Evaluating Glomerular Filtration Rate Slope as a Surrogate Endpoint for ESKD in Clinical Trials:

An Individual Participant Meta-Analysis of Observational Data

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SIGNIFICANCE

Randomized clinical trials of interventions to slow chronic kidney disease progression often require large sample sizes and long follow-up due to low numbers of clinical events, particularly in populations with earlier stages of CKD. This observational meta-analysis of 14 cohorts evaluated the validity of use of slope of eGFR decline as a surrogate endpoint for established clinical outcomes. Addressing a central tenet of surrogacy, lesser eGFR decline was significantly associated with lower risk of end-stage kidney disease in all populations, including those with relatively preserved kidney function. In conjunction with recent work in clinical trials and statistical simulation, these results may support the validity of eGFR slope as a surrogate endpoint in certain clinical trials.

ABSTRACT

Background: Decline in GFR is a biologically plausible surrogate endpoint for progression of chronic kidney disease (CKD) in clinical trials. The aim of this observational study was to investigate the utility of 1-, 2-, and 3-year eGFR slope as a surrogate by quantifying its association with clinical events over a longer time horizon, with a particular emphasis on the population with higher baseline eGFR, in which clinical events are relatively rare.

Methods: Using random-effects, individual-participant data meta-analysis, we estimated the association between eGFR slope and end-stage kidney disease (ESKD) in individuals with baseline eGFR ≥60 ml/min/1.73 m^2 (N=3,758,551) and eGFR <60 ml/min/1.73 m^2 (N=122,664) in 14 cohorts followed on average for 4.2 years.

Results: A lesser eGFR decline by 0.75 ml/min/1.73 m^2/year over two years was related to lower risk of ESKD in participants with baseline eGFR ≥60 and <60 ml/min/1.73 m^2 (adjusted hazard ratios, 0.70 [95% CI: 0.68-0.72] and 0.71 [95% CI: 0.68-0.74], respectively), with stronger associations when estimated over longer time periods. For a rapidly progressing population with predicted 5-year risk of ESKD of 8.3%, an intervention that reduced eGFR decline by 0.75 ml/min/1.73 m^2/year could reduce the ESKD risk by 1.6%. For a hypothetical low-risk population with a predicted 5-year ESKD risk of 0.58%, the same intervention would reduce the risk by only 0.13%.

Conclusions: Lesser decline in eGFR was associated with lower risk of subsequent ESKD, even in participants with eGFR ≥60 ml/min/1.73 m^2, but the magnitude of potential benefit varies with the underlying risk of the population.

INTRODUCTION

There are few therapies that slow or prevent chronic kidney disease (CKD) progression, particularly in early-stage CKD.[1, 2] New interventions must be developed and tested in randomized controlled trials. Unfortunately, clinical trials in persons with earlier stages of CKD can be impractical and costly due to the necessary large sample size and long duration of follow-up, since established clinical endpoints such as end-stage kidney disease (ESKD) and doubling of serum creatinine are uncommon and occur late in the disease process. In March 2018, the National Kidney Foundation, in collaboration with the Food and Drug Administration and European Medicines Agency, sponsored a workshop entitled "Change in Albuminuria and GFR as End Points for Clinical Trials in Early Stages of Chronic Kidney Disease" to evaluate the validity of surrogate endpoints that occur earlier in CKD progression, with the goal of facilitating the development and testing of novel therapies.[3-5]

This study is the first in a series of manuscripts that report analyses undertaken for the workshop that evaluate glomerular filtration rate (GFR) decline as a surrogate endpoint for CKD progression in clinical trials.[6] A clinical trial designed to show a difference in slope of GFR decline between randomized treatment arms could require a smaller sample size and shorter follow-up than a trial designed to show a difference in the occurrence of clinical endpoints (e.g., ESKD or even the surrogate endpoints of 30-40% decline in GFR, sometimes used by the US Food and Drug Administration and European Medicines Agency), particularly in a population with higher baseline GFR. However, potential surrogates must undergo rigorous evaluation in a variety of settings.[6, 7] The current study was designed to address the first tenet for surrogacy put forth by Prentice, namely that a surrogate have a strong association with the clinical endpoint.[7] The second manuscript in this series evaluates the evidence for the tenet that a treatment effect on the surrogate must capture the treatment effect on the clinical endpoint.[8] The third,

a statistic simulation, demonstrates clinical trial settings which might benefit from the use of GFR slope as an endpoint while preserving a low risk of false conclusions.[9]

The current study used individual-participant data from observational cohorts participating in the CKD Prognosis Consortium (CKD-PC) for the following goals: 1) to quantify the magnitude of association between eGFR decline over a 1-, 2-, and 3-year time frame with subsequent, longer-term risk of ESKD; 2) to determine whether the magnitude of association was similar in different subgroups of participants, particularly those with baseline eGFR ≥60 ml/min/1.73 m^2; 3) to consider different methods of estimating individual slope, and the implications of using these methods on the associations with the clinical endpoint; 4) to confirm that associations with death were consistent in direction to those observed with ESKD; and 5) to provide insight on groups of patients in which GFR slope would (and would not) be a plausible candidate surrogate endpoint given expected absolute risk reduction.

METHODS

Study Design and Data Sources

The CKD-PC is an open, international research group that currently includes over 70 cohorts with data on eGFR, albuminuria, and clinical outcomes.[10] For the current study, we included cohorts that could participate in all of the 1-, 2-, and 3-year baseline periods and had subsequent longitudinal follow-up for ESKD. Slope during the baseline period was estimated for all participants with at least two eGFR measures separated by the desired time window, which was defined as 1, 2, or 3 years +/- 33%, respectively, but we required that at least some of the participants have three measures, so as to be able to detect a difference between mixed model and empirical estimates of slope. We stratified analyses by baseline eGFR, conducting separate meta-analyses for individuals with eGFR < and ≥60

ml/min/1.73 m^2. Included cohorts could contribute to both meta-analyses if there were sufficient numbers of individuals who developed ESKD (>10 events) within the given eGFR subgroup.

A total of 14 cohorts had the requisite data and agreed to participate (**eAppendix 1**). From these 14 cohorts, we included participants aged ≥18 years old without ESKD that developed during or before the baseline period. The Johns Hopkins Bloomberg School of Public Health Institutional Review Board approved this study.

Estimating eGFR Slope

Outpatient serum creatinine values were converted to eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[11] Clinical trials have generally estimated eGFR slope using mixed models to reduce the variance derived from unreliable estimates. Thus, as a primary exposure, we used linear mixed models with an unstructured variance-covariance matrix and random intercept and random slope for each individual to estimate slope (*mixed model slope*).[12] Models took the form $eGFR_i(t) = b0 + b0_i + (b1+b1_i)*t + e_i$, where t is time, b0 and b1 are the fixed intercept and slope, and $b0_i$ and $b1_i$ are the random intercept and slope, respectively. For comparison, slope was also empirically estimated for each individual using least squares linear regression of all measures of eGFR on time (*least squares slope*) during the given baseline period (1-, 2-, or 3-years). The 2-year slopes were considered the primary exposure of interest.

Outcome

The primary outcome was ESKD, defined as the initiation of kidney replacement therapy (**eAppendix 1**). The secondary outcome was all-cause mortality. Time at risk for both outcomes began on the date of the last creatinine used in the eGFR slope estimate.

Statistical Analysis

Individual cohort characteristics were summarized using means and standard deviation for continuous variables, and proportions for categorical variables. These characteristics – age, sex, race (black, non-black), baseline eGFR, systolic blood pressure, diabetes mellitus status, history of cardiovascular disease, smoking status, and total cholesterol – were measured within one year before the first serum creatinine used in the slope estimation, and used as adjustment variables in subsequent models. Cox models related individual eGFR slope estimates during the baseline period to risk of ESKD and mortality thereafter, with eGFR slope modeled as a two-piece linear spline with a knot at 0 ml/min/1.73 m^2 per year. This was repeated within strata of age, sex, and diabetes, hypertension, and cardiovascular disease status. Within-cohort coefficients for each spline piece of eGFR slope were combined using random effects meta-analysis. Heterogeneity in estimates was evaluated visually through forest plots and quantified using the I^2 statistic. In sensitivity analyses, we assessed the impact of varying numbers of eGFR measurements by focusing on study participants with 5 or more measures of eGFR. We compared estimates of the eGFR slope-ESKD association using all eGFR measures to those that assessed slope using only 3 measures.

We estimated the absolute risk reduction of ESKD for an individual assuming a difference in eGFR slope of 0.75 ml/min/1.73 m^2/year by applying hazard ratios from the mixed model slopes to baseline subhazard of ESKD risk (estimated by the method of Fine and Gray and using mortality as a competing event).[13] The scenarios consisted of baseline eGFR 75 ml/min/1.73 m^2, fixed levels of covariates (chosen to reflect the mean value across cohorts), and predicted eGFR slopes of -1, -3, and -5 ml/min per 1.73 m^2 per year over two years for baseline urine albumin-to-creatinine of 10 mg/g, 30 mg/g and 100 mg/g, assuming no change in albuminuria. We then estimated the absolute risk reduction of ESKD for a

hypothetical population by assuming variation (standard deviation of 4 ml/min/1.73 m^2 per year) around the mean eGFR slope of -1, -3, and -5 ml/min/1.73 m^2 per year over two years based on the same covariates. We also examined the proportion of individuals reaching a 30% and 40% reduction in eGFR during the baseline period. Analyses were performed using Stata/MP 14.2 software for Windows (www.stata.com).

RESULTS

Baseline characteristics of included cohorts

Across the 14 cohorts, there were 3,353,210 individuals included in the 1-year eGFR slope analysis, 3,881,215 in the 2-year analyses, and 3,943,212 in the 3-year analyses, respectively (**Table 1**). There were 12 cohorts in the eGFR <60 ml/min/1.73 m^2 analyses, and 7 in the eGFR ≥60 ml/min/1.73 m^2 analyses (5 of the cohorts were in both). In the 2-year eGFR <60 ml/min/1.73 m^2 analyses, average age was 71 years, 56% were women, and 3% were black. Mean eGFR was 47 ml/min/1.73 m^2 and 28% had diabetes mellitus. In the 2-year eGFR ≥60 ml/min/1.73 m^2 analyses, average age was 56 years, 24% were women, and 11% were black. Mean eGFR was 89 ml/min/1.73 m^2 and 21% had diabetes mellitus. Cohort characteristics were fairly similar in the 1- and 3-year observation periods (**eTable 1-2**).

Summary of eGFR slope within cohorts

Over the 2-year baseline period, the within-cohort median number of serum creatinine measurements ranged from 3 to 13 in the eGFR <60 ml/min/1.73 m^2 cohorts, and 3 to 5 in the eGFR ≥60 ml/min/1.73 m^2 cohorts. Subsequent to this baseline period, there were 6,083 ESKD events and 44,135 deaths over a mean follow up of 3.3 years in the eGFR <60 ml/min/1.73 m^2 cohorts and 6,552 ESKD events and 520,061 deaths over 4.2 years in the eGFR ≥60 ml/min/1.73 m^2 cohorts (**eTable 3**). Median number of serum creatinine measurements and subsequent follow-up time and number of events for the 1- and 3-

year baseline periods are shown in **eTable 4** and **eTable 5**. The 2-year mixed model mean slope ranged from -4.92 to 0.27 ml/min/1.73 m^2 per year and -3.71 to -1.06 ml/min/1.73 m^2 per year in the eGFR <60 and ≥60 ml/min/1.73 m^2 cohorts, respectively (**eTable 6**). Standard deviations of eGFR slopes were smaller with longer observation periods (median for ≥60 ml/min/1.73 m^2 cohorts: 6.0, 3.7, and 3.1 for 1-year, 2-year, and 3-year slopes, respectively), and mean slopes were generally more modest. Even among rapid progressors with 2-year eGFR slope <-3 ml/min/1.73 m^2/year, few clinical endpoints of 30% or 40% change occurred, particularly at higher eGFR: 15.6% and 5.6%, respectively, among eGFR ≥60 ml/min/1.73 m^2 and 48.2% and 23.8%, respectively, among eGFR <60 ml/min/1.73 m^2.

Associations of eGFR slope with subsequent ESKD within cohorts

In both unadjusted and covariate-adjusted analyses, a steeper eGFR decline over a 2-year observation period was associated with higher risk of subsequent ESKD. This association was statistically significant in meta-analysis within both strata of eGFR and over all observation periods (**Figure 1a & 1B, eFigure 1**). A lesser eGFR decline by 0.75 ml/min/1.73 m^2 per year was associated with lower risk of ESKD in all individual cohorts (**eTable 7**) and within strata of age, sex, and diabetes, hypertension, and cardiovascular disease status (**eFigure 2-6**). Associations were stronger when estimated over a longer baseline period and weaker when estimated using least squares (**Figure 2A**). Conditioned on having a complete 2-year baseline period, the association between 2-year slope and ESKD was not stronger when eGFR decline was estimated using 5 or more eGFR measurements compared to eGFR decline based on 3 eGFR measurements. Overall, a reduction in mixed model slope of eGFR decline by 0.75 ml/min/1.73 m^2 per year over 2-years was associated with a 29% and 30% lower risk of subsequent ESKD in participants with baseline eGFR <60 and ≥60 ml/min/1.73 m^2, with some quantitative but little qualitative heterogeneity in associations across cohorts (**Figure 3**). Findings were similar when stratified by use of ACE-I/ARB at the beginning and end of the baseline period (**eFigure 7**).

Associations of eGFR slope with subsequent mortality within cohorts

A lesser eGFR decline by 0.75 ml/min/1.73 m^2 per year was associated with lower risk of subsequent mortality, although the magnitude of this association was small compared to the association with ESKD and not statistically significant in every cohort (**eTable 8**). Associations were also stronger when slopes were observed over longer baseline periods (**Figure 2B**).

Absolute risk reduction of ESKD associated with a lesser slope of eGFR decline

The expected reduction in absolute risk of ESKD associated with a 0.75 ml/min/1.73 m^2 per year lesser slope of eGFR decline was greatest in individuals with a greater predicted eGFR decline (**Figure 4A**). For a hypothetical population with mean eGFR of 75 ml/min/1.73 m^2 and mean (standard deviation) eGFR decline of -5 (4) ml/min/1.73 m^2 per year, the predicted 5-year risk of ESKD was 8.3%. A treatment effect that reduced eGFR decline by 0.75 ml/min/1.73 m^2 per year would be expected to reduce the 5-year ESKD risk to 6.7% (**Figure 4B**). On the other hand, the expected reduction in absolute risk of ESKD would be much lower in a population with slower decline: the same intervention would reduce 5-year ESKD risk from 0.58% to 0.45% in a population with a mean eGFR decline of -1 (4) ml/min/1.73 m^2 per year.

DISCUSSION

In this global, individual-participant data meta-analysis spanning more than 3 million participants, we provide evidence that short-term eGFR decline exhibits a strong and robust association with risk of subsequent ESKD, with a reduction in slope of eGFR decline by 0.75 ml/min/1.73 m^2 per year over 2-years associated with a 30% lower risk of subsequent ESKD. These results add to the analyses of clinical trials – where a treatment effect of 0.75 ml/min/1.73 m^2/year in the total slope was associated with a 27% lower hazard for the treatment effect on the clinical endpoint – by quantifying the associations

between slope measured over the relative short-term with the subsequent long-term risk of clinical events, and by demonstrating consistency, even in populations with eGFR ≥60 ml/min/1.73 m^2. Coupled with simulation studies, however, they also suggest that eGFR slope as a surrogate endpoint may not be useful in slowly progressive populations, nor in short-term studies, particularly when a treatment has an acute effect on eGFR.

Theoretically, treating patients early in the disease course, before substantial GFR decline occurs, may be more beneficial than a treatment delivered in advanced disease, when little is preventable. Some causes of CKD, such as polycystic kidney disease (PKD), diabetes mellitus, and diseases with severely increased albuminuria, are considered high risk for progression to ESKD, even with higher GFR. However, drug development in a high-risk population with early disease is challenging in the absence of accepted surrogate biomarkers. When the expected timeframe for developing clinical events is long, such as is the case for ESKD or even a 30-40% decrease in GFR, trials may be prohibitively expensive. For example, an individual with baseline eGFR of 75 ml/min/1.73 m^2 and a rapid eGFR decline of 5 ml/min/1.73 m^2 per year would take 4.5 years to experience a 30% decrease in eGFR. In our study, even in the subpopulation with 2-year mixed model slopes <-3 ml/min/1.73 m^2, only 15.6% of participants with eGFR ≥60 ml/min/1.73 m^2 experienced a 30% decrease in eGFR (5.6% reached a 40% decrease), providing limited power for a theoretical clinical trial.

Slope of GFR decline is a biologically plausible surrogate since it is on the path to ESKD, and there are previous trials which have used eGFR slope as a primary or secondary endpoint.[3, 4, 14-18 19] Although our results provide support for the use of difference in eGFR slope by treatment arms as an endpoint in clinical trials, we note several points of caution. First, our analyses only evaluated efficacy with respect to end-stage kidney disease and death. Specific interventions may have associated harms and, no matter

the magnitude of those risks, the risk-benefit ratio increases when the expected benefit is diminished. Second, although simulation studies have shown that the use of eGFR slope as a surrogate will provide greater efficiency in trials with high mean baseline GFR, our results suggest that a reduction in slope has likely benefit with respect to preventing kidney outcomes only in rapidly progressive populations. Third, a substantial portion of the study population had positive slopes, and an intervention that may improve GFR by increasing single nephron GFR rather than reducing nephron loss may not result in long-term benefit. Fourth, a surrogate endpoint will likely not be useful for clinical trials in populations with high risks of competing events such as death.

An interesting question in the design of clinical trials is how often and how long to assess eGFR during an intervention. Data from our study suggests stronger associations with the clinical endpoint with longer periods of observation. Although we observed no difference in associations between 2-year slope and ESKD whether using 3 or 5+ measures of creatinine, we caution that this analysis was conditioned on complete observation for slope. Clinical trialists cannot know which participants will complete the trial at enrollment; thus, a study design with infrequent interval eGFR risks losing information on participants who are lost to follow-up. Analyses of clinical trials and simulations suggest that a longer duration of follow-up helps mitigate bias from any acute effect of an intervention.[8, 9] Further studies are needed to test whether adding additional filtration markers, such as cystatin C or other low molecular weight serum proteins, or measurement of GFR using clearance of filtration markers, may help further reduce measurement error in slope estimation.

Strengths of the present study include the large sample size, rigorous individual participant-level data meta-analysis, evaluation of association within strata of age, sex, eGFR, diabetes, and other comorbidities, and investigation of different observation periods to estimate eGFR slope. However,

some limitations must also be mentioned. We evaluate differences in slopes between persons, not a response to therapy within a person or between therapeutic groups. The reason individuals have different slopes is unknown, and thus we extrapolate in the application to clinical trials and the effect of an intervention. We did not model non-linearity in slope nor changes in therapy during the observation period, preferring to focus on the approach with fewest assumptions and most closely resembling an intention-to-treat analysis. Nonetheless, recent studies do suggest that eGFR trajectories during 1-4 years among clinical trial participants are most often compatible with linearity.[20] Finally, the estimates of absolute risk reduction reflect a scenario in which there is no change in albuminuria in the baseline period.[13]

In summary, results from this global, individual participant-level meta-analysis demonstrate a consistent association between eGFR slope and subsequent development of ESKD, even when the slope difference is small and observed over only one to three years. Results were consistent with those estimated from clinical trials[8] and suggest the validity of GFR slope as a surrogate endpoint in clinical trials designed to slow kidney disease progression. Our results were robust in individuals with eGFR >60 ml/min/1.73 m^2, an important population where early therapy may be most effective to prevent long term outcomes but time to event analyses have little power. However, eGFR slopes do not address safety, and they are unlikely to be useful in the short-term for a treatment with an acute effect, or a population with low risk of CKD progression. In conjunction with recent work in clinical trials and statistical simulation,[8, 9] these results may support the validity of eGFR slope as a surrogate endpoint in select clinical trials.

Author contributions: MEG, YS, SHB, KM, and JC had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. MEG, KM, LAI, RTG, ASL, and JC were responsible for the study concept and design. MEG, YS, SHB, KM, LAI, and JC with the CKD-PC investigators/collaborators listed below were involved in the acquisition of data. MEG, YS, and JC drafted the manuscript. All the authors contributed to the analysis and interpretation of data and to the critical revision of the manuscript for important intellectual content. MEG guarantees the integrity of the work. All authors approved the final version of the manuscript.

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Supplementary Material

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eFigure 6. Forest plot of adjusted hazard ratios for end-stage kidney disease associated with a 0.75 ml/min per 1.73 m^2 per year change in estimated glomerular filtration rate over 2-years estimated using linear mixed models, stratified by baseline estimated glomerular filtration rate and history of cardiovascular disease status

eFigure 7. Adjusted hazard ratios for end-stage kidney disease associated with a 0.75 ml/min/1.73 m2 per year change eGFR over 2-years estimated using linear mixed models, stratified by baseline estimated glomerular filtration rate and including an interaction term for category of ACE/ARB use at first and last visit (e.g. New use corresponds to no use at the first visit and use at the last visit of the baseline period used to calculate the slope of eGFR decline).

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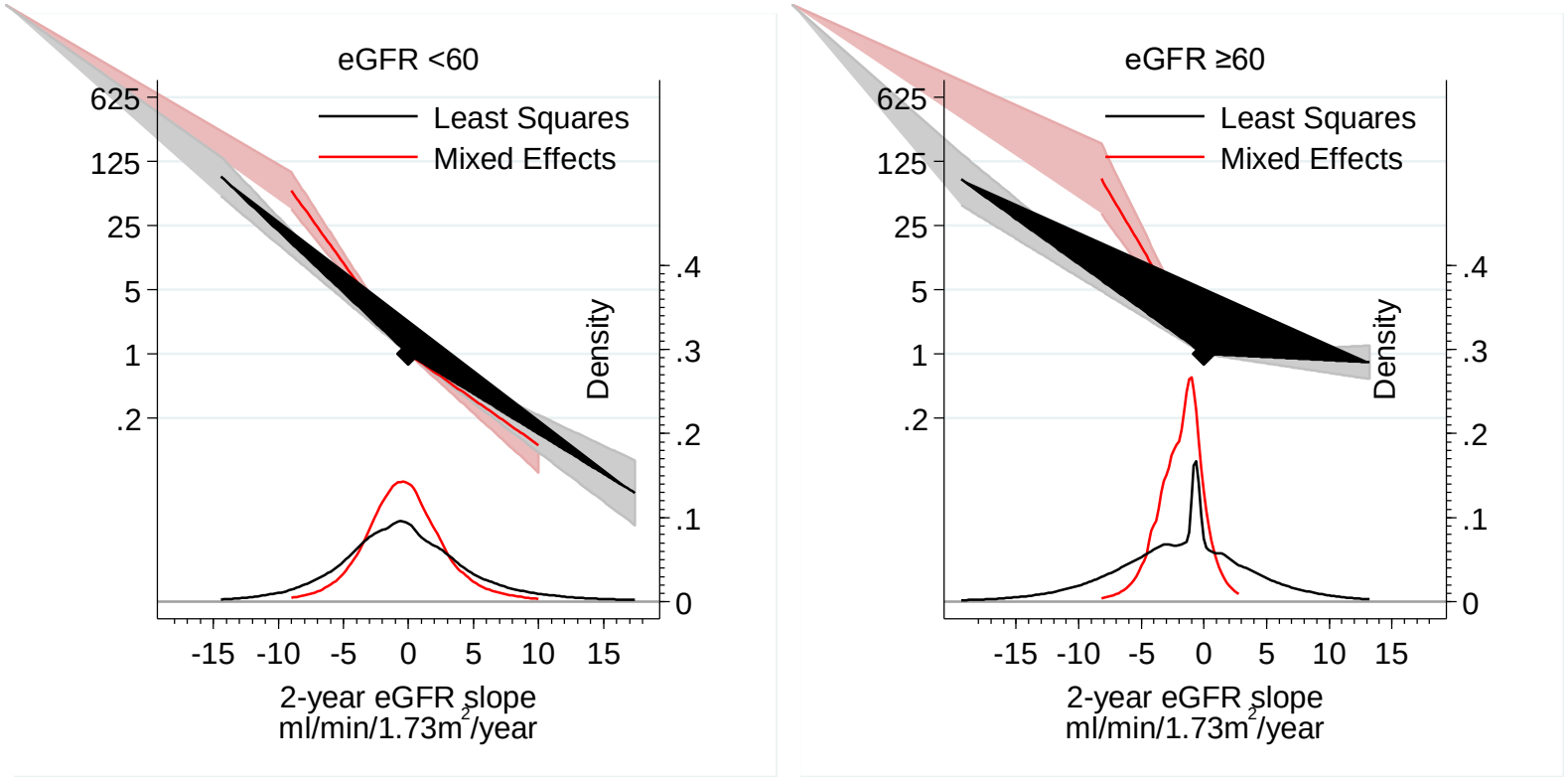
Table 1. Baseline characteristics of individuals in cohorts participating in the 2-year observation period for change in estimated glomerular filtration rate over time, stratified by baseline estimated glomerular filtration rate

eGFR<60	**N**	**Age, years**	**Female, %**	**Black, %**	**eGFR, ml/min /1.73m^2**	**SBP, mmHg**	**Diabetes, %**	**History of CVD, %**	**Current smoker, %**	**Former smoker, %**	**TC, mmol/L**
AASK	744	54 (11)	39	100	42 (11)	150 (24)	0	53	44	28	5.5 (1.1)
BC CKD	8950	70 (13)	46	0	32 (11)	136 (23)	44	24	2.6	6.1	NA
CCF	18873	72 (11)	55	12	47 (10)	131 (19)	25	25	0.2	2.3	4.7 (1.1)
Geisinger	19200	73 (12)	62	0.8	47 (11)	134 (20)	28	42	8.4	27	5.0 (1.1)
KP Hawaii	5468	71 (11)	53	0	47 (10)	137 (22)	52	35	7.4	NA	4.7 (1.1)
Maccabi	29211	74 (11)	50	0	49 (10)	134 (19)	32	47	1.09	19	4.8 (1.1)
MASTERPLAN	513	61 (12)	31	0	36 (11)	136 (20)	24	30	21	53	4.8 (1.1)
MDRD	591	52 (12)	38	6.6	35 (11)	132 (18)	3.9	13	10	NA	5.6 (1.1)
NZDCS	1913	71 (9)	57	0	48 (10)	142 (21)	100	1.7	8.1	33	5.3 (1.2)
RENAAL	1139	60 (7)	37	14	38 (11)	NA	100	NA	17.2	NA	NA
SCREAM	35049	69 (10)	61	0	48 (10)	NA	15	36	NA	NA	5.2 (1.2)
Sunnybrook	1013	70 (13)	42	0	35 (12)	NA	52	16	7.2	19	NA
Subtotal	**122,664**	**71 (11)**	**56**	**3**	**47 (10)**	**134 (20)**	**28**	**37**	**4.2**	**18**	**5.0 (1.2)**
eGFR 60+											
ADVANCE	8457	66 (6)	40	0.4	83 (13)	144 (21)	100	24	16	27	5.2 (1.2)
Geisinger	138682	55 (15)	56	1.7	92 (17)	128 (18)	16	15	17	24	5.1 (1.0)
KP Hawaii	15140	58 (13)	49	0	86 (16)	135 (20)	67	16	13	NA	4.8 (1.2)
Maccabi	720012	47 (16)	59	0	101 (17)	124 (17)	9	9	2.1	23	5.0 (1.0)
NZDCS	7093	59 (13)	49	0.11	86 (16)	138 (19)	100	0.54	16	30	5.4 (1.1)
RCAV	2408814	61 (13)	5.9	16.8	83 (15)	134 (18)	27	20	NA	NA	NA
SCREAM	460353	48 (15)	54	0	97 (17)	NA	6.2	8.7	NA	NA	5.4 (1.1)
Subtotal	**3,758,551**	**56 (15)**	**24**	**11**	**89 (18)**	**132 (18)**	**21**	**16**	**5.0**	**23**	**5.0 (1.1)**
Total	**3,881,215**	**57 (15)**	**25**	**11**	**87 (19)**	**132 (19)**	**21**	**17**	**4.9**	**23**	**5.0 (1.1)**

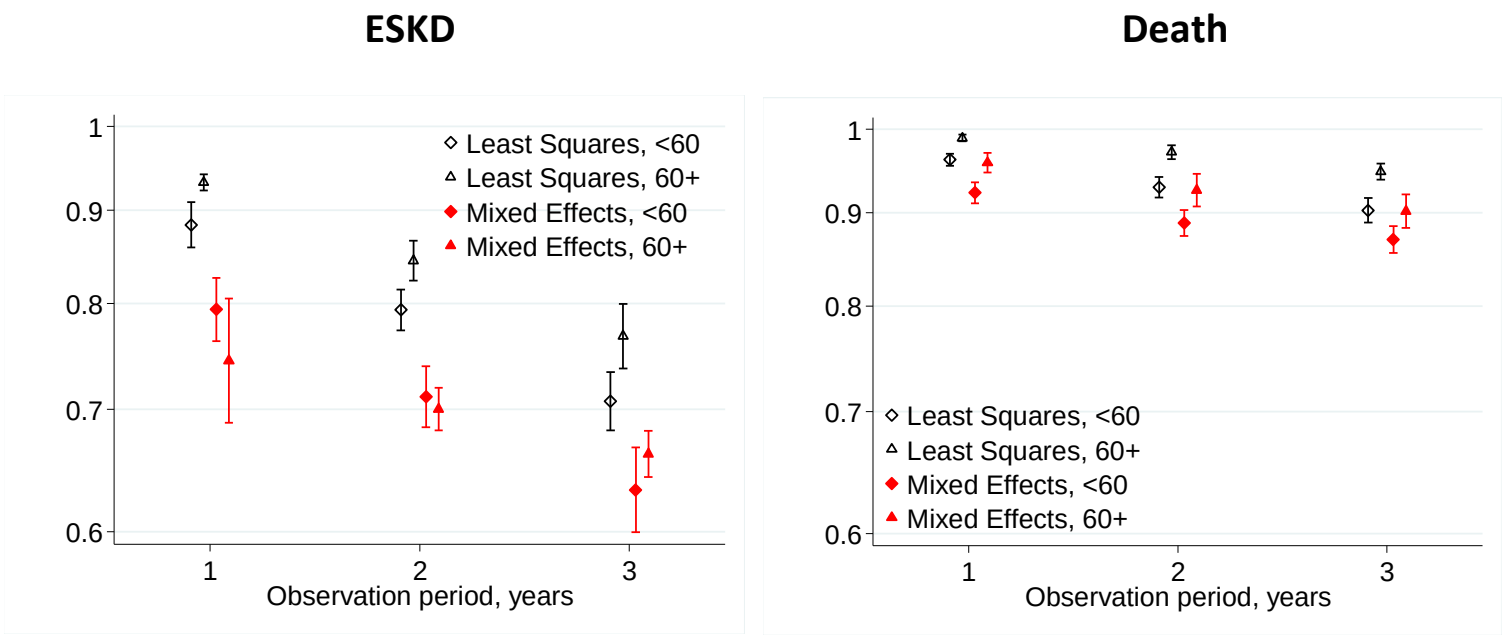
*Variables missing more than 50% were marked not available (NA).

Figure 1. Meta-analyzed adjusted hazard ratios for end-stage renal disease associated with and distributions of 2-year least squares and mixed effects eGFR slopes



Mixed effects indicates the best linear unbiased prediction from linear mixed models; the least squares is the beta coefficient from linear regression of eGFR on time. The distribution of slopes is shown in the kernel density plot in the bottom half of the graph, demonstrating the substantial shrinkage, particularly in the higher eGFR group.

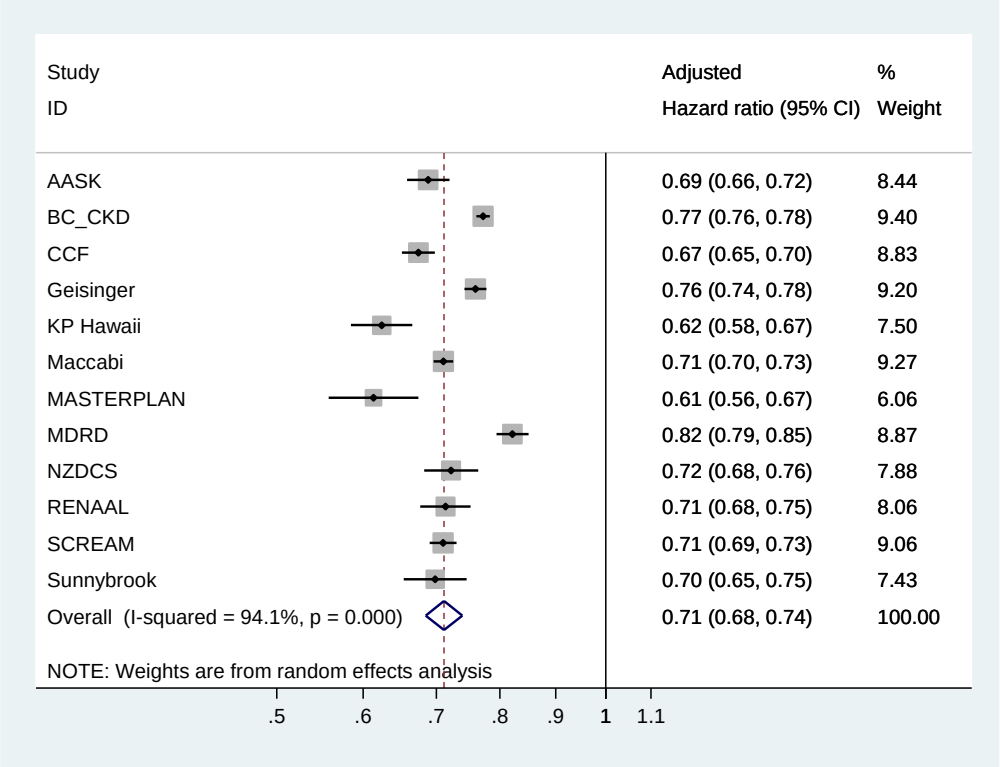
Figure 2. Meta-analyzed adjusted hazard ratios for end-stage kidney disease and death for a 0.75 ml/min/1.73 m^2 per year change in estimated glomerular filtration rate over time, separately by 1- 2- and 3-year observation period, stratified by baseline estimated glomerular filtration rate, estimated using linear mixed models and linear regression



Mixed effects indicates the best linear unbiased prediction from linear mixed models; the least squares is the beta coefficient from linear regression of eGFR on time. All eGFR values within a given observation period (1-, 2-, 3- years +/- 30%) were used to estimate slope coefficient. The hazard ratios refer to a lesser eGFR decline, e.g., -3.25 ml/min/1.73 m^2 per year vs. -4 ml/min/1.73 m^2 per year.

Figure 3. Forest plot of adjusted hazard ratios for end-stage kidney disease associated with a 0.75 ml/min/1.73 m^2 per year change in estimated glomerular filtration rate over 2-years estimated using linear mixed models, stratified by baseline estimated glomerular filtration rate

eGFR<60 ml/min/1.73 m^2



eGFR 60+ ml/min/1.73 m^2

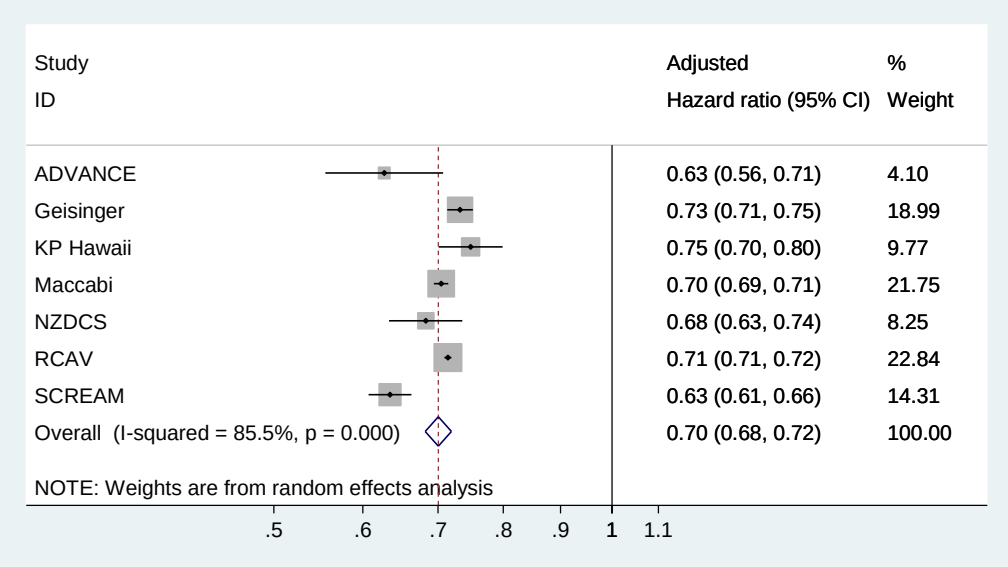
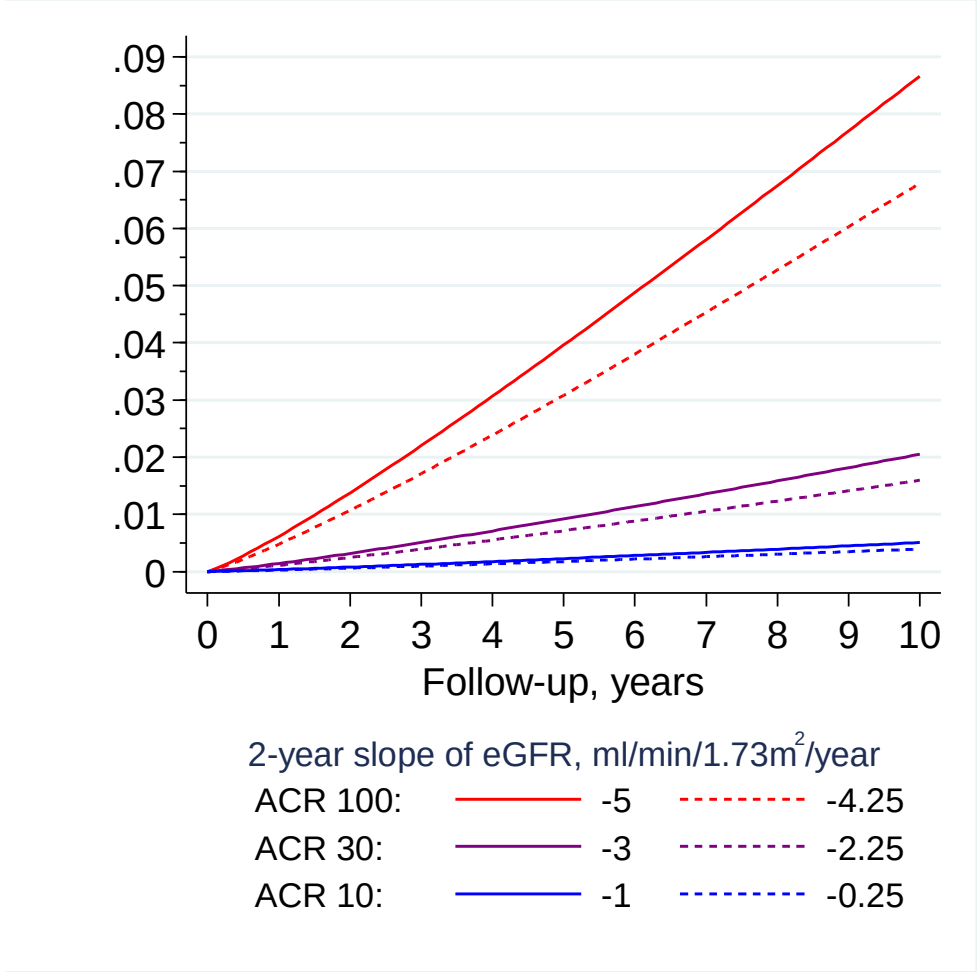
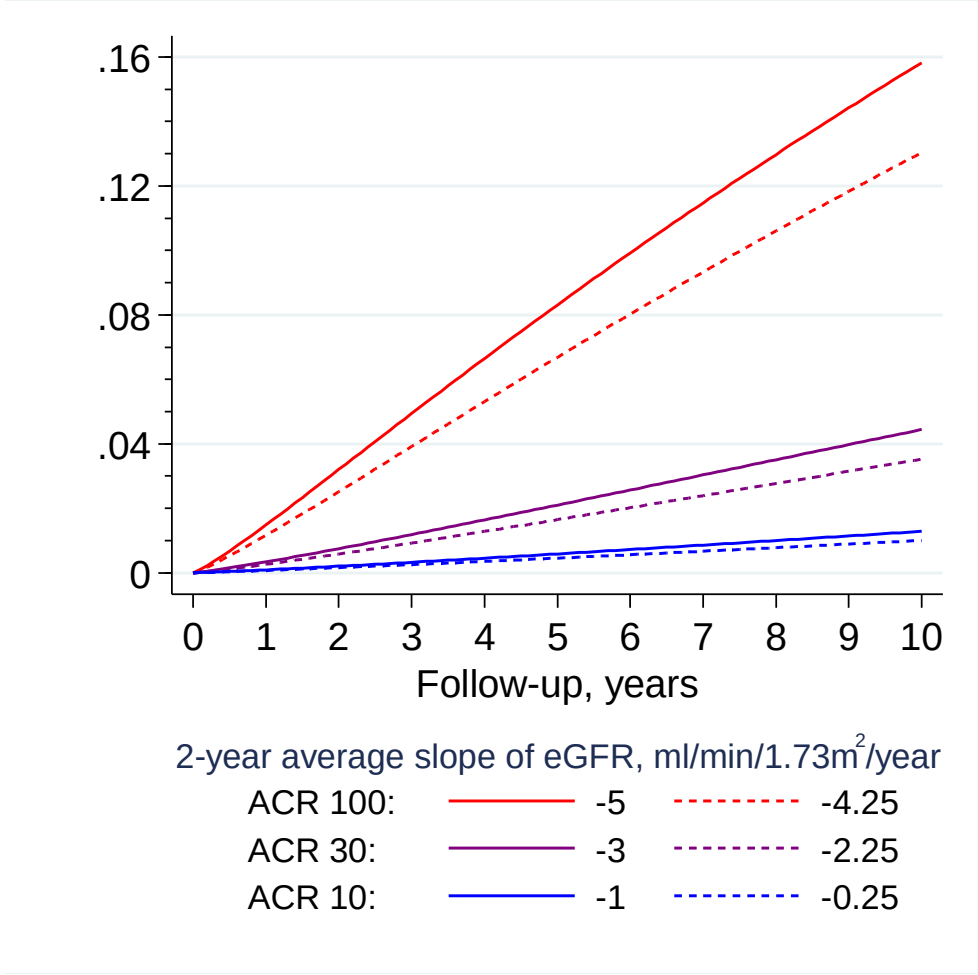


Figure 4. Expected absolute risk of end-stage kidney disease for a 2-year eGFR decline of -5, -3, and -1 ml/min/1.73 m^2 per year (solid lines) and a 0.75 ml/min/1.73 m^2 per year slower eGFR decline (dotted line) for (**A**) a person with baseline eGFR 75 ml/min/1.73 m^2 and albuminuria-to-creatinine ratio as shown and (**B**) a population of people with mean eGFR decline of -5, -3, and -1 ml/min/1.73 m^2 per year, standard deviation of 4 ml/min/1.73 m^2 per year, and the same covariates

(A)



(B)



*Other characteristics assumed in calculating absolute risk of end-stage kidney disease: age 60 years, 50% male, non-black, systolic blood pressure 140, 25% diabetes mellitus, total cholesterol 5.2 mmol/L, 25% cardiovascular disease, 25% current smoker.