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Change in Albuminuria and Risk of Renal and Cardiovascular Outcomes: Natural Variation Should Be Taken into Account

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Introduction: Changes in urinary albumin-to-creatinine ratio (UACR) may affect the risk of advanced chronic kidney disease (CKD). How much the association changes after taking account for natural variation in UACR and the length of time taken to observe changes in UACR is unknown.

Methods: English Clinical Practice Research Datalink records (2000–2015) with linkage to secondary care and death certification were used to identify prospective cohorts with at least 2 measures of UACR within 1, 2, and 3 years. Adjusted Cox regression assessed the separate relevance of the baseline UACR and the UACR change to the risk of developing stages 4 to 5 CKD and end-stage renal disease (ESRD). Associations were compared before and after accounting for the effects of the natural variation in UACR (i.e., regression to the mean).

Results: A total of 212,810 individuals had baseline UACR measurements; 22% had a UACR ≥3.4 mg/mmol, and 3% had UACR ≥33.9 mg/mmol. During a median 4-year follow-up, 5976 developed stage 4 to 5 CKD, and 1076 developed ESRD. There were strong associations between baseline UACR and stage 4 to 5 CKD or ESRD risk, which doubled in strength after accounting for regression to the mean. Over 3 years, the hazard ratios (95% confidence intervals) for stage 4 to 5 CKD, relative to stable UACR, were 0.62 (0.50–0.77) for at least a halving of UACR and 2.68 (2.29–3.14) for at least a doubling of UACR. Associations were weaker for shorter exposure windows (and for cardiovascular disease or death), but strengthened after allowing for regression to the mean.

Conclusion: Baseline values and subsequent medium-term increases in albuminuria are both associated with substantially increased risk of developing advanced CKD. Standard analyses, not allowing for natural variation in UACR, may underestimate these associations.

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In the United Kingdom, the current prevalence of chronic kidney disease (CKD) is approximately 10%,[1] and this is expected to rise as the population ages and diabetes mellitus becomes more common.[2] Progression of CKD to end-stage renal disease (ESRD) usually takes many years, and individuals with CKD often die before any need for renal replacement therapy arises.[3] Nonetheless, avoidance of CKD progression is highly desirable due to the association of CKD with a wide range of health risks[4–6] and substantial health resource use.[7–9]

In 2012, the National Kidney Foundation and the US Food and Drugs Administration sponsored a scientific workshop that concluded that a sustained 30% to 40% decline in the estimated glomerular filtration rate (eGFR) might be an appropriate surrogate for progression to ESRD in certain circumstances.[10,11] This outcome has since been used in a phase III diabetes trial.[12] Albuminuria represents an important independent risk factor for progressive CKD,[6] and international guidelines have incorporated albuminuria levels together with eGFR to subclassify CKD.[13] Findings from previous trials, and particularly studies of

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inhibitors of the renin-angiotensin-aldosterone system (RAAS) in diabetic kidney disease,[14–16] suggest that a sustained reduction in albuminuria may also indicate the nephroprotective potential of intervention. However, it is uncertain whether any drug mechanism that reduces albuminuria also slows the rate of CKD progression,[17] and if this is true for the full range of causes of CKD.[18] In March 2018, a National Kidney Foundation/Food and Drug Administration/European Medical Agency scientific workshop presented such data and discussed whether a change in albuminuria is a reliable surrogate endpoint for CKD progression.[19]

Recently, a 2006 to 2012 observational cohort of nearly 20,000 people from the Stockholm Creatinine Measurements (SCREAM) project who had ≥2 urinary albumin-to-creatinine ratio (UACR) measurements showed that an increase in UACR over 2 years was strongly associated with a future risk of ESRD and death, but this study only considered fatal cardiovascular outcomes.[20] However, UACR can vary considerably within individuals in the short-term,[21,22] representing in part, the natural biological variation rather than pathogenic progression of underlying kidney disease. Such variability is observed by the phenomenon of repeat measures of UACR that tend to regress to the population mean. If this effect is not taken into account, it can result in regression-dilution bias. Furthermore, it is unclear whether changes over 2 years are the most useful measure of a medium-term change in UACR when assessing risk. We therefore aimed to replicate and extend the SCREAM cohort findings and to assess the impact of natural regression to the mean on renal, cardiovascular, and fatal outcomes.

MATERIALS AND METHODS

Data Sources

The Clinical Practice Research Datalink (CPRD) data set is a collection of anonymous primary care records from approximately 700 United Kingdom practices[23] that has been shown to be a useful resource for prospective analyses of continuous exposures, including blood pressure and body mass index.[24–26] Because English primary care physicians were contracted to screen at-risk people for albuminuria and maintain CKD registers,[27] it provides an opportunity to investigate current uncertainties about the relevance of albuminuria to a range of outcomes. This study used data from the three-quarters of CPRD English practices that are linked to the English Hospital Episode Statistics, and used mortality data from the UK Office for National Statistics, as well as patient-level social deprivation indexes.

Study Populations and Exposures

UACR (mg/mmol) was calculated from separate urinary albumin and creatinine results recorded on the same day or from the recorded UACR value if the separate measurements were not available. Patients with at least 1 UACR test result recorded at ages 20 to 79 years, during 2000 to 2015, and with at least 1 year of preceding research quality data were eligible for inclusion in the study population (Supplementary Figure S1). A total of 685,169 eligible UACR tests were identified from 213,120 patients. One data set for analysis of baseline UACR and 3 data sets for analysis of UACR change were then extracted from CPRD based on these UACR tests and their dates.

The first UACR that satisfied the study criteria was selected for analyses of baseline UACR as the exposure. Individuals with at least 2 UACR measurements within a specified baseline exposure window were selected for data sets with UACR change as the exposure (Supplementary Figure S2). Three different data sets were made in which different exposure windows (1 year with a margin of ±4 months; 2 years ± 8 months; and 3 years ± 12 months) were used to define the change. For each data set, the first pair of UACR measurements that fulfilled the relevant criteria was selected for each individual. The UACR value closest to the end of the baseline exposure window was compared with the one at the start of baseline. Change was calculated by dividing the last UACR in the window by the first one, and then annualized. Participants with a baseline UACR (the first UACR in the exposure window for UACR change) >500 mg/mmol or women who were pregnant at the time (identified from the CPRD pregnancy register) were excluded from analyses.

Outcomes

In analyses of baseline UACR, follow-up for each participant began on the date of the baseline UACR test. For studies of UACR change, the start of follow-up was taken as the date of the last UACR value in the baseline exposure window (Supplementary Figure S2). Follow-up continued until the practice stopped providing data to CPRD, the patient died or left the practice, or December 31, 2015 (whichever was earliest). The outcome of incident identified stage 4 to 5 CKD was derived using internationally accepted clinical definitions[28] and an algorithm that incorporated death certificates, inpatient diagnostic or procedural codes, and primary care diagnostic and/or laboratory test results (as used in previous work[26]). When laboratory results were available, eGFR was calculated from creatinine results using the CKD Epidemiology Collaboration formula.[29] Stage 4 to 5 CKD was also accepted if

there were at least 2 eGFR measurements of <30 ml/min per 1.73 m^2, spaced at least 90 days apart, with no eGFR result of ≥30 ml/min per 1.73 m^2 in the intervening period. Incident ESRD included those who died with a diagnosis of ESRD or who underwent kidney transplantation or maintenance dialysis (which was distinguished from acute dialysis by a record of stage 5 CKD, permanent arteriovenous dialysis access, or peritoneal dialysis). Cardiovascular disease (CVD) was defined by the Cardiovascular Research using Linked Bespoke Studies and Electronic Health Records (CALIBER) program.[25] Deaths from any cause were identified from the full-coverage national mortality registry.

Covariates

For each data set, covariates were defined from information recorded on or before the date of the baseline UACR of each individual. For change in UACR, the baseline UACR was the earliest of the pair of UACR measurements used to define change. Covariates included any previous CVD (using CALIBER definitions), and previous diabetes (defined as a diagnostic or treatment-related code, a prescription of antidiabetic medication, or a measured glycated hemoglobin of ≥6.5%). Current smokers were defined based on the most recent smoking code. Treatment with antihypertensive agents, including RAAS blockers, was defined as at least 1 relevant prescription on or within 1 year before baseline. Estimates of systolic blood pressure (SBP), CKD Epidemiology Collaboration eGFR, and total cholesterol were extracted from the latest physical measurement and laboratory data within the year preceding the baseline UACR. Missing values of SBP, eGFR, and total cholesterol were imputed using multiple imputation. The 2010 Index of Multiple Deprivation was used to define socioeconomic status.

Statistical Analyses

Cox regression models adjusted for relevant confounders were used to calculate hazard ratios (HRs) for associations of baseline UACR or change in UACR with subsequent risk of stage 4 to 5 CKD, ESRD, CVD, or death. The proportional hazards assumption was assessed graphically. Those with stage 4 to 5 CKD or ESRD before the start of follow-up were excluded from analyses. For analyses of the CVD outcome, individuals with CVD before the start of follow-up were also excluded. Confounders included age, sex, and socioeconomic status (basic model), with the addition of previous diabetes, previous CVD (when not already excluded), current smoking, SBP (continuous), total cholesterol (continuous), and eGFR (linear spline with a knot at 60 ml/min per 1.73 m^2) in fully adjusted models. All models were fitted to the complete data. Results using imputed data were compared in supplementary analyses. All statistical analyses used Stata version 14 (StataCorp 2015, College Station, TX).

In analyses of baseline UACR as the exposure, UACR was first included in models as an ordered categorical variable (cutpoints at 1.1, 3.4, 11.3, and 33.9 mg/mmol). Models were also fitted to baseline log-transformed UACR as a continuous variable, to estimate HRs of outcomes per 10 times higher UACR at baseline. To allow for any nonlinearity, a linear spline model was also used for log-transformed UACR (knots at 1.1, 3.4, 11.3, and 33.9 mg/mmol). On average, a high or a low baseline UACR in a patient would be expected to be followed by a UACR closer to the average (a phenomenon known as regression to the mean, which causes an underestimation of the association, which is also known as regression-dilution bias). To correct for regression to the mean, the log HRs for associations with continuous $\log_e$-UACR were divided by a regression-dilution coefficient calculated using the MacMahon-Peto method.[30] Corrected HRs then represented the association between the outcome and long-term average UACR.

In analyses of change in UACR, HRs were estimated for categorical annual times change in UACR (cutpoints at 0.5-, 0.77-, 1.3-, and 2-times change, corresponding to a 2-fold decrease, a 1.3-fold decrease, a 1.3-fold increase, and 2-fold increase per year, respectively). The stable UACR category (i.e., 1.3-fold decrease to 1.3-fold increase) was used as the reference group. Log-transformed baseline UACR was included in fully adjusted models as well as the previously described confounders. The shapes of associations with log-transformed annual change in UACR were also investigated by fitting linear splines with knots at the previously listed cutpoints. For subgroup analyses by sex, baseline age group, smoking status, and previous diabetes, HRs were calculated for a >1.3-fold annual increase and a >1.3-fold annual decrease in UACR versus stable UACR.

To try to control for the effect of regression to the mean in analyses of UACR change, the categories of change in UACR (>1.3-fold decrease, stable, and >1.3-fold increase) were further divided according to thirds of the baseline UACR (Supplementary Figure S3). This matrix was used to categorize UACR changes as underlying increases or decreases, or as regression to the mean. For example, increases of >1.3-fold per year from a baseline UACR in the middle or upper third were considered to represent an underlying increase in UACR. Stable UACR from a baseline UACR in the upper third were also considered to represent an underlying increase in UACR. However, a >1.3-fold decrease per

year from a baseline UACR in the upper third was considered as a regression to the mean. An underlying decrease in UACR was defined in an analogous manner.[31] HRs for an underlying increase and underlying increase versus regression to the mean were then calculated.

RESULTS

The data set for analysis of baseline UACR as the exposure consisted of 212,810 individuals, median age 64 years, of whom 45% were women, and 64% had a history of diabetes (Table 1). Of these, 167,139 (78%) had a UACR <3.4 mg/mmol, 39,379 (19%) had a UACR of 3.4 to 33.8 mg/mmol, and 6292 (3%) had a UACR ≥33.9 mg/mmol. Baseline characteristics overall and by category of baseline UACR or UACR change are displayed for this population and the 3 populations with UACR changes as the exposure in the Supplementary Material (Supplementary Tables S1–S4). Data on annual change in UACR estimated over a 3-year exposure window were available from 92,854 individuals, 19% of whom had a >1.3-fold decrease in UACR per year (i.e., <0.77 times), and 24% of whom had a >1.3-fold increase per year (Table 1). There was a somewhat higher proportion of people with diabetes in this subpopulation than the baseline UACR population (77% vs. 64%) and a higher prevalence of recent prescriptions of antihypertensive medication (any: 74% vs. 70%; RAAS blocker: 57% vs. 52%), but other population characteristics were generally comparable. Data on annual change in UACR estimated over 2- and 1-year exposure windows were available from 99,107 and 99,393 individuals, respectively (Supplementary Tables S3 and S4). For the 2-year window, 25% of individuals had a >1.3-fold decrease in UACR per year and 30% had a >1.3-fold increase per year. Equivalent percentages for the 1-year time window were 34% and 37%, respectively.

Table 1. Baseline characteristics for individuals with at least 1 urinary albumin-to-creatinine ratio (UACR) measurement[a]

Variables	Overall (at least one UACR measurement) $N = 212,810$	Subset (At least 2 UACR measurements) $n = 92,854$
Age (yr)	64 (54–72)	65 (56–72)
Female	96,818 (45.5)	40,354 (43.5)
Current smoker	37,753 (17.7)	15,595 (16.8)
UACR, mg/mmol	1.1 (0.5–2.8)	1.1 (0.6–2.8)
UACR categories		
≤3.3	167,139 (78.5)	72,676 (78.3)
3.4–33.8	39,379 (18.5)	17,895 (19.3)
≥33.9	6292 (3.0)	2283 (2.5)
UACR annual times change	—	1.0 (0.8–1.3)
UACR annual change categories		
>1.3-fold decrease	—	17,394 (18.7)
Stable	—	52,989 (57.1)
>1.3-fold increase	—	22,471 (24.2)
eGFR (ml/min per 1.73 m^2)	74.1 (58.0–90.5)	72.2 (56.9–88.6)
Total cholesterol (mg/dl)	4.6 (3.9–5.5)	4.5 (3.9–5.3)
SBP (mm Hg)	136 (126–145)	137 (127–145)
Antihypertensive medication		
Any antihypertensive	148,318 (69.7)	68,486 (73.8)
RAAS blocker	110,141 (51.8)	52,447 (56.5)
Prevalent disease		
Diabetes	135,482 (63.7)	71,596 (77.1)
CVD	49,803 (23.4)	23,315 (25.1)
Stage 4–5 CKD	4614 (2.2)	1846 (2.0)
ESRD	929 (0.4)	270 (0.3)

CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; IQR, interquartile range; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure.
Data are median (IQR), or *n* (%).
In the overall population, there were 26,721 (12.6%) missing cholesterol; 10,888 (5.1%) missing SBP, and 12,862 (6.0%) missing eGFR. In the subset of patients with at least 2 UACR measurements, there were 7882 (8.5%) missing cholesterol, 3444 (3.7%) missing SBP, and 4218 (4.5%) missing eGFR.
[a]Statistics were calculated for the overall population with at least 1 urinary albumin-to-creatinine ratio (UACR) measurement and the subset of patients with at least 2 UACR measurements within a 3-year exposure window.

Association Between Baseline UACR and Risk of Outcomes

Median follow-up time was 4.0 years. Follow-up ceased due to death (22,271 [10%] patients), end of the study period (88,515 [42%]), the practice stopped contributing data (74,388 [35%]), or patients transferred out of the practice (27,636 [13%]). During follow-up, 5976 individuals developed stage 4 to 5 CKD, 1076 developed ESRD, and 20,332 had a CVD event (Supplementary Table S1). HRs (95% confidence intervals [CIs]) and numbers of events and individuals by category of UACR are displayed in Supplementary Table S5. Multiple imputation for missing values had no appreciable impact on HRs (Supplementary Table S5). The relationship between $\log_e$-UACR and HRs for all 4 outcomes appeared to be log-linear in the linear spline plots (Supplementary Figure S4). HRs (95% CIs) per 10 times higher UACR, adjusted for sex, age, and socioeconomic status (basic model) were 3.48 (3.35−3.61) for stage 4 to 5 CKD and 7.14 (6.44−7.92) for ESRD (Figure 1). After full adjustment, these were attenuated to 2.43 (2.33−2.53) and 4.86 (4.29–5.51), respectively. In basic models, there were moderately strong associations between baseline UACR and risk of CVD (HR: 1.57; 95% CI: 1.53−1.60) and risk of death (HR: 1.89; 95% CI: 1.85−1.93), which were only slightly attenuated after full adjustment.

Association Between Long-term Average UACR and Risk of Outcomes

For UACR, there was evidence of substantial regression to the mean (Supplementary Figure S5): regression-dilution coefficients for 1, 2, 3, 4, 5, and 6 years were 0.72, 0.68, 0.63, 0.60, 0.60, and 0.56, respectively.

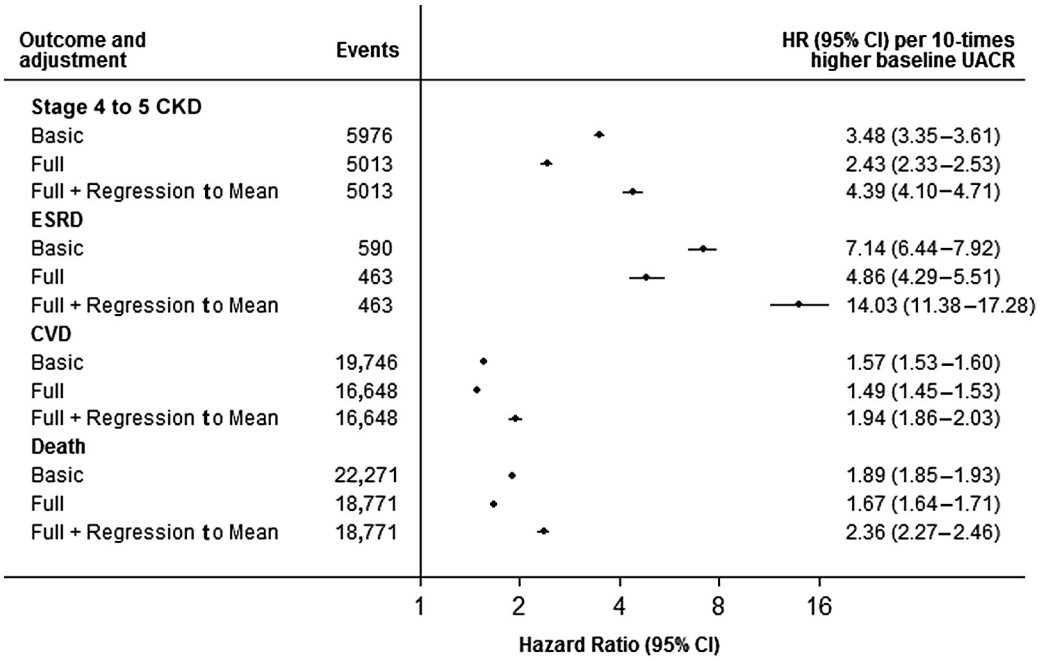

Figure 1. Hazard ratios (HRs) and 95% confidence interval (CIs) for associations of 10 times higher baseline urinary albumin-to-creatinine ratio (UACR) with incidence of stage 4 to 5 chronic kidney disease (CKD), end-stage renal disease (ESRD), cardiovascular disease (CVD), or death. HRs were calculated on the overall study population with at least 1 UACR measurement, using continuous $\log_e$-UACR as the exposure variable. Basic and full adjustments include sex, baseline age, and fifths of deprivation. Full adjustment also includes previous CVD, previous diabetes, current smoking, systolic blood pressure, total cholesterol, and estimated glomerular filtration rate (eGFR) (spline knot at 60 ml/min per 1.73 m^2). Full adjustment excludes people with missing systolic blood pressure, total cholesterol, or eGFR. Those with prevalent stage 4 to 5 CKD or ESRD were excluded from analyses with outcomes of stage 4 to 5 CKD or CVD. For analyses of the CVD outcome, people with prevalent CVD were also excluded. HRs and 95% CIs were corrected for regression to the mean using the regression-dilution coefficient for $\log_e$-UACR of 0.60.

Figure 1 also provides HRs for a 10-times increase in UACR for all outcomes after full adjustment for confounders and then additional correction for (4 year, which was the median length of follow-up) regression-dilution bias. It shows how the effect of long-term average (or "usual") UACR on all 4 endpoints was substantially greater than baseline UACR, as befits the size of the regression-dilution coefficient. Associations between usual UACR and risk of stage 4 to 5 CKD and ESRD were approximately 80% (HR: 4.39; 95% CI: 4.10−4.71) and 190% (HR: 14.03; 95% CI: 11.38−17.28) bigger than associations with baseline UACR (Figure 1).

Associations Between Changes in UACR and Risk of Outcomes

During a median of 2.9 years of follow-up after the final UACR in the exposure period, 2621 people developed stage 4 to 5 CKD, 391 developed ESRD, 7321 developed CVD, and there were 9949 deaths in the population, with UACR change estimated over a 3-year period (Supplementary Table S2). Numbers of events in the other UACR change data sets were similar (Supplementary Tables S3 and S4).

HRs (95% CIs) and numbers of events, and individuals by category of UACR change for the 3-year exposure window are displayed in Table 2. As with absolute values of UACR, risk increased across ordinal categories of change in UACR for all 4 outcomes. The fully adjusted HRs (95% CIs) for a >2-fold annual increase in UACR was 2.68 (2.29−3.14) for stage 4 to 5 CKD and 0.62 (0.50−0.77) for a >2-fold decrease per year, with both compared to a stable UACR (i.e., 1.3-fold decrease to 1.3-fold increase) (Table 2). Corresponding results for ESRD were an HR of 9.67 (95% CI: 5.92−15.78) and an HR of 0.29 (95% CI: 0.10−0.81). Multiple imputation for missing values had no substantive effect on these results (Table 2).

For the 3-year exposure window, the associations of HR with $\log_e$-UACR change did not appear to be log-linear (Figure 2). With the exception of CVD, associations for an increase in UACR were generally stronger than associations for the equivalent annual decrease. Therefore, further analyses were based on categorical change in UACR, comparing the >1.3-fold annual increase or decrease in UACR with stable UACR. Using these categories, there was no strong evidence for effect modification by age, sex, smoking, or diabetes for any of the associations between change in UACR and advanced stage 4 to 5 CKD, ESRD, CVD, or death outcomes (Supplementary Figure S6).

HRs for different time windows were also compared (Figure 3). The HRs for an observed >1.3-fold annual

Table 2. Hazard ratios (HRs) and 95% confidence intervals (CIs) for associations of annual change in urinary albumin-to-creatinine ratio (UACR) with incidence of stage 4 to 5 chronic kidney disease (CKD), end-stage renal disease (ESRD), cardiovascular disease (CVD), and death[a]

	Basic adjustment, complete data[b]			Full adjustment, complete data			Full adjustment + imputation[b]
Annual change in UACR	Events	*n*	HR (95% CI)	Events	*n*	HR (95% CI)	HR (95% CI)
Stage 4 to 5 CKD	2621	89,360		2297	77,981		
>2-fold decrease	113	3066	0.52 (0.43–0.64)	100	2588	0.62 (0.50–0.77)	0.59 (0.48–0.72)
>1.3–2 fold decrease	394	13,620	0.74 (0.66–0.82)	341	11,752	0.76 (0.67–0.86)	0.76 (0.68–0.86)
Stable	1243	51,345	1.0	1091	44,962	1.0	1.0
>1.3–2 fold increase	648	16,976	1.93 (1.75–2.12)	576	14,884	1.77 (1.60–1.96)	1.75 (1.59–1.93)
>2-fold increase	223	4353	3.43 (2.97–3.96)	189	3795	2.68 (2.29–3.14)	2.90 (2.51–3.36)
ESRD	162	89,360		149	77,981		
>2-fold decrease	6	3066	0.38 (0.16–0.89)	4	2588	0.29 (0.10–0.81)	0.40 (0.17–0.95)
>1.3–2 fold decrease	27	13,620	0.86 (0.54–1.36)	26	11,752	0.89 (0.56–1.43)	0.88 (0.56–1.40)
Stable	59	51,345	1.00	56	44,962	1.0	1.0
>1.3–2 fold increase	43	16,976	3.34 (2.25–4.97)	39	14,884	2.90 (1.92–4.39)	3.03 (2.03–4.51)
>2-fold increase	27	4353	12.15 (7.64–19.31)	24	3795	9.67 (5.92–15.78)	10.64 (6.67–16.98)
CVD	7041	67,506		6199	57,963		
>2-fold decrease	223	2365	0.61 (0.53–0.71)	199	1962	0.67 (0.58–0.78)	0.63 (0.55–0.73)
>1.3–2 fold decrease	1051	10,420	0.79 (0.74–0.85)	909	8824	0.80 (0.74–0.86)	0.80 (0.75–0.86)
Stable	4042	39,384	1.00	3567	33,985	1.0	1.0
>1.3–2 fold increase	1378	12,286	1.22 (1.15–1.30)	1216	10,577	1.21 (1.13–1.29)	1.21 (1.14–1.29)
>2-fold increase	347	3051	1.47 (1.32–1.65)	308	2615	1.46 (1.30–1.64)	1.44 (1.29–1.61)
Death	9949	92,854		8807	80,782		
>2-fold decrease	425	3267	0.78 (0.71–0.87)	370	2743	0.85 (0.77–0.95)	0.85 (0.76–0.94)
>1.3–2 fold decrease	1504	14,127	0.85 (0.81–0.91)	1314	12,151	0.88 (0.82–0.93)	0.88 (0.83–0.94)
Stable	5027	52,989	1.00	4479	46,273	1.0	1.0
>1.3–2 fold increase	2204	17,782	1.42 (1.35–1.50)	1942	15,542	1.33 (1.26–1.40)	1.35 (1.29–1.42)
>2-fold increase	789	4689	2.31 (2.14–2.49)	702	4073	2.09 (1.92–2.26)	2.12 (1.96–2.28)

Basic and full adjustments include sex, baseline age, fifths of deprivation. Full adjustment also includes previous cardiovascular disease, previous diabetes, current smoking, systolic blood pressure, total cholesterol, estimated glomerular filtration rate (spline knot at 60 ml/min per 1.73 m^2), and baseline $\log_e$ urinary albumin-to-creatinine ratio (UACR). Those with prevalent stage 4 to 5 CKD or end-stage renal disease were excluded from analyses with outcomes of stage 4 to 5 CKD or CVD. For analyses of the CVD outcome, individuals with prevalent CVD were also excluded.

[a]Change in UACR was estimated over a 3-year exposure window

[b]Missing systolic blood pressure, total cholesterol, and eGFR were imputed using multiple imputation. There were no missing data for the basic adjustment, so numbers of events and individuals are the same as for the full adjustment with imputation.

increase, compared with a stable UACR, were generally higher for changes calculated over the longer exposure windows (and therefore, an increase in the lapsed time between the original and subsequent UACR measurement). This trend was less evident for a >1.3-fold decrease in UACR compared with a stable UACR (Figure 3).

Associations Between Change in UACR and Risk of Outcomes After Taking Account of Natural Variation in UACR

We then explored how the effect of natural variation in UACR might affect the observed associations between change in UACR and future risk of outcomes (i.e., regression-dilution bias). For the 3-year exposure window (n = 92,854), UACR change was categorized as an underlying increase in 25,521 people and an underlying decrease in 26,552 people (i.e., the observed change was more than might be expected from regression to the mean). In the remaining 40,781 individuals, UACR was stable or considered to be regression to the mean (Supplementary Figure S3). Figure 3 compares HRs for an observed annual increase or decrease in UACR of >1.3-fold versus stable UACR, with HRs for an underlying increase or decrease in UACR versus "regression to the mean or stable UACR". For all outcomes, and for both increases and decreases in UACR, the effect sizes for 1- and 2-year changes became larger after taking account of regression to the mean, but this was not always the case for 3-year changes.

DISCUSSION

In this cohort of >200,000 individuals with at least 1 UACR test result and 90,000 with a second measurement within approximately 3 years, we found that higher baseline UACR, higher long-term average UACR, and increases in UACR over time were all separately associated with a higher risk of developing advanced CKD. Decreases in UACR were also associated with a lower risk of developing all outcomes (except ESRD, for which there were few events in relevant categories of UACR change) but were somewhat weaker than corresponding associations with an increase in UACR. Associations between changes in UACR using annualized 1- or 2-year changes were also smaller compared to those with an annualized 3-year change.

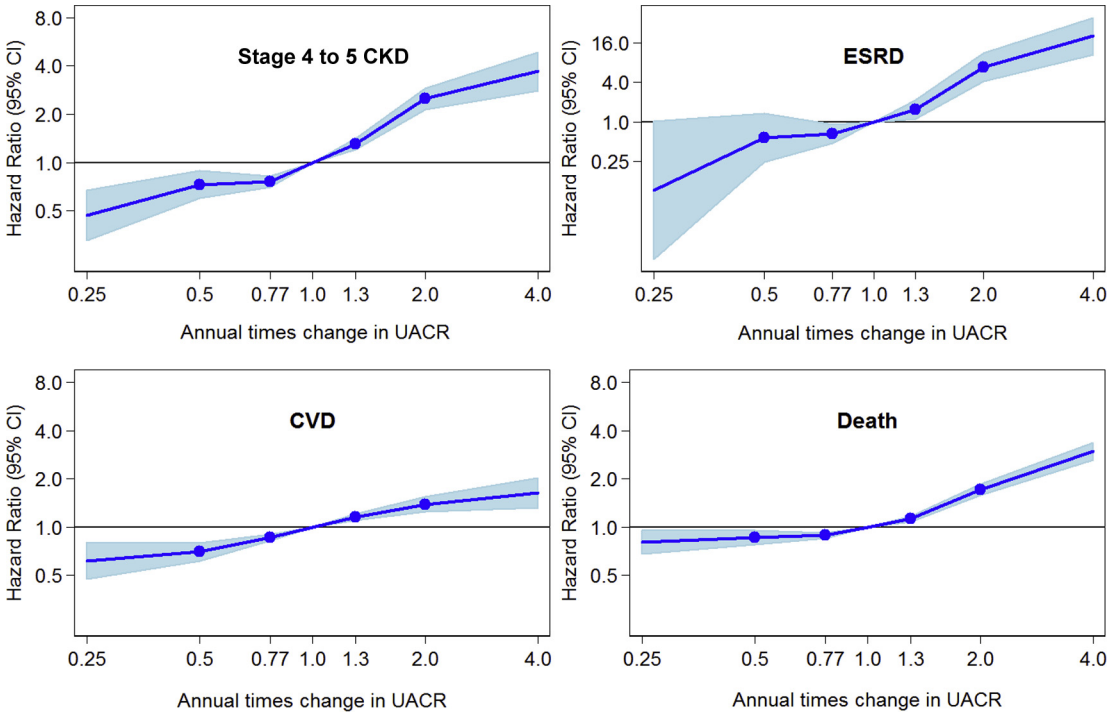

Figure 2. Associations of annual times change in urinary albumin-to-creatinine ratio (UACR) estimated over a 3-year exposure window with incidence of stage 4 to 5 chronic kidney disease (CKD), end-stage renal disease (ESRD), cardiovascular disease (CVD), and death. Log-transformed times change in UACR was modeled as a linear spline with knots indicated by dots and reference no change. Associations were adjusted for sex, baseline age, fifths of deprivation, previous CVD, previous diabetes, current smoking, systolic blood pressure, total cholesterol, estimated glomerular filtration rate (eGFR) (spline knot at 60 ml/min per 1.73 m^2) and baseline log_e-UACR. Individuals with missing systolic blood pressure, total cholesterol, or eGFR were excluded. CI, confidence interval.

In analyses that corrected for the medium-term variability in UACR, the weaker associations for UACR changes observed over the 1-year observation period were strengthened substantially, whereas associations with a UACR change over 2 or 3 years were modified less.

An annualized 3-year change in UACR requires an observed absolute difference in log_e-UACR of 3 times that of an annualized 1-year change. A larger proportion of the observed absolute change in UACR for an individual over 3 years, compared with 1 year, would then more likely be due to a medium-term change in UACR than day-to-day variability. Regression to the mean corrections would therefore be expected to tend to equalize these associations. These results suggest that UACR changes that are both large (in absolute terms) and observed over at least 2 years are more likely to represent a real change in UACR, which is associated with increased CKD risk. However, although our methodology demonstrates the potential importance of considering day-to-day variability in UACR, it only provides an approximate correction for regression-dilution bias. Further work using data with repeat measures taken closer together, as well as at different times, is required to construct and test statistical models that appropriately account for the measurement error in UACR change over successive exposure windows.

Consistent with other studies, we found an association between increasing UACR and risk of CVD.[31,32] This present study was also large enough to find that a reduction in UACR over time was associated with lower CVD risk. However, the association between change in UACR and CVD risk was smaller in size than associations with advanced CKD outcomes, and we could not rule out residual confounding as an explanation for these (or any of the other) associations. Such bias could result from the lack of systematic baseline or follow-up assessments in these data, which were derived solely from routinely collected health care sources.

Other limitations included some missing data for covariates. However, the percentage of missing data was quite modest and associations using full adjustment (complete data) and full adjustment (imputed data) were comparable in size. It is therefore unlikely that missing data would have caused bias. In addition, 13% of patients were censored early due to transferring out of their practice, and 35% were censored because their practice stopped contributing to CPRD. If this censoring was differentially related to the outcomes, a bias could remain. Lastly, UACR testing in the

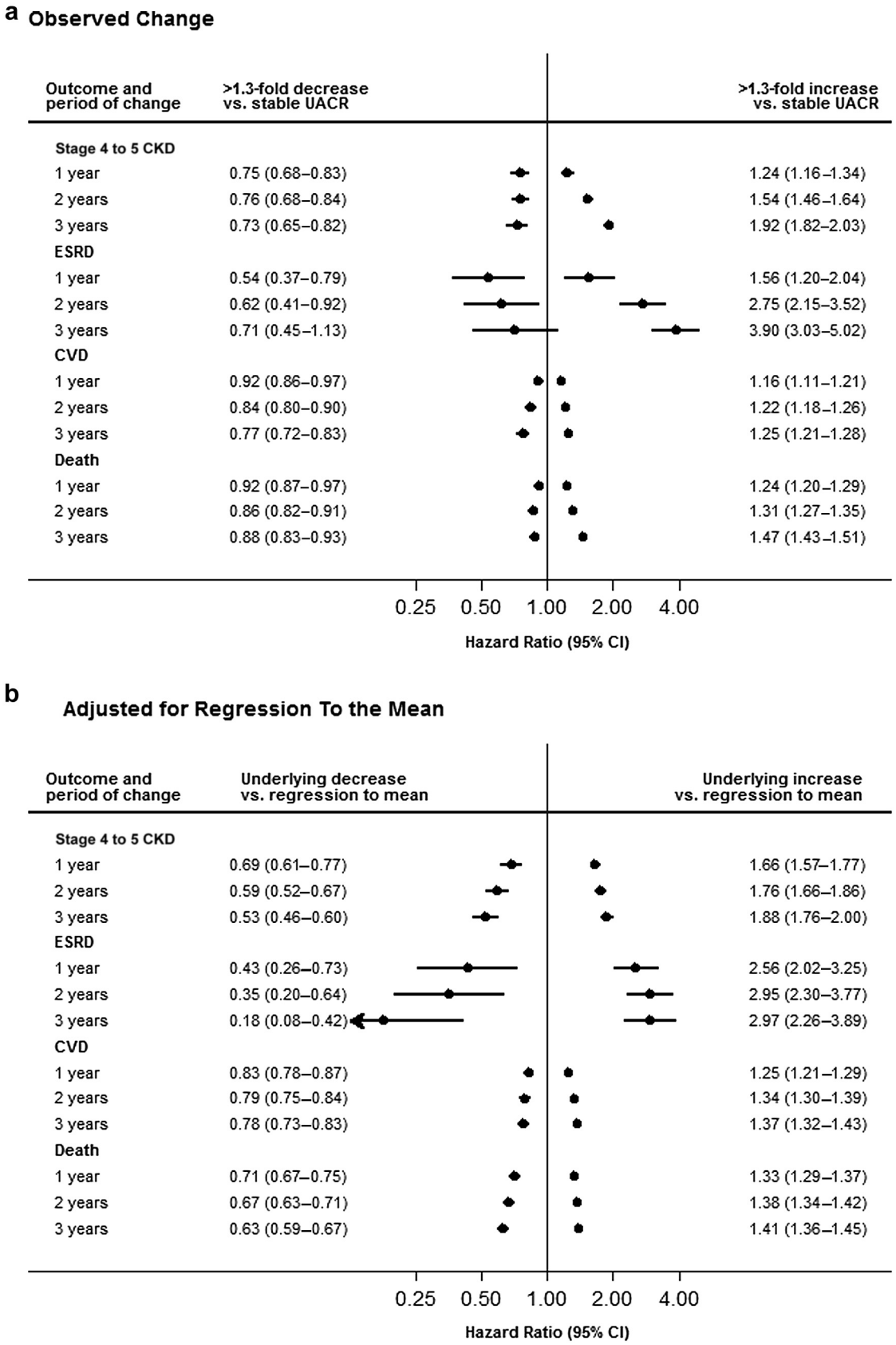

Figure 3. Hazard ratios (HRs) and 95% confidence interval (CIs) for associations of annual change in urinary albumin-to-creatinine ratio (UACR) with incidence of stage 4 to 5 chronic kidney disease (CKD), end-stage renal disease (ESRD), cardiovascular disease (CVD), or death. UACR change was calculated over exposure windows of 1, 2, or 3 years. (a) Associations in observed data of a >1.3-fold decrease per year or >1.3-fold increase per year versus stable UACR. (b) Associations of an underlying decrease or increase after allowing for regression to (continued)

real world is for selected individuals who are considered at risk of progressive CKD. This is likely the key explanation for the over-representation of people with diabetes in the study. It also means that these results are only generalizable to those considered at risk of CKD.

In conclusion, we have replicated and extended findings from the SCREAM cohort[20] and demonstrated that increases in UACR over 1 to 3 years were associated with an increased risk of advanced CKD and, to a lesser extent, with CVD or death. However, we concluded that not taking into account natural variation in albuminuria (i.e., regression-dilution bias), is likely to result in underestimation of the full association between a change in UACR and risk. Lastly, annual UACR changes observed over a 3-year period were more strongly associated with risk than annual UACR changes over 1 or 2 years, but this difference was reduced after associations were adjusted for natural variation in UACR. If change in UACR is to be used as a surrogate of CKD progression in renal trials, the optimum period of observation and frequency of UACR measurement need consideration.

DISCLOSURE

WGH receives funding from Boehringer Ingelheim. MWo is a consultant to Amgen. All the other authors declared no competing interests.

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AUTHOR CONTRIBUTIONS

The study idea was conceived by MWo, MS, and WGH, and the statistical analyses were designed by all authors. Analyses were conducted by MS and MWe. MS and WGH wrote the first draft with revisions by MWo and comments by MWe, FDRH, and CB.

SUPPLEMENTARY MATERIAL

Figure S1. Selection of the study population. These counts also exclude a further (n = 310) (A), (n = 75) (B), (n = 17) (C), and (n = 76) (D) patients who were pregnant, had a urinary albumin-to-creatinine ratio (UACR) value >500 mg/mmol, or with missing data on social deprivation. CPRD, Clinical Practice Research Datalink; HES, Health Episode Statistics; ONS, Office for National Statistics.

Figure S2. Example timeline for calculating change in urinary albumin-to-creatinine ratio (UACR) based on a 3-year exposure window. Triangles represent UACR test results. UACR change is calculated as the difference between the baseline UACR and a subsequent result falling within 2 to 4 years (3 years ± 1 year) of the baseline UACR. If there is >1 UACR within this 2 to 4 years, then the one closest in absolute terms to 3 years from the baseline UACR is used to calculate change. The period for identifying baseline covariates starts on the date of the baseline UACR (see the Methods section for details of how covariates were defined). Follow-up starts from the date of the other UACR used to calculate UACR change.

Figure S3. Diagram showing how people with change in the urinary albumin-to-creatinine ratio (UACR) estimated over 3 years (n = 92,854) were categorized into hypothesized outcomes of underlying change and regression to the mean according to thirds of baseline UACR and the subsequent change in UACR.

Figure S4. Associations of the baseline urinary albumin-to-creatinine ratio (UACR) with incidence of stage 4 to 5 chronic kidney disease (CKD), end-stage renal disease (ESRD), cardiovascular disease (CVD), and death. Baseline $\log_e$-UACR was modeled as a linear spline. Knots are indicated by dots, and the reference UACR is 0.6 mg/mmol. Associations were adjusted for sex, baseline age, fifths of

Figure 3. (continued) the mean versus stable UACR or regression to the mean (see Supplementary Figure S3). Associations were adjusted for sex, baseline age, fifths of deprivation, previous CVD, previous diabetes, current smoking, systolic blood pressure, total cholesterol, and estimated glomerular filtration rate (eGFR) (spline knot at 60 ml/min per 1.73 m^2). Analyses of observed changes were also adjusted for baseline $\log_e$-UACR. Individuals with missing systolic blood pressure, total cholesterol, or eGFR were excluded.

deprivation, previous CVD, previous diabetes, current smoking, systolic blood pressure, total cholesterol, estimated glomerular filtration rate (eGFR) (spline knot at 60 ml/min per 1.73 m^2). Individuals with missing systolic blood pressure, total cholesterol, or eGFR levels were excluded.

Figure S5. Means of the log-transformed urinary albumin-to-creatinine ratio (UACR) at baseline and after 1 to 6 years of follow-up, for groups defined as tenths of baseline UACR. The regression-dilution coefficient (MacMahon-Peto method) is the difference between the top and bottom group means for the second observation of $\log_e$-UACR, divided by the equivalent difference between group means for baseline $\log_e$-UACR.

Figure S6. Hazard ratios (HRs) and 95% confidence intervals (CIs) for a >1.3-fold decrease per year or >1.3-fold increase per year in the urinary albumin-to-creatinine ratio (UACR) versus stable UACR by subgroups of age, sex, smoking, and diabetes at baseline. Outcomes are the incidence of stage 4 to 5 chronic kidney disease (CKD), end-stage renal disease (ESRD), cardiovascular disease (CVD), and death. Change in UACR was estimated over a 3-year exposure window. Associations were adjusted for sex, baseline age, fifths of deprivation, previous CVD, previous diabetes, current smoking, systolic blood pressure, total cholesterol, estimated glomerular filtration rate (eGFR) (spline knot at 60 ml/min per 1.73 m^2), and baseline $\log_e$-UACR. Individuals with missing systolic blood pressure, total cholesterol, or eGFR levels were excluded. *P* indicates the test for interaction among subgroups.

Table S1. Characteristics of the study population with at least 1 urinary albumin-to-creatinine ratio (UACR) measurement, overall and by categories of baseline UACR.

Table S2. Characteristics of the subset of patients with at least 2 urinary albumin-to-creatinine ratio (UACR) measurements made within a 3-year exposure window, overall and by annual change in UACR.

Table S3. Characteristics of the subset of patients with at least 2 urinary albumin-to-creatinine ratio (UACR) measurements made within a 2-year exposure window, overall and by annual change in UACR.

Table S4. Characteristics of the subset of patients with at least 2 urinary albumin-to-creatinine ratio (UACR) measurements made within a 1-year exposure window, overall and by annual change in UACR.

Table S5. Hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between the baseline urinary albumin-to-creatinine ratio (UACR) and incidence of stage 4 to 5 chronic kidney disease (CKD), end-stage renal disease (ESRD), cardiovascular disease (CVD), and death.

Supplementary material is linked to the online version of the paper at www.kireports.org.

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