), but the eGFR closest to the baseline period of interest was selected for each participant. All covariates were assessed at the time of last eGFR (Supplemental Appendix 2 shows details for specific cohorts).

We defined diabetes 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 glucose-lowering drugs, or self-reported diabetes. Participants with a history of myocardial infarction, coronary revascularization, heart failure, or stroke were considered to have a history of CVD. Albuminuria was not available in all cohorts at the time of last eGFR, and hence, we adjusted for its severity only in sensitivity analyses. Our primary measure of albuminuria was the urine albumin-to-creatinine ratio, but we also included studies with urine albumin excretion rate, urine protein-to-creatinine ratio, or semiquantitative dipstick protein.[33]

The primary outcome of interest was ESRD after the end of the baseline period. We defined ESRD as initiation of RRT or death caused by kidney disease other than AKI. Patients with ESRD before the baseline period were excluded from the analyses.

Statistical Analyses

We applied a two–stage meta-analysis, with each study first analyzed separately followed by a random effects meta–analysis. The overview of the analysis and analytic notes for individual studies are provided in Supplemental Appendix 2. We imputed missing values of covariates but not the main exposure (change in eGFR) using cohort–specific mean values. We quantified heterogeneity with the I^2 statistic and Cochran Q test and explored sources of heterogeneity with random effects meta-regression analysis. Because the absolute risk of ESRD and the implication of change in eGFR vary substantially depending on the type of patient population, analyses were first stratified by type of cohort (CKD versus other).

We modeled the adjusted HRs of subsequent ESRD as a spline function of eGFR slopes. In each study, we fitted piecewise linear splines for eGFR slopes (knots were placed 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/ethnicity (black versus nonblack), systolic BP, total cholesterol, diabetes, history of CVD, and last eGFR used to calculate slopes for each evaluation period. Potential effect modifiers with change in eGFR were assessed by incorporating interaction terms. To assess the association of the past slope of eGFR with ESRD in the context of the level of the last eGFR, we present HRs according to eGFR slopes by prespecified levels of the last eGFR (20, 30, 40, and 50 ml/min per 1.73 m^2) using no change in eGFR with last eGFR of 50 ml/min per 1.73 m^2 as the reference. We selected these eGFR levels because of their relevance to progression to ESRD in the near future.

We translated meta–analyzed adjusted HRs for eGFR slopes stratified by level of last eGFR to absolute risk of ESRD at 1, 3, 5, and 10 years after the baseline period using the weighted average baseline risk; 1-year baseline risk in each cohort was calculated for the following combination of covariates: 60 years old, nonblack, men, no change in eGFR, last eGFR of 50 ml/min per 1.73 m^2, systolic BP of 130 mmHg, total cholesterol of 5 mmol/L, and no history of diabetes or CVD. Risk was scaled for longer follow-up and pooled across cohorts using a weighted average (Supplemental Appendix 2). In sensitivity analyses, we applied the adjusted sub-HRs from competing risk models accounting for death as a competing end point.[34] In additional sensitivity analyses, we examined the association between eGFR slopes and ESRD in subgroups of patients divided by exposure to RAAS inhibitor medications during the slope evaluation period.

Analyses were performed using Stata/SE 12 software (StataCorp., College Station, TX; www.stata.com). We considered P values <0.05 statistically significant.

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DISCLOSURES

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Supplementary Online Content

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]
AKDN:	Alberta Kidney Disease Network[3]
ARIC:	Atherosclerosis Risk in Communities Study[4]
BC CKD	British Columbia CKD Study[5]
CCF:	Cleveland Clinic CKD Registry Study[6]
CHS:	Cardiovascular Health Study[7]
CRIB:	Chronic Renal Impairment in Birmingham[8]
Geisinger:	Geisinger CKD Study[9]
GLOMMS-1:	Grampian Laboratory Outcomes, Morbidity and Mortality Studies – 1[10]
KP Hawaii:	Kaiser Permanente Hawaii Cohort[11]
KPNW:	Kaiser Permanente Northwest[12]
Maccabi:	Maccabi[13]
MASTERPLAN:	Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of a Nurse Practitioner[14]
MDRD:	Modification of Diet in Renal Disease Study[15]
MRFIT:	Multiple Risk Factor Intervention Trial[16]
Nephro Test:	NephroTest Study[17]
NZDCS:	New Zealand Diabetes Cohort Study[18]
Pima:	Pima Indian Study[19]
RENAAL:	Reduction of Endpoints in Non-insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan[20]
Sunnybrook:	Sunnybrook Cohort[21]
VA CKD:	Veterans' Administration CKD Study[22]

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

2.1 Overview:

As previously reported,[23, 24] 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, taking glucose lowering drugs, or self-reported diabetes.

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 albumin-to-creatinine ration (ACR) were treated as 0.1 for log transformation. For other covariates in the models (total cholesterol, systolic blood pressure, diabetes mellitus, and prevalent cardiovascular disease) with missing values we imputed with the mean value of the covariate only if the missing values were less than 50%. If missing values were more than 50% in some covariates, we excluded those covariates from the models. Values of covariates, e.g., systolic blood pressure <50 or >300 mmHg were excluded from the analysis. Multiple imputation was not feasible in all studies but a sensitivity analysis in cohorts with data at Hopkins where multiple imputation was feasible showed very similar results (section 2.5). Multiple imputation was conducted for missing data on total cholesterol, systolic blood pressure, diabetes mellitus and prevalent cardiovascular disease with 20 imputations using the *mi* command in Stata.

Out of 29 studies with repeated serum creatinine, 7 studies (CARE FOR HOMe, ESTHER, HUNT, Okinawa, PREVEND, Rancho Bernardo, ULSAM) did not have enough data within baseline periods of interest for the present study. For 16 of the 22 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 fewer than 10 outcomes in any stratum for a particular analysis were excluded from that analysis.

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, NZDCS, VA CKD) and studies where the creatinine standardization was not done (AASK, ADVANCE, ARIC, British Columbia CKD, CHS, CRIB, KP Hawaii, MASTERPLAN, MDRD, MRFIT, Pima, RENAAL, Sunnybrook). 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 (60 for high eGFR stratum), 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 period across cohorts were averaged with weights based on square root of the number of events. Successive times 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.

The pooled HRs in this meta-analysis should be interpreted as the average hazard ratio over follow-up time acknowledging that some variation in the hazard ratio over time may exist within individual studies.

2.2 Notes for individual studies:

CKD cohorts:

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

BC CKD: Includes patients referred to nephrologists and maintained in follow-up practice or with eGFR <60 ml/min/1.73m^2 at enrollment. Total cholesterol and systolic blood pressure were available in 87% and 62% of participants, respectively.

CCF: Includes patients who had at least one face-to-face outpatient encounter with a Cleveland Clinic health care provider and (1) had two eGFR < 60 ml/min/1.73m^2 90 days apart and/or (2) were patients with International Classification of Diseases (ICD-9) diagnosis codes for various kidney diseases. Total cholesterol and systolic blood pressure were available in 69% and 91% of participants, respectively. Albuminuria was available in 35% of participants.

CRIB: This study includes hospital nephrology outpatients with creatinine >130 μmol/L. Serum creatinine was repeated two years apart and this cohort could contribute to 2-y baseline 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. Total cholesterol and systolic blood pressure were available in 74% and 94% of participants, respectively. Albuminuria was available in 22% 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.[25]

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 and has not collected use of anti-diabetic medications. Total cholesterol and systolic blood pressure were available in 45% and 88% of participants, respectively. Not enough participants with ESRD events had repeated creatinine in 3-year window.

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

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

NephroTest: This study includes nephrologist referred patients with diagnosed CKD stages 1-5. Systolic blood pressure was available in 95% of participants.

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. Total cholesterol and systolic blood pressure were available in 29% and 6% of participants, respectively. Albuminuria was available in 30% of participants.

VA CKD: Includes all United States veterans with stable CKD stage 1-5 but not on dialysis. Total cholesterol and systolic blood pressure were available in 67% and 44% of participants, respectively. Albuminuria was available in 16% of participants.

Other cohorts:

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%[3]. 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. Albuminuria was available in 88% of participants.

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

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 baseline period analysis only. Albuminuria was not available in this time frame.

KP Hawaii: In this study for participants with only ACR, PCR was imputed by ACR * 1.5. Albuminuria was available in 33% of participants. Total cholesterol and systolic blood pressure were available in 77% and 94% of participants, respectively.

Maccabi: Total cholesterol and systolic blood pressure were available in 88% and 77% of participants, respectively. Albuminuria available in 11% of participants.

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.

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

Pima: This study consists entirely of Pima and the closely-related Tohono O'odham Indians. ACR was measured in a spot urine specimen. History of cardiovascular disease was not recorded in this study. Serum creatinine was repeated two and three years apart and thus this cohort could not contribute to 1-y baseline period analysis. Majority of participants in this study had a baseline eGFR≥60.

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
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.
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 U01HL080295 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 R01AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org.
CRIB	British Renal Society Project Grant Award British Heart Foundation Project Grant Award.
Geisinger	Geisinger Clinic
GLOMMS-1	Chief Scientist Office CZH/4/656
KP Hawaii	N/A
KPNW	Amgen
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
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,

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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.
Pima	This work was supported by the Intramural Research Program of the National Institute of Diabetes and Digestive and Kidney Diseases.
RENAAL	The RENAAL trial was supported by Merck and Company.
Sunnybrook	
VA CKD	This study was supported by resources from the US Department of Veterans Affairs. Support for VA/CMS data is provided by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Health Services Research and Development, VA Information Resource Center (Project Numbers SDR 02-237 and 98-004) Opinions expressed in this paper are those of the authors' and do not represent the official opinion of the US Department of Veterans Affairs.

Supplemental Table 1. 3-year baseline period characteristics by slope category in other cohorts.

		Slope <-5ml/y						Slope ≥-5ml/y to ≤5ml/y						Slope >5ml/y					
Study	Total N	%N	% DM	% CVD	eGFR First	eGFR Last	% Alb*	%N	% DM	% CVD	eGFR First	eGFR Last	% Alb*	%N	% DM	% CVD	eGFR First	eGFR Last	% Alb*
Other cohorts																			
ADVANCE	9402	20	100	30	85 (16)	59 (15)	33	72	100	28	78 (17)	76 (17)	30	9	100	28	66 (13)	88 (11)	30
AKDN	230470	11	12	7	90 (20)	68 (21)		84	8	5	84 (20)	82 (20)		4	8	7	71 (18)	92 (17)	
ARIC	13833	20	18	12	100 (14)	78 (15)		78	15	11	95 (14)	91 (14)		3	22	12	76 (12)	97 (12)	
CHS	4012	6	25	70	77 (13)	57 (14)		86	16	63	68 (15)	69 (15)		8	16	64	61 (11)	80 (10)	
KP Hawaii	13350	13	84	24	80 (22)	58 (24)	67	81	72	22	76 (23)	75 (24)	49	5	65	22	67 (19)	86 (18)	47
Maccabi	560426	9	17	4	100 (21)	79 (22)	28	87	15	3	96 (20)	94 (20)	17	4	10	3	85 (17)	104 (18)	17
MRFIT	11306	6	10	8	94 (12)	74 (13)	7	89	10	4	88 (13)	88 (13)	5	5	15	4	78 (9)	97 (9)	3
NZDCS	4388	26	100	17	86 (22)	59 (22)	15	69	100	11	76 (21)	73 (21)	8	4	100	11	66 (20)	87 (19)	7
Pima	786	8	54	0	115 (28)	87 (34)	57	89	32	0	123 (15)	121 (15)	20	3	31	0	110 (19)	132 (20)	12
Total	**847973**	**10**	**20**	**7**	**96 (21)**	**74 (22)**	**29**	**86**	**15**	**4**	**92 (21)**	**90 (21)**	**17**	**4**	**13**	**5**	**80 (19)**	**99 (18)**	**17**

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 eGFR 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

DM: diabetes mellitus; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate

*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+

Supplemental Table 2. 3-year baseline period events by slope category in other cohorts

	Slope <-5ml/y				Slope ≥-5ml/y to ≤5ml/y				Slope >5ml/y			
Cohorts (n=9)	**N**	**ESRD events**	**Mean (SD) Follow-up**	**Median # Scre (IQR)**	**N**	**ESRD events**	**Mean (SD) Follow-up**	**Median # Scre (IQR)**	**N**	**ESRD events**	**Mean (SD) Follow-up**	**Median # Scre (IQR)**
Other cohorts												
ADVANCE	1860	17	2 (0)	5 (5-5)	6734	6	2 (0)	5 (5-5)	808	1	2 (0)	5 (5-5)
AKDN	26003	68	1 (1)	5 (3-7)	194160	66	1 (1)	4 (3-6)	10307	3	1 (1)	4 (3-6)
ARIC	2718	128	17 (5)	2 (2-2)	10739	269	17 (5)	2 (2-2)	376	11	17 (5)	2 (2-2)
CHS	240	15	8 (3)	2 (2-2)	3467	44	9 (3)	2 (2-2)	305	1	8 (3)	2 (2-2)
KP Hawaii	1800	53	1 (0)	10 (6-16)	10825	30	1 (0)	8 (6-11)	725	0	1 (0)	8 (5-13)
Maccabi	50304	410	2 (1)	5 (3-7)	486959	344	2 (1)	5 (3-7)	23163	3	2 (1)	4 (3-6)
MRFIT	678	21	20 (6)	4 (4-4)	10062	241	20 (6)	4 (4-4)	566	9	20 (6)	4 (4-4)
NZDCS	1156	64	5 (2)	4 (3-8)	3049	56	6 (1)	4 (3-7)	183	2	6 (2)	4 (3-4)
Pima	63	20	9 (7)	2 (2-2)	697	24	11 (7)	2 (2-2)	26	1	12 (8)	2 (2-2)
Total	**84822**	**796**	**2 (3)**	**5 (5-9)**	**726692**	**1080**	**2 (3)**	**5 (5-5)**	**36459**	**31**	**2 (3)**	**4 (4-7)**

Supplemental Table 3. 3y baseline period characteristics

	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	84	73 (13)	47	0	3	67 (15)	52	0.5
CCF	10	73 (12)	54	18	85	75 (11)	54	12	6	72 (13)	65	14
CRIB												
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												
MASTERPLAN	8	59 (15)	30	0	90	64 (12)	31	0	1.5	54 (15)	50	0
MDRD	20	49 (12)	42	6	79	56 (12)	38	4	0.6	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 (.)	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	81	76 (9)	2	9	8	74 (10)	4	11
Subtotal	12	73 (11)	10	14	81	76 (10)	10	9	7	73 (10)	11	10
Other cohorts												
ADVANCE	20	69 (6)	48	0.3	72	69 (6)	39	0.4	9	69 (6)	57	0.2
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
CHS	6	76 (6)	71	6	86	75 (5)	56	4	8	75 (5)	58	4
KP Hawaii	13	63 (13)	52	0	81	65 (13)	49	0	5	62 (14)	52	0
Maccabi	9	53 (17)	59	0	87	53 (16)	58	0	4	47 (17)	70	0
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	0.07	4	63 (14)	58	0
Pima	8	40 (14)	73	0	89	34 (13)	60	0	3	31 (12)	77	0
Subtotal	10	55 (17)	60	1	86	55 (16)	57	0	4	51 (17)	65	1

Total	10	60 (17)	48	4	85	59 (17)	47	2	5	58 (19)	48	4

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 eGFR 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

Blank lines for cohorts indicate that the cohorts that did not have enough information in the specified baseline period to contribute to analyses, but are included in the other baseline period analyses.

Supplemental Table 4. 2y baseline period characteristics

	Slope <-5ml/y									Slope ≥-5ml/y to ≤5ml/y									Slope >5ml/y								
Study	% N	Age	% Female	% Black	% DM	% CVD	eGFR First	eGFR Last	% Alb *	% N	Age	% Female	% Black	% DM	% CV D	eGFR First	eGFR Last	% Alb *	% N	Age	% Female	% Blac k	% D M	% CV D	eGFR First	eGFR Last	% Alb *
CKD cohorts																											
AASK	19	55 (12)	33	100	0	54	46 (15)	29 (15)	79	70	57 (10)	39	100	0	50	46 (14)	45 (16)	65	11	57 (11)	45	100	0	57	51 (14)	67 (14)	59
BC CKD	19	66 (14)	42	1	65	13	46 (20)	28 (17)	82	74	72 (13)	47	0	50	15	34 (14)	32 (15)	69	7	68 (14)	53	0.5	51	18	38 (16)	52 (19)	60
CCF	16	74 (12)	55	16	37	30	49 (9)	35 (11)	41	71	75 (11)	54	11	30	28	47 (10)	47 (12)	27	13	72 (12)	60	13	32	27	47 (10)	65 (13)	27
CRIB	11	60 (15)	24	10	19	52	32 (10)	20 (9)		87	63 (15)	36	5	16	43	27 (9)	25 (10)		2	74 (4)	0	0	0	67	29 (12)	80 (77)	
Geisinger	16	72 (10)	58	2	50	38	53 (7)	42 (12)	62	65	72 (9)	59	1	35	24	52 (7)	54 (10)	44	19	70 (10)	62	1	39	28	50 (9)	68 (12)	46
GLOMMS 1	12	66 (17)	48	0	69	47	38 (11)	22 (9)	92	79	73 (11)	48	0	63	49	33 (8)	34 (11)	69	10	73 (12)	54	0	51	52	33 (7)	49 (10)	52
KPNW	34	70 (10)	55	4	53	54	68 (16)	46 (13)	6	54	72 (10)	48	2	45	52	52 (14)	50 (12)	9	13	68 (9)	52	3	46	45	48 (12)	58 (13)	7
MASTERPLAN	14	58 (14)	28	0	33	32	43 (18)	29 (17)	54	83	63 (12)	31	0	26	29	39 (15)	37 (16)	39	3.5	61 (14)	35	0	20	40	45 (16)	58 (15)	12
MDRD	31	50 (12)	37	9	6	12	38 (13)	24 (12)	89	67	55 (12)	40	5	3	12	36 (13)	33 (14)	80	2.1	60 (8)	46	15	0	15	41 (9)	55 (11)	69
NephroTest	19	58 (15)	40	11	29	20	52 (22)	36 (22)	95	73	61 (15)	30	11	24	17	40 (17)	38 (18)	97	8	61 (15)	36	11	13	17	46 (16)	61 (18)	91
RENAAL	49	62 (7)	33	17	100	44	44 (13)	26 (13)	99	50	63 (7)	39	13	100	45	41 (13)	37 (14)	97	1.4	59 (6)	24	29	100	41	49 (16)	58 (19)	93
Sunnybrook	29	62 (17)	42	0	47	49	69 (29)	50 (28)	82	62	65 (17)	42	0	39	51	58 (31)	57 (31)	79	9	59 (19)	52	0	37	49	57 (28)	75 (28)	73
VA_CKD	18	74 (10)	3	12	56	45	61 (17)	46 (17)	66	69	76 (9)	2	8	44	42	53 (15)	53 (15)	57	14	74 (10)	3	9	42	42	54 (12)	69 (14)	51
Subtotal	18	74 (11)	9	12	55	43	60 (17)	45 (17)	65	69	75 (10)	9	8	43	40	52 (15)	52 (16)	56	14	74 (10)	10	9	41	40	53 (12)	68 (14)	50
Other cohorts																											
ADVANCE	26	68 (6)	46	0.2	100	29	83 (16)	63 (16)	31	60	68 (6)	39	0.3	100	27	78 (17)	77 (17)	30	13	68 (6)	50	0.7	100	26	68 (14)	87 (13)	30
AKDN	18	57 (17)	63	0	10	7	90 (20)	73 (20)		71	59 (15)	58	0	8	5	84 (20)	83 (20)		11	56 (16)	60	0	8	6	74 (18)	91 (18)	
ARIC																											
CHS																											

KP Hawaii	21	62 (14)	52	0	75	22	81 (22)	64 (23)	57	65	64 (13)	49	0	62	20	75 (23)	75 (23)	46	14	62 (13)	54	0	49	20	69 (18)	84 (18)	40
Maccabi	16	50 (17)	58	0	13	3	101 (21)	85 (21)	25	73	52 (16)	58	0	14	2	97 (20)	96 (20)	18	12	49 (17)	65	0	12	3	86 (18)	101 (18)	17
MRFIT	17	49 (6)	0	9	7	4	95 (11)	81 (12)	5	73	50 (6)	0	6	8	3	88 (13)	88 (13)	4	9	49 (6)	0	10	10	3	79 (11)	95 (12)	4
NZDCS	32	63 (13)	53	0	100	10	84 (21)	62 (23)	13	58	64 (13)	49	0.10	100	9	76 (21)	74 (21)	8	10	62 (14)	56	0	100	8	68 (19)	86 (21)	7
Pima	13	36 (15)	60	0	42	0	122 (23)	104 (30)	36	81	34 (14)	63	0	29	0	122 (15)	121 (15)	18	6	35 (15)	61	0	37	0	111 (20)	126 (20)	27
Subtotal	17	53 (17)	59	0	17	5	96 (21)	79 (22)	26	72	54 (16)	57	0	14	4	92 (21)	91 (21)	19	11	52 (17)	62	0	13	4	82 (19)	97 (19)	18
Total	17	59 (18)	43	4	28	17	85 (26)	69 (26)	42	71	60 (17)	43	2	22	14	81 (26)	80 (26)	32	12	59 (18)	45	3	23	16	72 (22)	88 (22)	31

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 eGFR 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

DM: diabetes mellitus; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; alb: albuminuria

*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+

Blank lines for cohorts indicate that the cohorts that did not have enough information in the specified baseline period to contribute to analyses, but are included in the other baseline period analyses.

Supplemental Table 5. 1y baseline period characteristics

	Slope <-5ml/y									Slope ≥-5ml/y to ≤5ml/y									Slope >5ml/y								
Study	% N	Age	% Female	% Black	% DM	% CVD	eGFR First	eGFR Last	% Alb *	% N	Age	% Female	% Black	% DM	% CVD	eGFR First	eGFR Last	% Alb *	% N	Age	% Female	% Black	% DM	% CVD	eGFR First	eGFR Last	% Alb *
CKD cohorts																											
AASK	26	56 (11)	35	100	0	50	44 (15)	34 (16)	74	52	56 (11)	40	100	0	50	46 (15)	45 (15)	65	23	56 (10)	41	100	0	54	48 (13)	59 (14)	63
BC CKD	30	68 (14)	43	0	57	12	41 (19)	30 (17)	76	54	72 (13)	45	0	48	12	33 (14)	32 (14)	69	17	69 (13)	50	0.3	47	14	36 (15)	47 (17)	62
CCF	26	74 (12)	55	14	31	25	49 (10)	39 (11)	38	43	74 (11)	53	11	27	25	46 (11)	47 (11)	28	31	72 (12)	57	12	27	25	48 (10)	60 (13)	25
CRIB																											
Geisinger	23	71 (10)	58	1	42	29	53 (7)	44 (10)	58	40	71 (10)	58	1	33	20	52 (8)	54 (9)	45	36	70 (10)	60	1	37	22	50 (9)	64 (11)	46
GLOMMS 1	25	69 (15)	44	0	66	48	36 (11)	26 (11)	83	56	73 (12)	49	0	62	49	32 (8)	32 (9)	67	18	72 (13)	49	0	56	52	34 (8)	45 (10)	56
KPNW	36	71 (10)	59	3	44	49	60 (17)	46 (15)	6	37	72 (10)	53	2	37	39	46 (15)	46 (15)	11	27	70 (9)	56	4	41	45	48 (14)	59 (16)	8
MASTERPLAN	29	61 (13)	27	0	30	29	43 (17)	34 (16)	47	61	62 (12)	32	0	26	30	37 (14)	36 (15)	40	10.0	62 (13)	33	0	30	31	42 (15)	50 (14)	35
MDRD	44	51 (12)	38	10	7	12	36 (13)	27 (13)	88	50	54 (12)	40	4	4	13	35 (12)	33 (13)	80	6.7	56 (12)	36	12	4	16	40 (12)	49 (13)	58
NephroTest	28	57 (15)	30	12	27	17	44 (20)	33 (17)	96	58	62 (14)	28	9	26	23	39 (17)	38 (18)	96	13	61 (15)	24	12	29	12	42 (18)	52 (19)	95
RENAAL	55	60 (8)	38	16	100	46	41 (13)	29 (13)	99	38	62 (7)	38	12	100	44	40 (12)	39 (13)	99	6.8	61 (8)	21	19	100	43	48 (14)	56 (15)	98
Sunnybrook	37	62 (18)	44	0	40	46	67 (31)	54 (30)	80	41	65 (17)	43	0	38	46	60 (32)	59 (32)	77	22	62 (18)	45	0	34	45	57 (27)	70 (28)	74
VA_CKD	29	75 (10)	2	10	49	44	59 (16)	49 (15)	62	45	76 (9)	2	8	43	43	52 (15)	52 (15)	56	27	74 (10)	3	9	43	42	53 (13)	64 (14)	53
Subtotal	29	74 (10)	8	10	48	42	58 (16)	48 (16)	61	45	75 (10)	8	8	42	40	51 (15)	51 (15)	55	27	74 (10)	10	9	41	40	52 (13)	64 (14)	51
Other cohorts																											
ADVANCE	38	67 (6)	43	0.3	100	26	83 (16)	68 (16)	32	38	68 (6)	39	0.3	100	26	78 (17)	78 (17)	28	25	67 (6)	45	0.4	100	26	70 (15)	84 (15)	31
AKDN	31	57 (16)	60	0	9	6	88 (20)	76 (20)	8	46	58 (16)	58	0	8	5	85 (21)	84 (21)	6	23	56 (16)	60	0	8	6	77 (19)	89 (19)	7
ARIC																											
CHS																											

KP Hawaii	31	62 (14)	49	0	63	21	81 (23)	68 (22)	45	40	63 (14)	51	0	56	20	76 (24)	76 (24)	41	29	61 (14)	52	0	48	18	71 (19)	83 (19)	37
Maccabi	35	51 (17)	58	0	14	3	100 (20)	87 (21)	21	40	50 (16)	57	0	13	2	98 (20)	98 (20)	19	25	49 (17)	61	0	11	2	91 (19)	103 (19)	17
MRFIT	29	48 (6)	0	7	6	2	93 (13)	81 (13)	4	42	48 (6)	0	7	7	2	90 (13)	89 (13)	3	29	48 (6)	0	7	8	2	82 (11)	92 (12)	3
NZDCS	36	62 (13)	49	0	100	8	82 (22)	65 (24)	11	42	63 (13)	50	0.10	100	5	76 (22)	76 (22)	8	21	62 (14)	53	0	100	5	69 (19)	83 (20)	7
Pima																											
Subtotal	33	53 (17)	58	0	16	5	95 (21)	83 (22)	18	42	53 (16)	57	0	14	4	92 (22)	92 (21)	15	25	52 (17)	59	0	13	4	85 (20)	98 (20)	15
Total	32	59 (18)	43	3	26	16	84 (26)	72 (26)	31	43	61 (18)	40	3	24	17	78 (28)	78 (28)	29	25	60 (18)	42	3	23	17	74 (24)	85 (25)	28

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 eGFR 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

DM: diabetes mellitus; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; alb: albuminuria

*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+

Blank lines for cohorts indicate that the cohorts that did not have enough information in the specified baseline period to contribute to analyses, but are included in the other baseline period analyses.

Supplemental Table 6. Events by baseline period

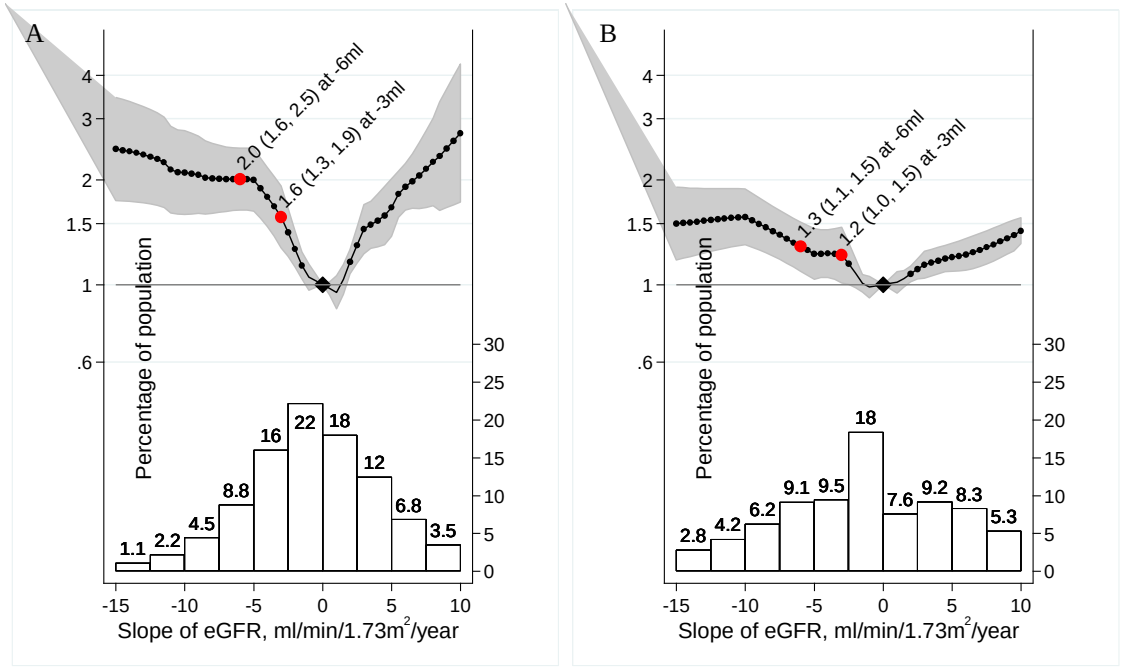
	1y Baseline Period				2y Baseline Period				3y Baseline Period			
Cohorts (n=22)	**N**	**ESRD events**	**Mean (SD) Follow-up**	**Median # Scre (IQR)**	**N**	**ESRD events**	**Mean (SD) Follow-up**	**Median # Scre (IQR)**	**N**	**ESRD events**	**Mean (SD) Follow-up**	**Median # Scre (IQR)**
CKD cohorts												
AASK	1005	296	7 (3)	5 (4-5)	913	251	6 (3)	7 (6-7)	831	206	6 (3)	9 (9-8)
BC CKD	10442	1637	3 (1)	6 (4-8)	8642	1231	2 (1)	10 (8-14)	6274	839	2 (1)	15 (11-20)
CCF	25159	520	2 (1)	3 (2-5)	17133	291	1 (1)	6 (4-9)	10563	111	1 (0.4)	8 (6-12)
CRIB	n/a	n/a	n/a	n/a	190	63	4 (2)	2 (2-2)	n/a	n/a	n/a	n/a
Geisinger	18317	338	4 (2)	4 (3-5)	14870	257	3 (2)	6 (4-9)	11587	179	3 (2)	9 (6-13)
GLOMMS 1	780	80	3 (2)	5 (3-7)	665	57	3 (1)	8 (6-12)	572	42	2 (1)	12 (8-17)
KPNW	1192	89	5 (2)	4 (3-7)	522	31	4 (2)	7 (4-12)	n/a	n/a	n/a	n/a
MASTERPLAN	607	121	4 (1)	5 (4-5)	579	114	4 (1)	8 (7-9)	546	94	3 (1)	11 (9-12)
MDRD	750	546	7 (5)	5 (5-5)	618	444	7 (5)	8 (7-8)	316	236	6 (5)	11 (10-11)
NephroTest	580	124	4 (2)	2 (2-2)	553	95	3 (2)	3 (2-3)	414	67	3 (2)	4 (3-4)
RENAAL	1425	325	2 (1)	6 (6-6)	1201	200	1 (1)	10 (9-10)	885	89	0.4 (0.3)	14 (13-14)
Sunnybrook	3846	248	3 (2)	4 (3-6)	2656	186	3 (2)	7 (5-11)	1888	115	3 (2)	10 (7-15)
VA_CKD	449848	5513	4 (2)	3 (2-4)	342068	3323	3 (1)	5 (4-7)	198374	1278	3 (1)	7 (5-11)
Sub-total	**513951**	**9837**	**2 (1)**	**3 (3-3)**	**390610**	**6543**	**2 (1)**	**5 (5-5)**	**232250**	**3256**	**1 (1)**	**7 (7-7)**
Other cohorts												
ADVANCE	10361	45	4 (1)	3 (3-3)	9999	37	3 (0.5)	4 (4-4)	9402	24	2 (0.4)	5 (5-5)
AKDN	309341	454	2 (1)	2 (2-3)	293214	269	2 (1)	3 (3-4)	230470	137	1 (0.5)	4 (3-6)
ARIC	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	13833	408	16 (4)	2 (2-2)
CHS	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	4012	60	9 (3)	2 (2-2)
KP Hawaii	27561	204	2 (1)	3 (2- 4)	20608	153	1 (0.7)	5 (4, 8)	13350	83	0.7 (0.4)	8 (6, 11)
Maccabi	641986	1023	4 (1)	2 (2-3)	604640	901	3 (1)	3 (3-5)	560426	757	2 (1)	5 (3-7)
MRFIT	11757	277	22 (6)	2 (2-2)	11527	269	21 (6)	3 (3-3)	11306	271	20 (6)	4 (4-4)
NZDCS	15748	518	6 (2)	2 (2-3)	9006	252	6 (2)	3 (3-5)	4388	122	6 (2)	4 (3-7)
Pima	n/a	n/a	n/a	n/a	1606	107	12 (8)	2 (2-2)	786	45	11 (7)	2 (2-2)
Sub-total	**1016754**	**2521**	**4 (3)**	**2 (2-2)**	**950600**	**1988**	**3 (3)**	**3 (3-3)**	**847973**	**1907**	**2 (3)**	**5 (4-5)**
Total	**1530705**	**12358**	**3.1 (2.3)**	**2 (2-3)**	**1341210**	**8531**	**2.4 (2.2)**	**3 (3-5)**	**1080223**	**5163**	**2.0 (2.9)**	**5 (5-5)**

N/A for cohorts indicate that the cohorts that did not have enough information in the specified baseline period to contribute to analyses, but are included in the other baseline period analyses.

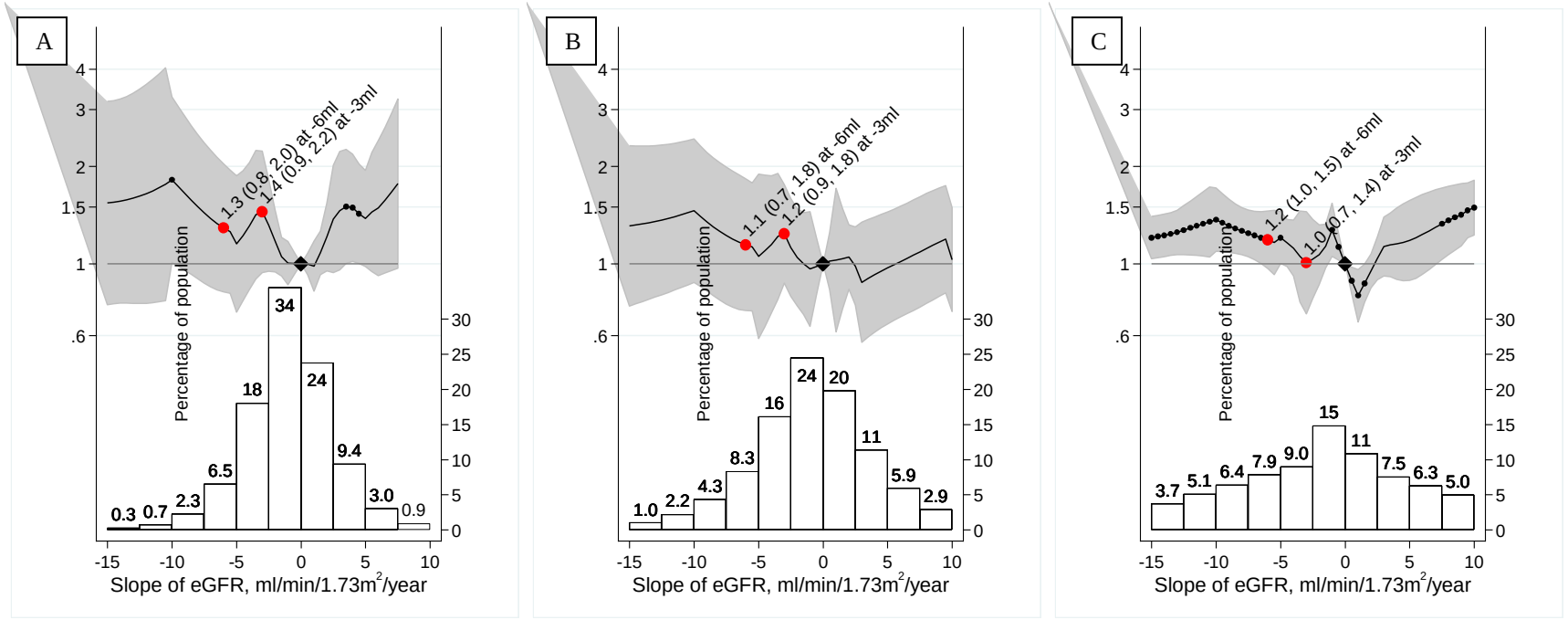
Supplemental Table 7. 1, 3, 5 and 10-year absolute risks of end-stage renal disease associated with slope of eGFR and different levels of last eGFR during a 3-year baseline period.

Follow up time	Last eGFR	6ml decline	4ml decline	2ml decline	Stable	2ml increase	4ml increase	6ml increase
	CKD cohorts							
1 year	20	16%	15%	11%	7.3%			
	35	2.1%	2.0%	1.4%	1.0%	0.89%		
	50	0.28%	0.25%	0.18%	0.13%	0.14%	0.18%	0.20%
3 year	20	45%	42%	32%	22%			
	35	6.9%	6.4%	4.6%	3.2%	2.9%		
	50	0.93%	0.84%	0.59%	0.42%	0.45%	0.58%	0.66%
5 year	20	64%	61%	49%	35%			
	35	12%	11%	7.9%	5.5%	5.0%		
	50	1.6%	1.5%	1.0%	0.73%	0.79%	1.0%	1.1%
10 year	20	90%	88%	79%	63%			
	35	25%	23%	17%	12%	11%		
	50	3.6%	3.3%	2.3%	1.6%	1.8%	2.3%	2.6%
	Other cohorts							
1 year	65	0.010%	0.010%	0.010%	0.006%	0.011%		
	80	0.0057%	0.0055%	0.0056%	0.0058%	0.0063%	0.0061%	0.0057%
3 year	65	0.055%	0.051%	0.053%	0.0343%	0.061%		
	80	0.030%	0.029%	0.030%	0.031%	0.033%	0.033%	0.031%
5 year	65	0.16%	0.15%	0.16%	0.10%	0.18%		
	80	0.091%	0.088%	0.089%	0.094%	0.10%	0.098%	0.092%
10 year	65	0.52%	0.49%	0.51%	0.33%	0.59%		
	80	0.29%	0.28%	0.29%	0.30%	0.32%	0.31%	0.29%

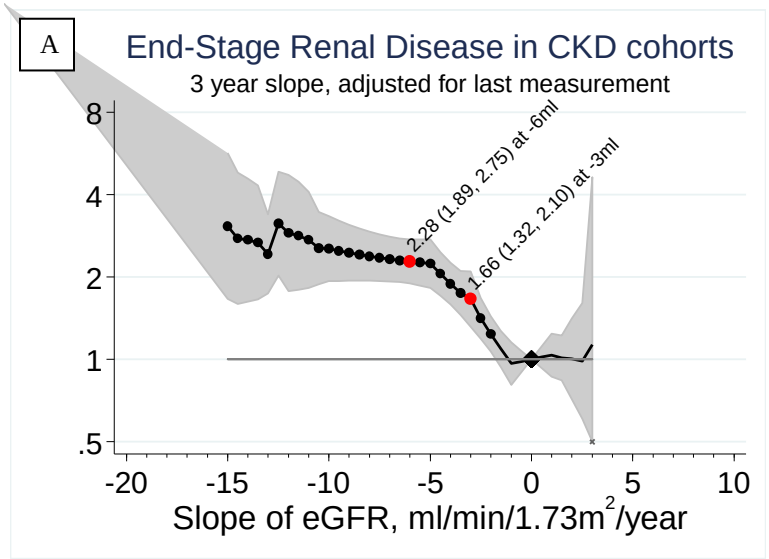
Supplemental Figure 1. Adjusted hazard ratio of end-stage renal disease associated with slope of eGFR during a 2-year (A) and 1-year (B) baseline period, and a histogram of the slope of eGFR in CKD cohorts. Values trimmed at -15ml slope (1.1%, 5.9% of the study population in 2-year, 1-year respectively) and 10ml slope (3.7%, 13.8% of the population 2-year, 1-year respectively). Black dots indicate statistical significance compared with the reference (diamond) slope of eGFR 0 ml/min/1.73m^2/year. Red dots show slope of eGFR -6 ml/min/1.73m^2/year and -3 ml/min/1.73m^2/year.

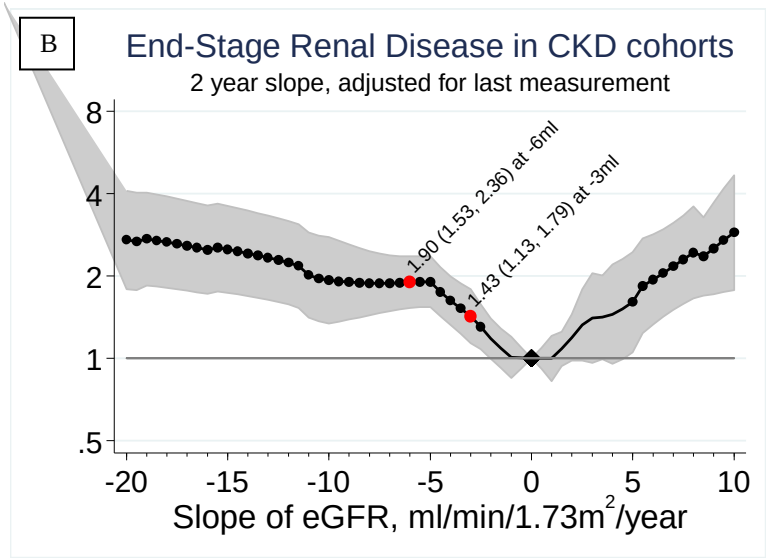


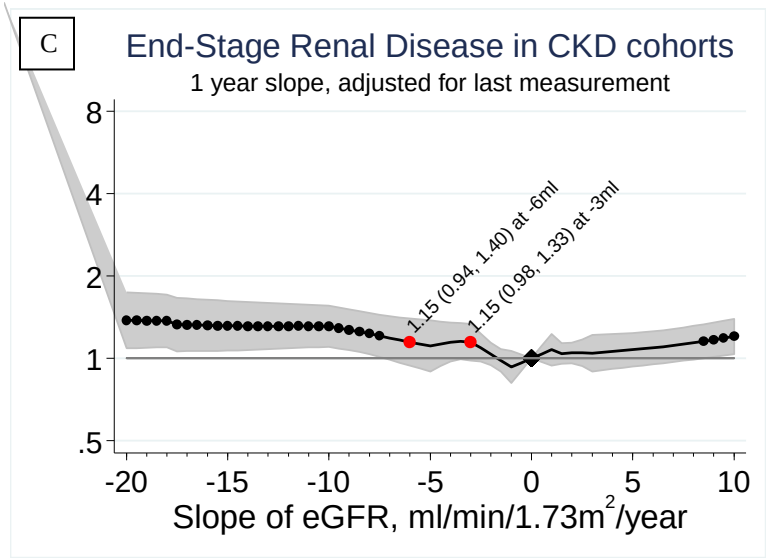
Supplemental Figure 2. Distribution and associated subsequent adjusted hazard ratio of end-stage renal disease by slope of eGFR during a 3-year baseline period (A), 2-year baseline period (B) and 1-year baseline period (C), in other cohorts



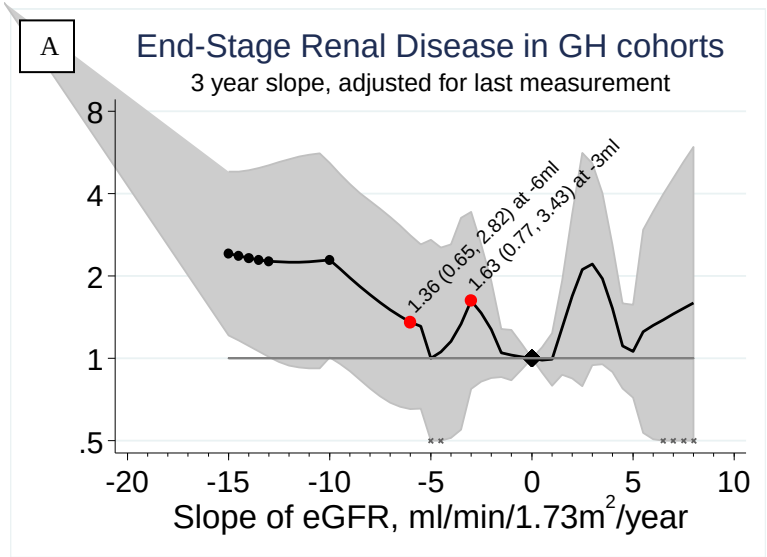
Supplemental Figure 3. Adjusted hazard ratio of end-stage renal disease by slope of eGFR during a 3-year baseline period (A) 2-year baseline period (B) and 1-year baseline period (C), further adjusted for albuminuria in CKD cohorts

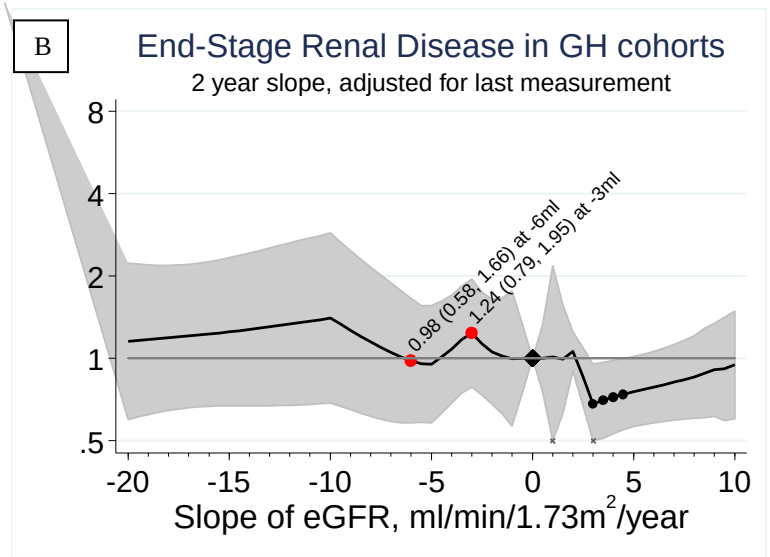


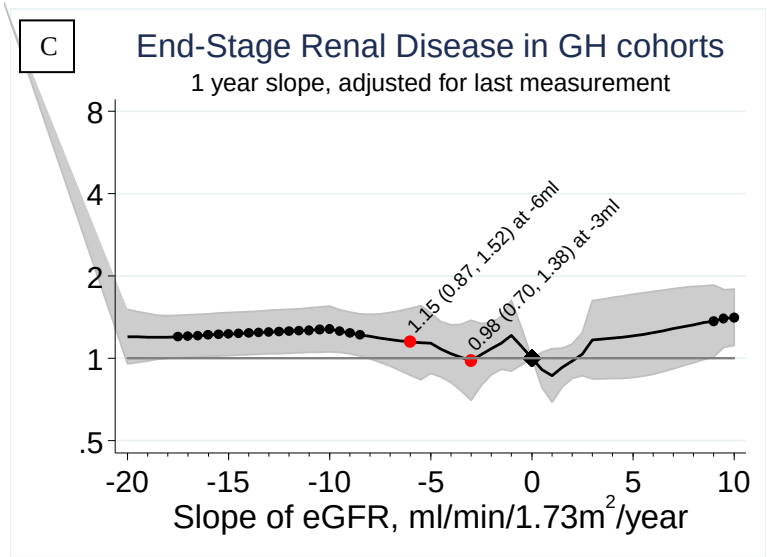




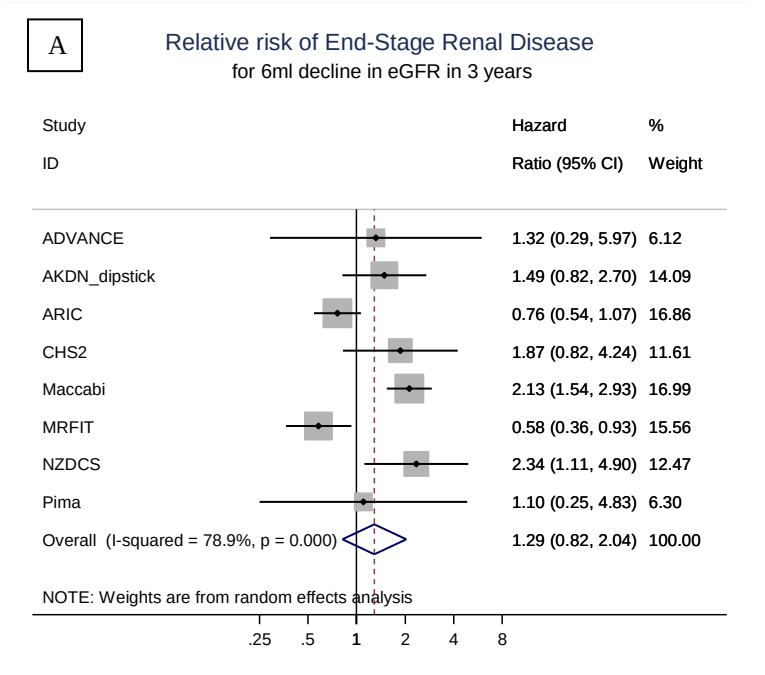
Supplemental Figure 4. Adjusted hazard ratio of end-stage renal disease by slope of eGFR during a 3-year baseline period (A) 2-year baseline period (B) and 1-year baseline period (C), further adjusted for albuminuria in other cohorts

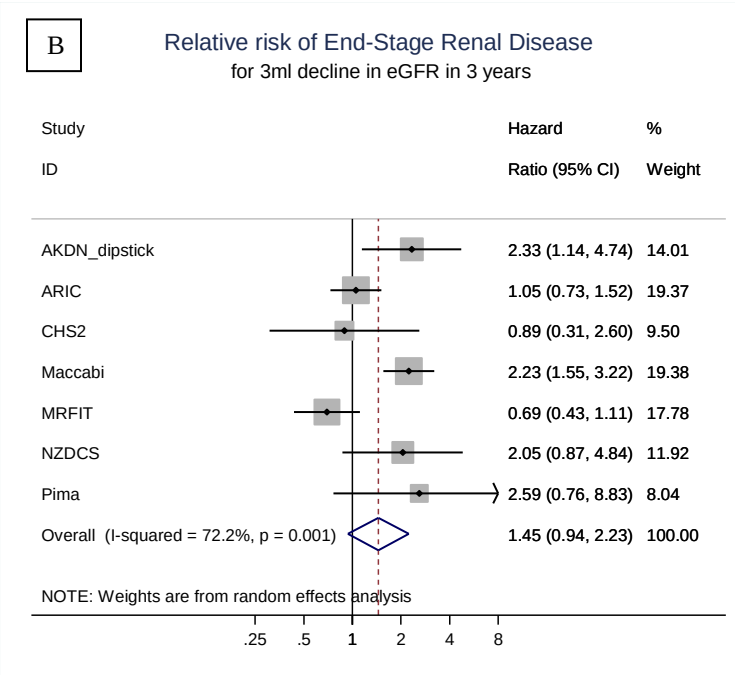




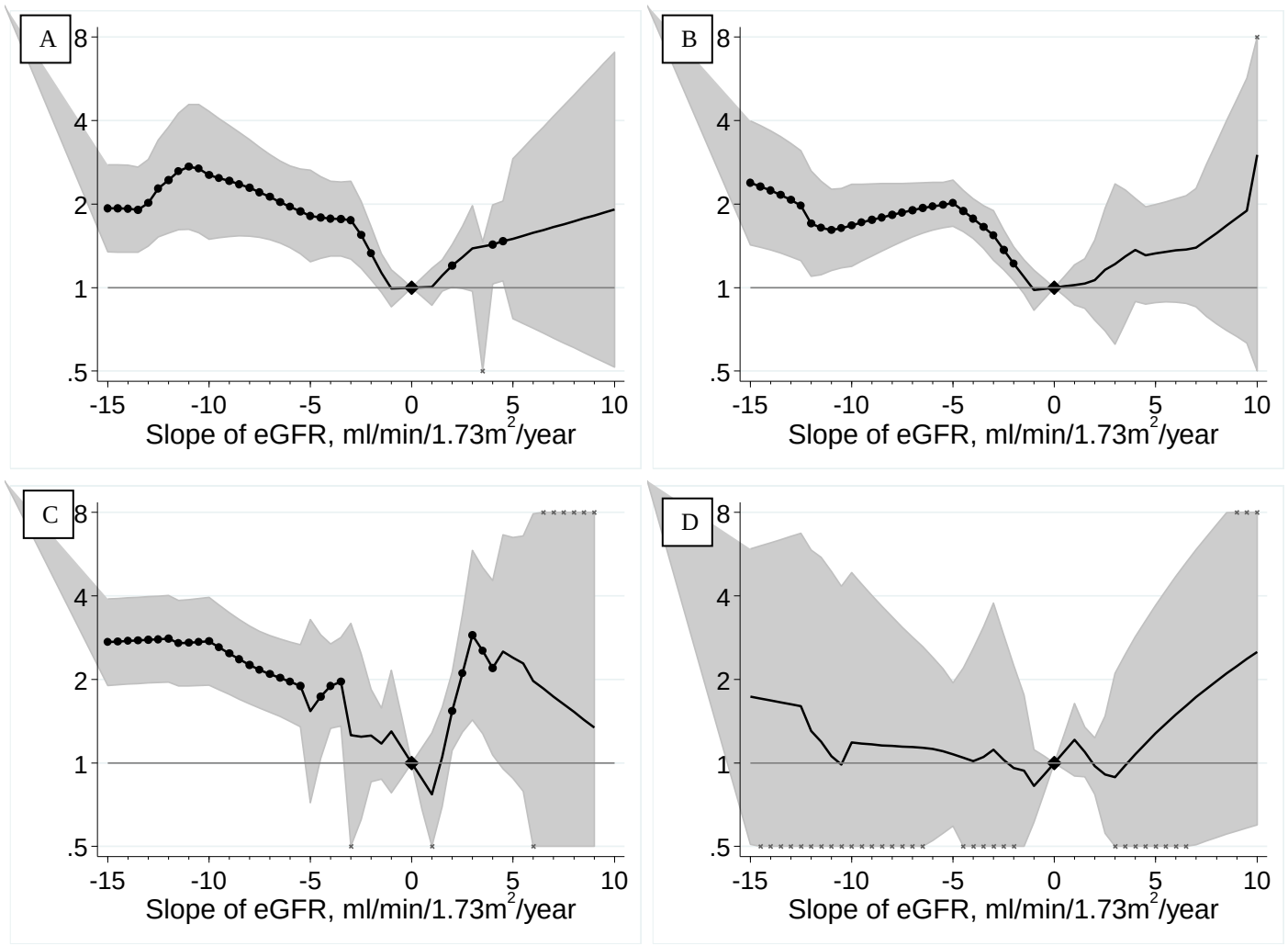


Supplemental Figure 5. Adjusted relative hazard of end-stage renal disease for 6ml (A) and 3ml (B) decline in eGFR in 3 years in other cohorts

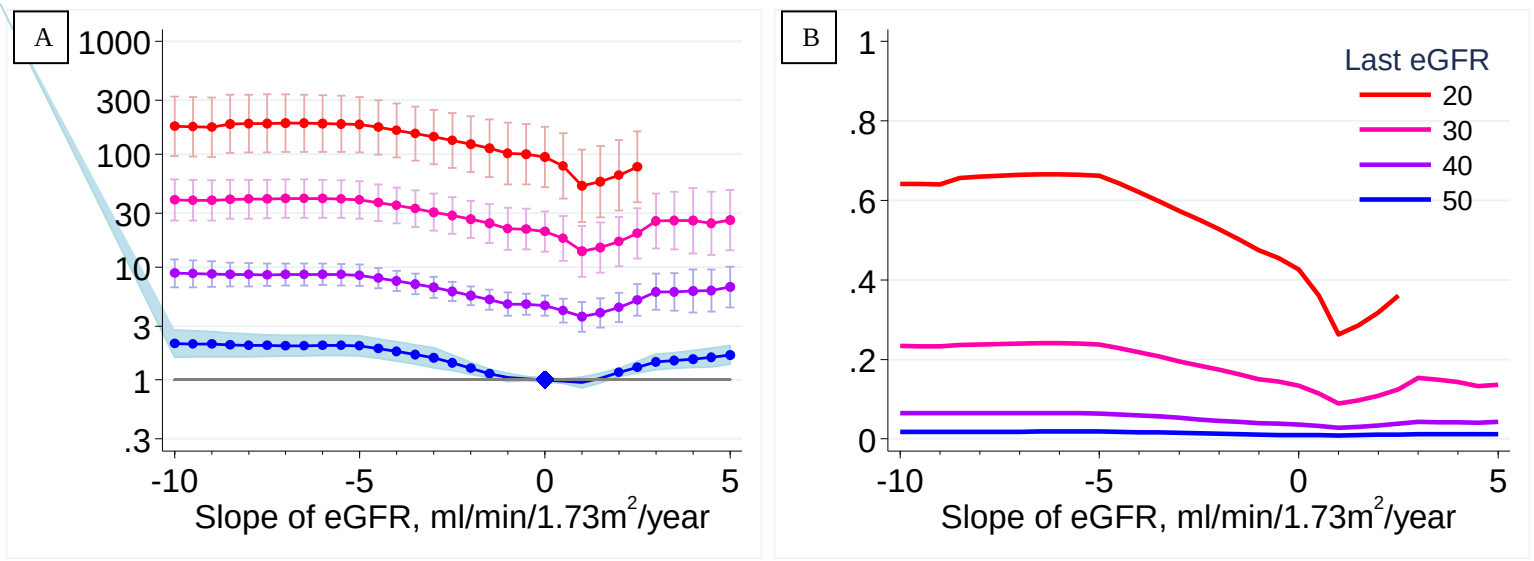




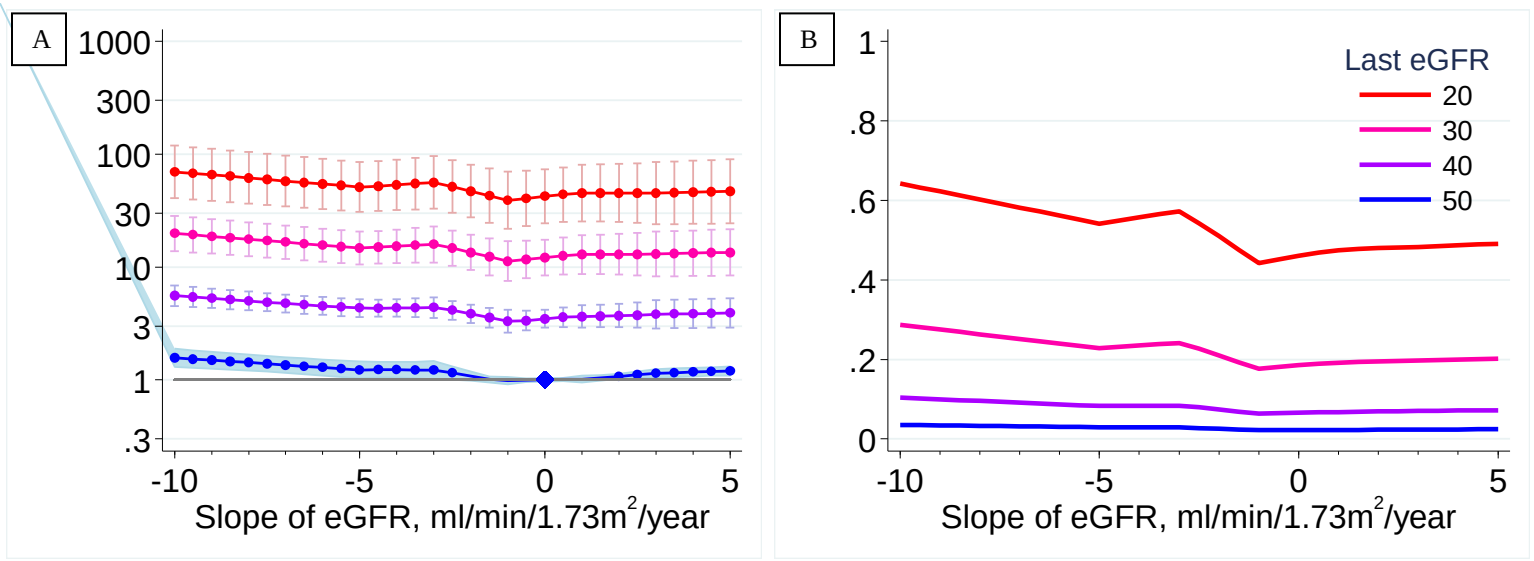
Supplemental Figure 6. Adjusted hazard ratio of end-stage renal disease by slope of eGFR during a 3-year baseline period in patients exposed to renin-angiotensin-aldosterone system inhibitor medications (A and C) and in those not exposed to such agents (B and D), in CKD (A and B) and in other cohorts (C and D).



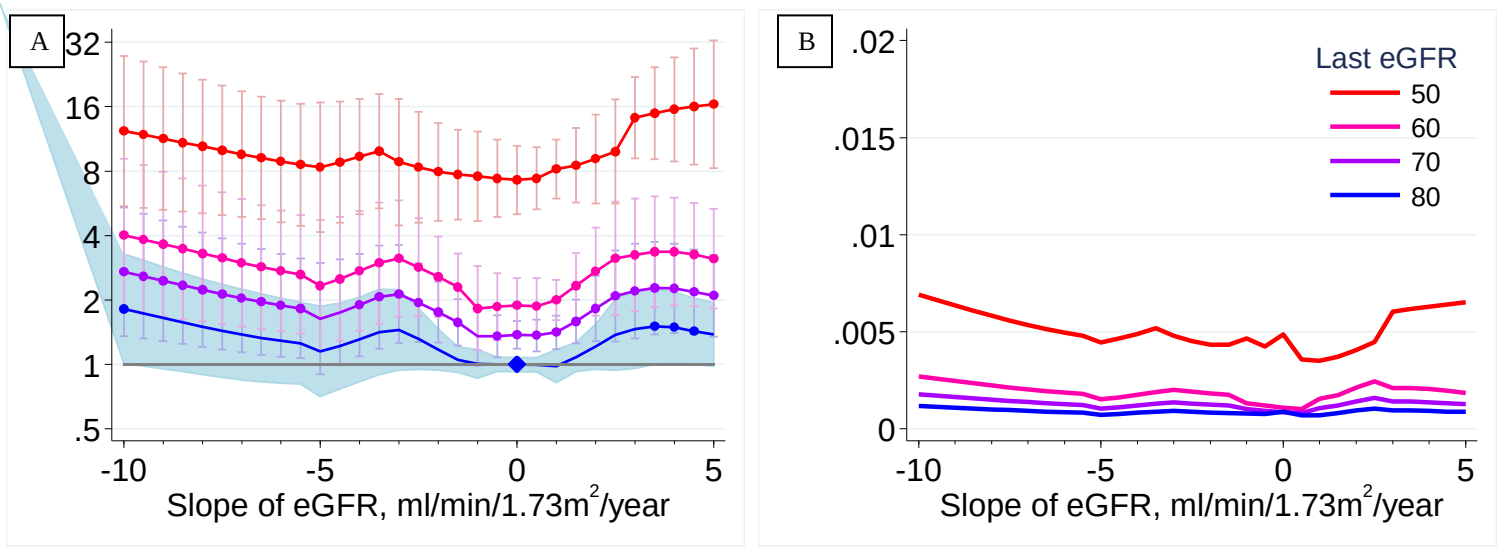
Supplemental Figure 7. Adjusted hazard ratio and absolute risk of end-stage renal disease, vs. slope of eGFR during a 2-year baseline period in CKD cohorts



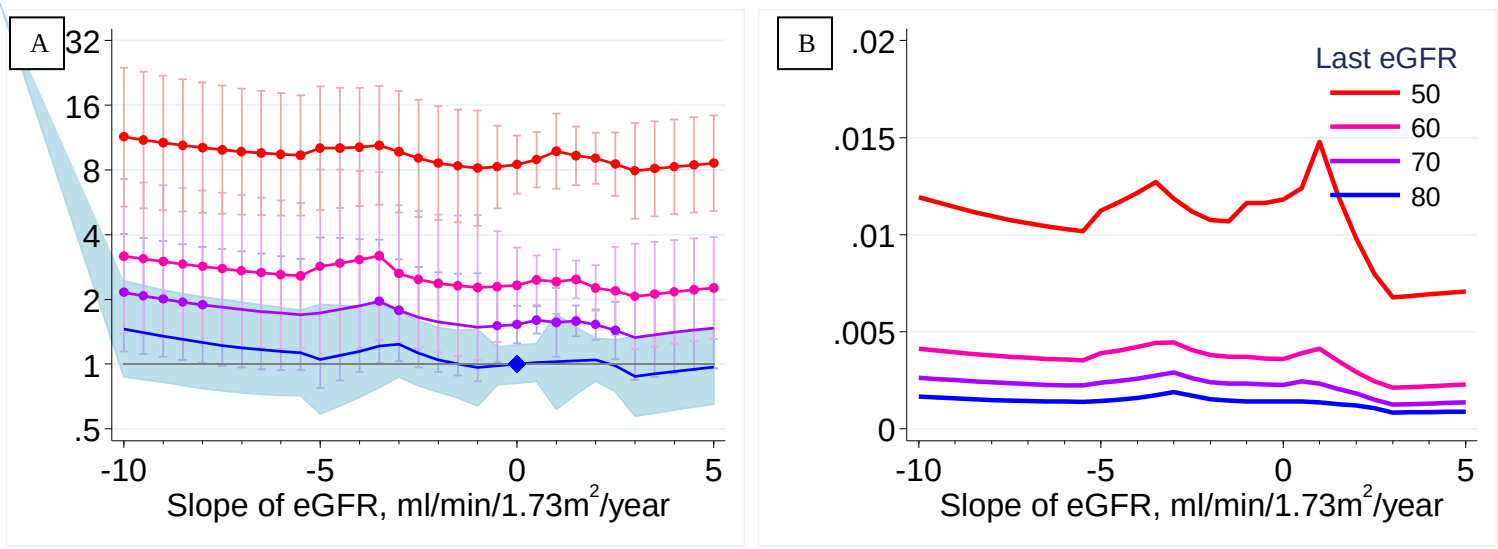
Supplemental Figure 8. Adjusted hazard ratio and absolute risk of end-stage renal disease, vs. slope of eGFR during a 1-year baseline period in CKD cohorts



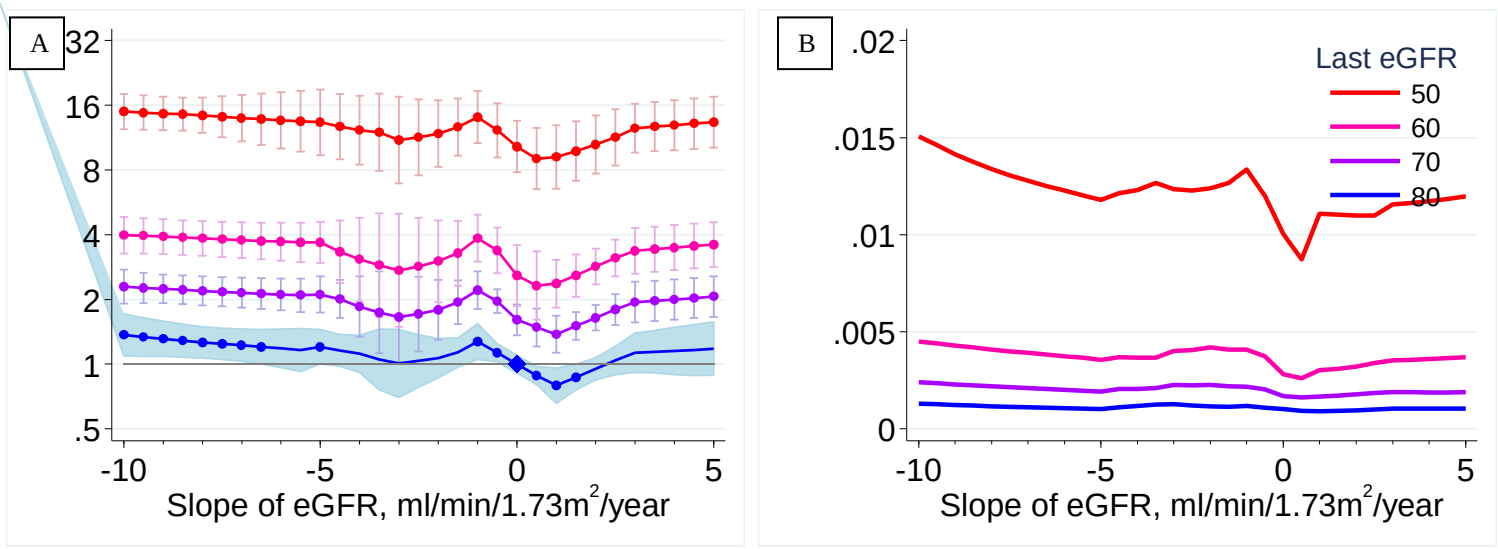
Supplemental Figure 9. Adjusted hazard ratio and absolute risk of end-stage renal disease, vs. slope of eGFR during a 3-year baseline period in other cohort



Supplemental Figure 10. Adjusted hazard ratio and absolute risk of end-stage renal disease, vs. slope of eGFR during a 2-year baseline period in other cohorts



Supplemental Figure 11. Adjusted hazard ratio and absolute risk of end-stage renal disease, vs. slope of eGFR during a 1-year baseline period in other cohorts



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