Article

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Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts

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We studied here the independent associations of estimated glomerular filtration rate (eGFR) and albuminuria with mortality and end-stage renal disease (ESRD) in individuals with chronic kidney disease (CKD). We performed a collaborative meta-analysis of 13 studies totaling 21,688 patients selected for CKD of diverse etiology. After adjustment for potential confounders and albuminuria, we found that a 15 ml/min per 1.73 m^2 lower eGFR below a threshold of 45 ml/min per 1.73 m^2 was significantly associated with mortality and ESRD (pooled hazard ratios (HRs) of 1.47 and 6.24, respectively). There was significant heterogeneity between studies for both HR estimates. After adjustment for risk factors and eGFR, an eightfold higher albumin- or protein-to-creatinine ratio was significantly associated with mortality (pooled HR 1.40) without evidence of significant heterogeneity and with ESRD (pooled HR 3.04), with significant heterogeneity between HR estimates. Lower eGFR and more severe albuminuria independently predict mortality and ESRD among individuals selected for CKD, with the associations stronger for ESRD than for mortality. Thus, these relationships are consistent with CKD stage classifications based on eGFR and suggest that albuminuria provides additional prognostic information among individuals with CKD.

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KEYWORDS: albuminuria; chronic kidney disease; epidemiology and outcomes

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This manuscript is the fourth in a series of manuscripts to report the results of collaborative meta-analyses of estimated glomerular filtration rate (eGFR) and albuminuria on outcomes of chronic kidney disease (CKD) undertaken by the CKD Prognosis Consortium. These analyses were conducted in conjunction with the 2009 Controversies Conference, sponsored by Kidney Disease Improving Global Outcomes (KDIGO), which sought to evaluate the current definition and classification of CKD and propose alternatives. The report of the Consensus Conference is included in this issue of *Kidney International*.[1]

The first three papers in this series dealt with all-cause and cardiovascular mortality and with kidney outcomes in general population cohorts and high-risk cohorts.[2–4] This paper reports the results of a collaborative meta-analysis of mortality and end-stage renal disease (ESRD) in 13 CKD cohorts, including predominantly individuals with CKD of diverse clinical diagnoses accompanied by decreased eGFR and elevated levels of albuminuria, corresponding to microalbuminuria or macroalbuminuria. We hypothesized *a priori* that both eGFR and albuminuria would be associated with these outcomes, independent of traditional cardiovascular risk factors and independent of each other, and despite inclusion of diverse study populations. Of particular relevance to these cohorts is the question of whether the severity of albuminuria provides additional prognostic information among individuals with CKD, over and above eGFR, as the current classification of CKD does not have separate stages by severity of albuminuria.[1,5] Previous reports of the associations of eGFR and albuminuria with outcomes in CKD studies did not use uniform analytic approaches, and most reports were not powered to evaluate the independent associations of eGFR and albuminuria with these outcomes.[6–8]

RESULTS

Characteristics of studies and participants

A total of 21,688 participants from 14 studies are included in at least one analysis, including 6 randomized controlled

Table 1 | Participating studies and incidence of mortality and end-stage renal disease

	Study design	Source/intervention	N	Mortality			End-stage renal disease		
				Follow-up, years	No. of events	Incidence rate[a]	Follow-up, years	No. of events	Incidence rate[a]
Studies with albumin-to-creatinine ratio									
British Columbia[9]	Observational	Referred	13,038	2.8	2449	66.1	2.5	2222	68.9
CRIB[10]	Observational	Referred	308	6.1	115	61.4	4.2	149	115.3
Grampian-ACR[23]	Observational	Identified by laboratory results	208	2.7	94	166.0	—	—	—
MASTERPLAN[12]	Clinical trial	Nurse practitioner-aided care	620	4.1	50	19.8	4.1	61	24.8
Nephro Test[14]	Observational	Referred	1021	—	—	—	2.5	142	55.1
RENAAL[8]	Clinical trial	Losartan	1513	2.8	313	67.2	3.4	341	79.3
Steno[17]	Observational	Clinic	380	8.9	115	33.9	7.5	54	18.6
Overall			17,088	—	3136	—	—	2969	—
Studies with protein-to-creatinine ratio									
AASK[7]	Clinical trial, followed by observational study	Antihypertensives and blood pressure goal	1084	8.7	250	26.4	7.5	311	38.5
Grampian-PCR[23]	Observational	Identified by laboratory results	159	2.3	94	254.7	—	—	—
MDRD[6]	Clinical trial, followed by observational study	Dietary protein restriction	839	9.5	208	26.1	6.2	553	105.8
MMKD[13]	Observational	Referred	203	—	—	—	4.0	73	89.8
REIN[15]	Clinical trial	Ramipril	352	—	—	—	2.6	81	88.8
REIN 2 (ref. 16)	Clinical trial	Ramipril	335	—	—	—	1.9	72	113.0
Overall			2972	—	552	—	—	1090	—
Studies with dipstick proteinuria									
Kaiser Permanente Northwest[11]	Observational	Identified by laboratory results	1628	4.5	686	92.6	4.4	98	13.6
Overall			21,688	—	4374	—	—	4157	—

Abbreviations: AASK, African American Study of Kidney Disease and Hypertension; CRIB, Chronic Renal Impairment in Birmingham; MASTERPLAN, Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of a Nurse Practitioner; MDRD, Modification of Diet in Renal Disease; MMKD, Mild to Moderate Kidney Disease Study; REIN, Ramipril Efficacy in Nephropathy; REIN 2, Ramipril Efficacy in Nephropathy 2; RENAAL, Reduction of Endpoints in Non-insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan; Steno, Steno Type 1 Diabetes Study.
[a]Per 1000 person-years.

trials, 4 observational studies of referred patients, and 4 studies of participants identified by laboratory testing (Table 1 and Supplementary Appendix S1 online).[6–18] A total of 4374 deaths occurred in the 10 studies from which information on mortality was captured. Of these studies, six had data on albumin-to-creatinine ratio (ACR), three had data on protein-to-creatinine ratio (PCR), and one had data on dipstick proteinuria. The mortality incidence rate varied dramatically from 19.8 to 254.7 per 1000 person-years. A total of 4157 ESRD events occurred in the 12 studies from which such information was captured. Of these studies, six had data on ACR, five had data on PCR and one had data on dipstick proteinuria. The ESRD incidence rate varied markedly from 13.6 to 115.3 per 1000 person-years. The mean eGFR varied from 22.2 to 69.8 ml/min per 1.73 m^2. The median ACR varied from 26.5 to 1245.5 mg/g and the median PCR varied from 80.8 to 2337.4 mg/g (Table 2).

Independent associations of eGFR and albuminuria with mortality

The incidence rate of mortality was generally greater in lower eGFR categories, but there was wide variation in the incidence rate across studies at every eGFR category (Figure 1a). After adjustment, all eight of the studies included showed a positive association between lower eGFR category and mortality (Table 3). Four of the eight studies had a significantly higher hazard ratio (HR) for an eGFR of 30–44 ml/min per 1.73 m^2 compared with 45–74 ml/min per 1.73 m^2, and seven of eight studies had a significantly elevated HR for an eGFR of 15–29 ml/min per 1.73 m^2 compared with 45–74 ml/min per 1.73 m^2. In continuous analyses, additionally adjusted for category of ACR, PCR, or dipstick proteinuria, below an eGFR of 45 ml/min per 1.73 m^2, the association between a 15 ml/min per 1.73 m^2 lower eGFR and mortality was statistically significant in five of eight studies, with a pooled HR of 1.47 (95% confidence interval (CI): 1.22, 1.79; Figure 2a). There was significant heterogeneity between studies in the HR estimates ($I^2 = 82.7\%$; $P < 0.001$).

The incidence rate of mortality also varied within albuminuria categories, with a higher incidence with higher albuminuria categories in most studies (Figure 1b). After adjustment, a higher albuminuria category was also associated with the risk of mortality (Table 4). The third category of albuminuria, compared with the lowest category, had a statistically significant association with mortality risk in two of the five studies with ACR, in two of the three studies with

Table 2 | Baseline characteristics of participating study populations

	Mean age, years (s.d.)	Female, %	Black, %	CVD, %	DM, %	Smoking, %	Hypertension, %	Hypercholesterolemia, %	Median ACR/PCR, mg/g	Mean eGFR ml/min per 1.73 m^2 (s.d.)
Studies with albumin-to-creatinine ratio										
British Columbia	68.5 (13.9)	44.8	0.5	23.5	32.4	5.4	41.1	—	94.6	34.9 (17.9)
CRIB	61.7 (14.2)	34.1	5.8	45.5	17.2	13.3	90.6	—	467.2	22.2 (10.6)
Grampian-ACR	73.0 (11.4)	56.4	0	24.2	8.5	61.6	59.5	—	26.5	34.6 (5.8)
MASTERPLAN	60.5 (12.4)	31.0	2.7	30.2	24.3	20.2	95.4	18	119.1	36.3 (13.2)
Nephro Test	59.6 (15.0)	31.7	9.6	16.0	26.0	10.0	88.7	16.6	77.6	41.1 (20.1)
RENAAL	60.2 (7.4)	36.8	15.2	35.0	100	18.1	96.4	—	1245.5	39.8 (12.3)
Steno	42.6 (10.8)	38.1	0	10.2	100	51.9	82.2	36.9	498.0	69.8 (27.5)
Studies with protein-to-creatinine ratio										
AASK	54.6 (10.7)	38.8	100.0	51.6	0	29.3	100	55.6	80.8	42.5 (13.2)
Grampian-PCR	73.4 (14.8)	61.6	0	17.0	2.5	55.4	52.8	—	300.9	34.6 (6.2)
MDRD	51.7 (12.4)	39.5	7.9	9.6	5.1	16.6	86.2	23.0	268.5	32.6 (12.3)
MMKD	46.4 (12.3)	34.0	0	12.3	0	21.7	89.2	38.4	1035.0	43.4 (26.7)
REIN	49.5 (13.6)	23.6	0.6	0	7.7	18.2	86.4	—	2337.4	42.9 (18.5)
REIN 2	54.2 (15.0)	25.1	0	0	5.1	16.1	73.1	—	1875.3	31.0 (16.7)
Studies with dipstick proteinuria										
Kaiser Permanente Northwest	71.79 (9.73)	56.0	3.1	44.8	38.8	12.8	92.9	26.0	—	45.7 (10.5)

Abbreviations: AASK, African American Study of Kidney Disease and Hypertension; CRIB, Chronic Renal Impairment in Birmingham; MASTERPLAN, Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of a Nurse Practitioner; MDRD, Modification of Diet in Renal Disease; MMKD, Mild to Moderate Kidney Disease Study; REIN, Ramipril Efficacy in Nephropathy; REIN 2, Ramipril Efficacy in Nephropathy 2; RENAAL, Reduction of Endpoints in Non-insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan; Steno, Steno Type 1 Diabetes Study.

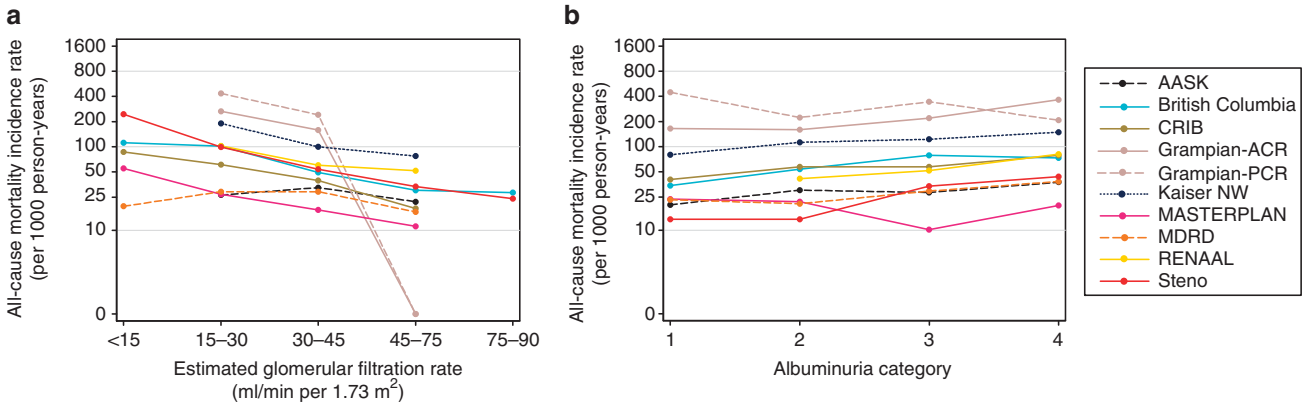

Figure 1 | Crude incidence rate of mortality by category of estimated glomerular filtration rate and category of albuminuria. Crude incidence rate of mortality (per 1000 person-years) by (**a**) category of estimated glomerular filtration rate and (**b**) category of albuminuria. Solid lines represent studies that assessed albuminuria using albumin-to-creatinine ratio (categories: <30, 30–299, 300–999, and ⩾1000 mg/g). Dashed lines represent studies that assessed albuminuria using protein-to-creatinine ratio (categories: <50, 50–499, 500–1499, and ⩾1500 mg/g). Dotted lines represent studies that assessed albuminuria using dipstick protein (categories: −/±, +, ++, and ⩾+++). Points with ⩽5 participants are excluded. AASK, African American Study of Kidney Disease; CRIB, Chronic Renal Impairment in Birmingham; Grampian-ACR, Grampian albumin-to-creatinine ratio; Grampian-PCR, Grampian protein-to-creatinine ratio; Kaiser NW, Kaiser Permanente Northwest; MASTERPLAN, Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of Nurse Practitioners; MDRD, Modification of Diet in Renal Disease; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; Steno, Steno Type 1 Diabetes Study.

PCR, and in one study with dipstick proteinuria. After additional adjustment for eGFR category, an eightfold higher ACR was significantly associated with mortality risk in four of seven studies, and an eightfold higher PCR was significantly associated with mortality in all three studies (Figure 2b). The pooled HR for ACR studies (1.36; 95% CI: 1.16, 1.59) was very similar to the pooled estimate for PCR studies (1.46; 95% CI: 1.28, 1.66), without evidence of significant heterogeneity overall ($I^2 = 39.9\%$; $P = 0.10$).

Independent associations of eGFR and albuminuria with ESRD

The incidence rate of ESRD was markedly greater with lower eGFR categories (Figure 3a). After adjustment, 9 of 11 studies had a significantly higher HR for an eGFR of 30–44 ml/min per 1.73 m^2 compared with 45–74 ml/min per 1.73 m^2, with a pooled HR of 2.72 (95% CI: 1.29, 3.37; Table 5). All 11 studies had a significantly elevated HR for an eGFR of 15–29 ml/min per 1.73 m^2 compared with 45–74 ml/min per 1.73 m^2.

Table 3 | Adjusted hazard ratio (95% confidence interval) for mortality, by estimated glomerular filtration rate category[a]

	Estimated glomerular filtration rate (ml/min per 1.73 m^2)			
	45–74	30–44	15–29	<15
Studies with albumin-to-creatinine ratio				
British Columbia	Reference	1.40 (1.20, 1.62)	3.06 (2.66, 3.52)	4.07 (3.42, 4.84)
CRIB	Reference	1.18 (0.14, 9.65)	1.93 (0.24, 15.32)	3.39 (0.43, 26.88)
MASTERPLAN	Reference	1.32 (0.54, 3.20)	2.62 (1.11, 6.21)	4.49 (1.08, 18.66)
RENAAL	Reference	1.13 (0.84, 1.50)	1.95 (1.43, 2.66)	—
Steno	Reference	1.46 (0.80, 2.68)	2.78 (1.48, 5.19)	5.90 (2.33, 14.96)
Studies with protein-to-creatinine ratio				
AASK	Reference	1.66 (1.25, 2.20)	1.55 (1.10, 2.19)	6.28 (0.85, 46.44)
MDRD	Reference	1.75 (1.10, 2.77)	1.79 (1.13, 2.85)	1.68 (0.79, 3.57)
Studies with dipstick proteinuria				
Kaiser Permanente Northwest	Reference	1.24 (1.05, 1.47)	2.41 (1.94, 2.99)	—
Overall	Reference	1.35 (1.23, 1.49)	2.25 (1.81, 2.79)	3.74 (2.69, 5.20)

Abbreviations: AASK, African American Study of Kidney Disease and Hypertension; CRIB, Chronic Renal Impairment in Birmingham; MASTERPLAN, Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of a Nurse Practitioner; MDRD, Modification of Diet in Renal Disease; RENAAL, Reduction of Endpoints in Non-insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan; Steno, Steno Type 1 Diabetes Study.
[a]Adjusted for age, sex, race, previous cardiovascular disease, smoking status, diabetes mellitus, systolic blood pressure, and serum total cholesterol concentration.

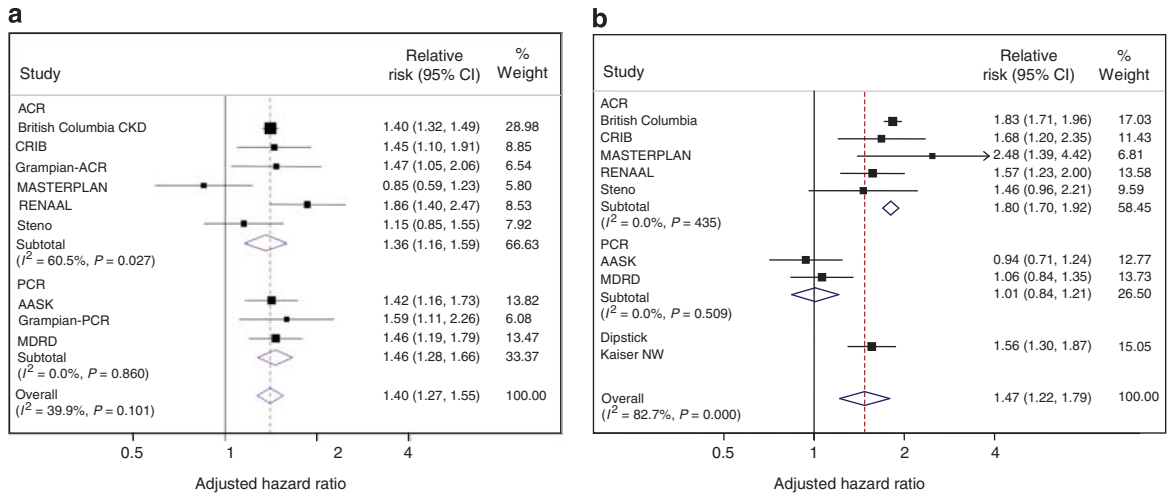

Figure 2 | Forest plot of adjusted hazard ratio for mortality associated a 15 ml/min per 1.73 m^2 lower estimated glomerular filtration rate and an eightfold higher albumin-to-creatinine ratio or protein-to-creatinine ratio. Forest plot of adjusted hazard ratio for mortality associated with (**a**) a 15 ml/min per 1.73 m^2 lower estimated glomerular filtration (eGFR) rate (below an eGFR of 45 ml/min per 1.73 m^2) and (**b**) an eightfold higher albumin-to-creatinine ratio or protein-to-creatinine ratio. The models are adjusted for age, sex, race, previous cardiovascular disease, smoking status, diabetes mellitus, systolic blood pressure, serum total cholesterol concentration, and albuminuria (**a**) or eGFR splines (**b**). AASK, African American Study of Kidney Disease; CI, confidence interval; CKD, chronic kidney disease; CRIB, Chronic Renal Impairment in Birmingham; Grampian-ACR, Grampian albumin-to-creatinine ratio; Grampian-PCR, Grampian protein-to-creatinine ratio; Kaiser NW, Kaiser Permanente Northwest; MASTERPLAN, Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of Nurse Practitioners; MDRD, Modification of Diet in Renal Disease; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; Steno, Steno Type 1 Diabetes Study.

In continuous analyses, additionally adjusting for ACR, PCR, or dipstick proteinuria category as appropriate, below an eGFR of 45 ml/min per 1.73 m^2, the association between a 15 ml/min per 1.73 m^2 lower eGFR and ESRD was statistically significant in all 12 studies (Figure 4a). Each 15 ml/min per 1.73 m^2 lower eGFR was associated with a 6.24-fold (95% CI: 4.84, 8.05) higher risk of ESRD after adjustment for albuminuria and other covariates. There was significant heterogeneity between studies in the HR estimates ($I^2 = 87.9\%$; $P < 0.001$).

The incidence rate of ESRD was also markedly greater with higher albuminuria categories (Figure 3b). The association of higher albuminuria category and risk of ESRD remained strong after adjustment (Table 6). The third category of albuminuria, compared with the lowest category, had a statistically significant association with ESRD risk in all four studies with ACR, in two of three studies with PCR, and in one study with dipstick proteinuria. In continuous analyses, additionally adjusted for eGFR splines, an eightfold higher ACR or PCR was significantly associated with ESRD risk in all 11 studies (Figure 4b). The pooled HR for ACR studies (2.92; 95% CI: 1.96, 4.35) was similar to the pooled estimate for PCR studies (3.42; 95% CI: 1.84, 6.37). In analyses

Table 4 | Adjusted hazard ratio (95% confidence interval) for mortality, by albuminuria category[a]

	Albumin-to creatinine ratio (mg/g)			
	<30	30–299	300–999	⩾1000
British Columbia	Reference	1.49 (1.26, 1.77)	2.42 (2.09, 2.81)	3.01 (2.51, 3.62)
CRIB	Reference	1.65 (0.83, 3.27)	2.15 (1.05, 4.40)	3.56 (1.80, 7.02)
Grampian-ACR	Reference	1.14 (0.05, 27.74)	14.91 (0.60, 369.78)	43.91 (1.90, 1014.98)
MASTERPLAN	Reference	1.12 (0.58, 2.14)	0.53 (0.19, 1.46)	1.10 (0.41, 2.90)
Steno	Reference	2.39 (0.96, 5.93)	1.95 (0.81, 4.69)	2.32 (0.94, 5.76)
Overall	Reference	1.50 (1.28, 1.75)	1.85 (1.08, 3.16)	2.73 (1.74, 4.26)
	Protein-to-creatinine ratio (mg/g)			
	<50	50–499	500–1499	⩾1500
AASK	Reference	1.82 (1.35, 2.45)	1.93 (1.30, 2.87)	2.60 (1.54, 4.40)
Grampian-PCR	Reference	0.53 (0.22, 1.27)	0.99 (0.40, 2.45)	0.73 (0.25, 2.14)
MDRD	Reference	0.99 (0.52, 1.88)	2.17 (1.06, 4.46)	1.80 (0.85, 3.80)
Overall	Reference	1.08 (0.54, 2.18)	1.81 (1.30, 2.53)	1.72 (0.90, 3.29)
	Dipstick category			
	−/±	+	++	+++
Kaiser Permanente Northwest	Reference	1.46 (1.16, 1.82)	1.58 (1.28, 1.95)	1.98 (1.48, 2.64)
Overall	Reference	1.46 (1.24, 1.71)	1.80 (1.38, 2.35)	2.26 (1.68, 3.04)

Abbreviations: AASK, African American Study of Kidney Disease and Hypertension; CRIB, Chronic Renal Impairment in Birmingham; MASTERPLAN, Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of a Nurse Practitioner; MDRD, Modification of Diet in Renal Disease; Steno, Steno Type 1 Diabetes Study.
[a]Adjusted for age, sex, race, previous cardiovascular disease, smoking status, diabetes mellitus, systolic blood pressure, and serum total cholesterol concentration.

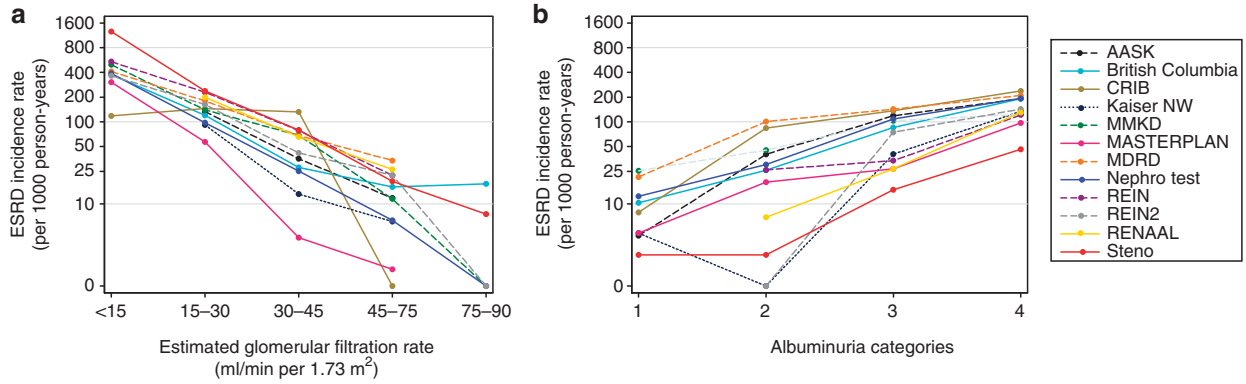

Figure 3 | Crude incidence rate of end-stage renal disease by category of estimated glomerular filtration rate and category of albuminuria. Crude incidence rate of end-stage renal disease (ESRD; per 1000 person-years) by (**a**) category of estimated glomerular filtration rate and (**b**) category of albuminuria. Solid lines represent studies that assessed albuminuria using albumin-to-creatinine ratio (categories: <30, 30–299, 300–999, and ⩾1000 mg/g). Dashed lines represent studies that assessed albuminuria using protein-to-creatinine ratio (categories: <50, 50–499, 500–1499, and ⩾1500 mg/g). Dotted lines represent studies that assessed albuminuria using dipstick protein (categories: −/±, +, ++, ⩾+++). Points with ⩽5 participants are excluded. AASK, African American Study of Kidney Disease; CRIB, Chronic Renal Impairment in Birmingham; Kaiser NW, Kaiser Permanente Northwest; MASTERPLAN, Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of Nurse Practitioners; MDRD, Modification of Diet in Renal Disease; MMKD, Mild to Moderate Kidney Disease; REIN, Ramipril Efficacy in Nephropathy; REIN 2, Ramipril Efficacy in Nephropathy 2; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; Steno, Steno Type 1 Diabetes Study.

combining studies with ACR and PCR, an eightfold higher ACR or PCR was associated with a 3.04-fold (95% CI: 2.27, 4.08) higher risk of ESRD after adjustment for eGFR and other covariates. There was evidence of significant heterogeneity between ACR studies and between PCR studies and overall ($I^2 = 93.6\%$; $P < 0.001$).

DISCUSSION

In this meta-analysis of 13 cohorts, including 21,688 individuals selected because of CKD, we found that lower eGFR and higher albuminuria were each independently associated with mortality and ESRD. Both eGFR and albuminuria were more strongly associated with ESRD than

Table 5 | Adjusted hazard ratio (95% confidence interval) for end-stage renal disease, by estimated glomerular filtration rate category[a]

	Estimated glomerular filtration rate (ml/min per 1.73 m^2)			
	45–74	30–44	15–29	<15
Studies with albumin-to-creatinine ratio				
British Columbia	1.0 (reference)	1.90 (1.54, 2.35)	8.34 (6.90, 10.07)	25.97 (21.24, 31.75)
MASTERPLAN	1.0 (reference)	2.51 (0.28, 22.51)	40.66 (5.57, 296.57)	203.60 (25.68, 1614.08)
NephroTest	1.0 (reference)	3.75 (1.41, 9.96)	14.67 (5.88, 36.61)	75.80 (29.73, 193.26)
RENAAL	1.0 (reference)	2.66 (1.85, 3.82)	9.33 (6.50, 13.40)	—
Steno	1.0 (reference)	4.17 (1.89, 9.18)	13.08 (6.05, 28.28)	156.93 (34.44, 715.10)
Studies with protein-to-creatinine ratio				
AASK	1.0 (reference)	3.49 (2.49, 4.88)	12.24 (8.88, 17.02)	118.85 (27.53, 513.09)
MDRD	1.0 (reference)	2.68 (1.92, 3.73)	6.75 (4.87, 9.34)	27.35 (17.85, 41.90)
MMKD	1.0 (reference)	9.34 (2.10, 41.52)	21.25 (5.01, 90.05)	121.44 (28.12, 524.42)
REIN	1.0 (reference)	3.69 (1.67, 8.14)	11.13 (5.27, 23.49)	63.43 (20.61, 195.19)
REIN 2	1.0 (reference)	1.44 (0.30, 6.91)	8.59 (2.06, 35.85)	27.37 (6.22, 120.48)
Studies with dipstick proteinuria				
Kaiser Permanente Northwest	1.0 (reference)	2.14 (1.29, 3.55)	15.08 (9.24, 14.60)	—
Overall	1.0 (reference)	2.72 (2.19, 3.37)	10.21 (8.36, 12.46)	51.48 (31.95, 82.97)

Abbreviations: AASK, African American Study of Kidney Disease and Hypertension; MASTERPLAN, Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of a Nurse Practitioner; MDRD, Modification of Diet in Renal Disease; MMKD, Mild to Moderate Kidney Disease Study; REIN, Ramipril Efficacy in Nephropathy; REIN 2, Ramipril Efficacy in Nephropathy 2; RENAAL, Reduction of Endpoints in Non-insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan; Steno, Steno Type 1 Diabetes Study.
[a]Adjusted for age, sex, race, previous cardiovascular disease, smoking status, diabetes mellitus, systolic blood pressure, and serum total cholesterol concentration.

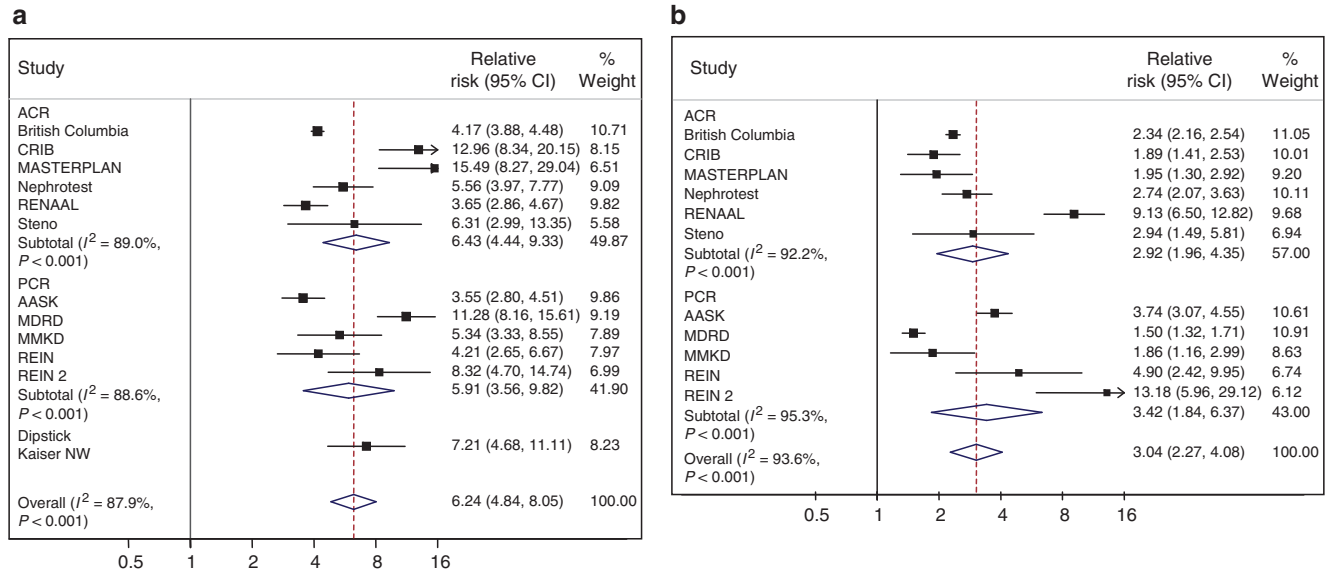

Figure 4 | Forest plot of adjusted hazard ratio for end-stage renal disease associated with a 15 ml/min per 1.73 m^2 lower estimated glomerular filtration rate and an eightfold higher albumin-to-creatinine ratio or protein-to-creatinine ratio. Forest plot of adjusted hazard ratio for end-stage renal disease associated with (**a**) a 15 ml/min per 1.73 m^2 lower estimated glomerular filtration rate (below an eGFR of 45 ml/min per 1.73 m^2) and (**b**) an eightfold higher albumin-to-creatinine ratio or protein-to-creatinine ratio. The models are adjusted for age, sex, race, previous cardiovascular disease, smoking status, diabetes mellitus, systolic blood pressure, serum total cholesterol concentration, and albuminuria (**a**) or eGFR splines (**b**). AASK, African American Study of Kidney Disease; CI, confidence interval; CRIB, Chronic Renal Impairment in Birmingham; Kaiser NW, Kaiser Permanente Northwest; MASTERPLAN, Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of Nurse Practitioners; MDRD, Modification of Diet in Renal Disease; MMKD, Mild to Moderate Kidney Disease; REIN, Ramipril Efficacy in Nephropathy; REIN 2, Ramipril Efficacy in Nephropathy 2; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; Steno, Steno Type 1 Diabetes Study.

with mortality in these cohorts of individuals with CKD. To our knowledge, this represents the largest and most generalizable study of CKD populations in which these independent associations have been explored, and confirms the strong and independent relationship of higher level of albuminuria and lower levels of eGFR with mortality and ESRD across a wide

Table 6 | Adjusted hazard ratio (95% confidence interval) for end-stage renal disease, by albuminuria category[a]

	Albumin-to-creatinine ratio (mg/g)			
	<30	30–299	300–999	⩾1000
British Columbia	Reference	2.42 (1.80, 3.26)	7.58 (5.83, 9.86)	12.91 (9.82, 16.95)
CRIB	Reference	9.78 (2.35, 40.63)	16.39 (3.95, 68.02)	29.72 (7.18, 123.10)
MASTERPLAN	Reference	4.14 (1.22, 14.04)	5.28 (1.49, 18.72)	18.87 (5.57, 63.91)
NephroTest	Reference	2.55 (1.26, 5.13)	10.40 (5.31, 20.37)	21.38 (10.86, 42.08)
Overall	Reference	2.87 (1.91, 4.34)	7.96 (6.27, 10.09)	14.61 (11.16, 19.13)
	Protein-to-creatinine ratio (mg/g)			
	<50	50–499	500–1499	⩾1500
AASK	Reference	5.63 (3.49, 9.10)	19.26 (11.75, 31.57)	34.60 (19.76, 60.58)
MDRD	Reference	2.18 (1.60, 2.99)	2.87 (2.06, 4.00)	4.47 (3.14, 6.37)
MMKD	Reference	1.77 (0.23, 13.82)	4.03 (0.54, 30.23)	4.30 (0.58, 31.74)
Overall	Reference	3.18 (1.40, 7.18)	6.38 (1.34, 30.34)	9.47 (1.81, 49.60)
	Dipstick category			
	−/±	+	++	+++
Kaiser Permanente Northwest	Reference	1.71 (0.76, 3.84)	7.22 (4.21, 12.97)	19.41 (11.06, 34.04)
Overall	Reference	2. 92 (2. 08, 4. 10)	7. 70 (4. 52, 13. 10)	15. 01 (8. 36, 26. 95)

Abbreviations: AASK, African American Study of Kidney Disease and Hypertension; CRIB, Chronic Renal Impairment in Birmingham; MASTERPLAN, Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of a Nurse Practitioner; MDRD, Modification of Diet in Renal Disease; MMKD, Mild to Moderate Kidney Disease Study; REIN, Ramipril Efficacy in Nephropathy; REIN 2, Ramipril Efficacy in Nephropathy 2; Steno, Steno Type 1 Diabetes Study.
[a]Adjusted for age, sex, race, previous cardiovascular disease, smoking status, diabetes mellitus, systolic blood pressure, and serum total cholesterol concentration.

range of clinical settings. The use of a uniform analysis plan also allows for comparisons of the magnitude of the associations across the studies included.

Compared with an eGFR of 45–74 ml/min per 1.73 m^2, progressively lower eGFR was associated with progressively greater risk of death and ESRD. The range of eGFR in the selected reference group was necessarily broad to enable analyses, and this precludes a precise determination of the level of eGFR below which risk begins increasing. Statements about subdividing CKD stage 3 are better addressed in higher GFR populations. All CKD studies had data below an eGFR of 45 ml/min per 1.73 m^2, in which each 15 ml/min per 1.73 m^2 lower eGFR was associated with a 47% higher risk of death and a sixfold higher risk of ESRD after adjustment for albuminuria. These results are consistent with the use eGFR stages in classification of CKD. Similarly, the relatively low number of participants and few events among individuals with negative dipstick results precluded separating negative dipstick from trace proteinuria. Including trace proteinuria in the reference group would result in lower HRs for +, ++, and +++ categories than would result from using only negative proteinuria as the reference group. Future studies should explore the clinical implications of trace dipstick proteinuria among individuals with known CKD.

We also found that higher albuminuria was associated with greater risk of death and strongly associated with greater risk of ESRD. The risk increased progressively with every higher level of albuminuria, and the associations were similar for studies using ACR, PCR, or dipstick proteinuria. An eightfold higher ACR or PCR was associated with an estimated 40% higher risk of death and an estimated threefold higher risk of ESRD after adjustment for eGFR. The current CKD classification system does not discriminate by severity of albuminuria among individuals with CKD.[19] These results suggest that adding data on the presence and severity of albuminuria to eGFR stages provides more prognostic information than the current classification system. This may be especially true for predicting the risk of ESRD. There were no substantial differences in the associations of ACR or PCR with either death or ESRD, suggesting that each measure provides useful prognostic information of broadly equal importance.

The associations of lower eGFR with higher risk of outcomes remained after adjustment for severity of albuminuria and, likewise, the associations of higher albuminuria remained after adjustment for eGFR. These results demonstrate that both lower eGFR and higher albuminuria predict mortality and ESRD, independent of one another.

There was a wide variation in the incidence rates for death and ESRD across the cohorts included in this meta-analysis, presumably reflecting variation in definition of CKD, causes and pathology of kidney disease, range in eGFR and albuminuria, comorbid conditions, and other eligibility criteria. We evaluated statistical heterogeneity using the I^2 statistic, which reflects the variability among effect sizes due to between-study differences as a percentage of the total variability. The within-study variation is relatively small, because the sample sizes of the studies included are relatively large. Thus, the percentage of total variability that is due to between-study variation is relatively large, but does not

reflect clinically important inconsistencies in relative risks, as shown in the forest plots.

The incidence rates of death and ESRD were of roughly similar magnitude within most studies. This differs substantially from the general population, in which the incidence rate of death is at least 10 times higher than the incidence rate of ESRD.[20] This difference may be due to a higher incidence of ESRD among individuals selected for CKD than individuals with CKD in the general population, which reduces the influence of the competing risk of mortality when studying incident ESRD. This emphasizes the differences in competing risk for ESRD and mortality, as well as other outcomes, in different study populations.

Lower eGFR and higher albuminuria were much more strongly associated with ESRD than with mortality. Decreased GFR and albuminuria are primary factors in the development of ESRD, whereas numerous comorbid conditions may affect the risk of mortality in these study participants. The much higher incidence of ESRD, relative to the incidence of death in these CKD cohorts, reduces the impact of the competing risk of death and may allow the direct associations between eGFR and albuminuria with ESRD to be observed more accurately than in the general population. These analyses of individuals with CKD also include a much higher proportion of deaths that occurred after ESRD than studies in the general population. Another factor to consider is the selection of participants for the studies included in this meta-analysis. Individuals with relatively high eGFR and/or low albuminuria, who are enrolled in these studies, likely have more severe comorbid conditions than most individuals with similar eGFR and albuminuria included in general population studies. If these comorbid conditions put the enrolled participants at higher risk of death, the observed associations of eGFR and albuminuria with mortality could be substantially confounded. These comorbid conditions may be less strongly associated with progression to ESRD and, therefore, would have less impact on the observed associations of eGFR and albuminuria with ESRD.

The populations of the participating studies comprise highly selected patients, with the majority enrolled in a randomized clinical trial or referred to a nephrologist.[6–8,10,14–17] The others are comprised of patients selected from clinical populations because of decreased eGFR or albuminuria.[11] There were no obvious differences in the HRs relating either eGFR or albuminuria with the risk of either outcome according to whether the study was a randomized trial or an observational study, although the baseline characteristics and resultant incidence rates of both outcomes varied widely and the number of studies within each category was small, limiting the usefulness of formal meta-regression models. Within observational studies, differences in study populations may also exist between those with protocol-driven study visits (CRIB (Chronic Renal Impairment in Birmingham), NephroTest, and Mild to Moderate Kidney Disease (MMKD)) and those based on administrative data (British Columbia, Grampian ACR and Grampian PCR, and Kaiser Permanente Northwest) or passive surveillance of clinical events (Steno). Among the studies included in this meta-analysis, those with protocol-driven examinations had higher incidence of ESRD than those based on administrative data. In addition, the incidence of ESRD was higher than the incidence of mortality among studies with protocol-driven examinations, whereas the incidence rates for these two outcomes were more similar among studies based on administrative data. We hypothesize that these differences are due to the differing selection criteria used to enroll participants in these two types of studies, such that studies with protocol-driven examinations would more likely enroll individuals with more severe disease and/or more comorbidities, whereas studies based on administrative data would be more likely to enroll all individuals eligible based on a limited number of easily identified diagnostic or laboratory criteria. Despite the differences in ESRD incidence rates, we did not observe any consistent differences in the strength of the associations of eGFR and ACR with both outcomes (that is, mortality and ESRD) across study types.

We acknowledge that this meta-analysis has limitations. First, we did not perform a systematic literature search to identify all potentially eligible cohorts. However, study selection was unbiased with respect to the associations of interest, and most of the included cohorts had not reported or investigated these associations before we performed our pooled analysis. Selection bias is therefore unlikely. Our analyses do not assess changes in eGFR, albuminuria, or covariates over time. Any bias from systematic differences in changes in the predictors after baseline, however, would presumably attenuate the associations between baseline predictors and outcomes. No data could be taken into account on the effects of treatment that was started during follow-up. Therefore, it cannot be excluded that the observed associations are influenced by the start of specific treatments. However, if such treatment is effective in preventing mortality and ESRD, as expected, then it would be expected to lead to an underestimation of the true relative risk of low eGFR and high albuminuria for these outcomes. There were no obvious differences in the associations by the proportion of diabetic individuals in the studies. However, it is difficult to isolate any effect modification by diabetes in this meta-analysis, as diabetic and non-diabetic participants were not analyzed separately, and the participating studies differed with respect to other inclusion and exclusion criteria as well.

Our findings have important implications for clinical practice and research in CKD. Traditionally, prognosis in CKD is based on the clinical diagnosis (cause and pathology) of CKD. Our findings that a higher level of albuminuria and lower level of eGFR increase the risk for mortality and ESRD consistently across cohorts, with diverse clinical diagnosis in diverse settings, suggest that these measures provide important prognostic information beyond clinical diagnosis and should be considered in predicting prognosis.

We acknowledge that the levels of eGFR and albuminuria among patients with CKD are likely to vary according to the clinical diagnosis and referral pattern. For example, patients with lower eGFR and higher albuminuria are likely to be younger and have primary kidney diseases, such as glomerular, tubulointerstitial, or cystic kidney diseases, whereas those with higher levels of eGFR or lower levels of albuminuria may be older and have kidney disease due to systemic vascular disease, such as hypertension or diabetes. Similarly, the risk for ESRD or mortality likely varies across clinical diagnosis of CKD and referral pattern, as well as by the level of albuminuria and eGFR. The risk for these outcomes is also influenced by age, sex, race, cardiovascular disease (CVD) risk factors, and history of CVD. On the basis of our results, it seems likely that prognosis is determined by all these factors, and development of risk prediction models and scores for these outcomes will need to take all these factors into account. Future studies should also consider the influence of clinical diagnosis and level of eGFR and albuminuria on the risk of concurrent complications of CKD, such as hypertension, anemia, malnutrition, bone and mineral disorders, and electrolyte disorders, as well as for prognosis related to other outcomes associated with CKD, such as infection or cognitive impairment.

In conclusion, we found that lower eGFR and more severe albuminuria independently predict mortality and ESRD among individuals with CKD. The observed associations provide evidence consistent with the use of eGFR stages in classification of CKD and suggest that addition of albuminuria stages may provide additional prognostic information among individuals with CKD.

MATERIALS AND METHODS

Study selection

Studies were identified by the planning committee and analytic team, and discussion between collaborators. This was enhanced by a call for participation at the World Congress of Nephrology in Milan (May, 2009), a published position statement of KDOQI (Kidney Disease Outcomes Quality Initiative) and KDIGO,[5] and an announcement on the KDIGO website (http://www.kdigo.org). To be eligible for inclusion in this meta-analysis, studies had to include primarily participants selected because of CKD, provide information at baseline on estimated or measured GFR and either urinary albumin or urinary protein excretion, and include at least 50 ESRD events or deaths to ensure sufficient outcomes in the reference cell. The definitions of CKD used in each study are available in the specific references. Individuals with ESRD were excluded from all studies.

Study variables

eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) Study equation using age, sex, race, and serum creatinine concentration.[1,21] Each participating study group was asked to standardize the serum creatinine measurements to isotope dilution mass spectrometry-traceable methods, but calibration was not uniform. Albuminuria was assessed as the urinary ACR or urinary PCR, preferably measured in a first morning void urine sample. If first morning voids were not available, spot urine samples or samples from 24-h urine collections were used. In studies in which no quantitative albuminuria measurements were available, data on dipstick proteinuria were collected.

History of CVD was defined as previous myocardial infarction, bypass grafting, percutaneous coronary intervention, heart failure, or stroke. Hypertension was defined as systolic blood pressure $\geqslant 140$ mm Hg or diastolic blood pressure $\geqslant 90$ mm Hg or use of antihypertensive medication. Hypercholesterolemia was defined as total cholesterol $\geqslant 5.0$ mmol/l in the case of a positive history of CVD and as $\geqslant 6.0$ mmol/l in the case of a negative history of CVD. Diabetes mellitus was defined as fasting glucose $\geqslant 7.0$ mmol/l or non-fasting glucose $\geqslant 11.1$ mmol/l or use of glucose-lowering drugs, or, if other data were not available, self-reported diabetes. Smoking status was dichotomized as current versus not current smoking. ESRD was defined as the start of renal replacement therapy or death due to decreased kidney function and not due to acute kidney injury. All deaths occurring before or after ESRD were included in the analyses. The clinical diagnosis (cause and pathology) of CKD was not included because it was not ascertained in all studies and it was not ascertained uniformly across studies in which it was recorded.

Statistical analysis

The primary objective of this study was to evaluate the independent associations of eGFR and albuminuria with the risk of all-cause mortality and ESRD. Investigators from each study newly analyzed their data following an *a priori* analytic plan using standard statistical programs supplied by the central analysis team. All analyses were conducted using Stata version 10 or 11 (Stata, College Station, TX), SAS version 9 (SAS Institute, Cary, NC), or R version 2.9.2 (R Foundation for Statistical Computing, Vienna, Austria).

Categories were created for eGFR (15–29, 30–44, 45–74, 75–89, 90–104, and $\geqslant 105$ ml/min per 1.73 m^2), ACR (<30, 30–299, 300–999, and $\geqslant 1000$ mg/g), PCR (<50, 50–499, 500–1499, and $\geqslant 1500$ mg/g), and dipstick proteinuria (negative/trace, +, ++, and $\geqslant$ +++). As to be expected for CKD cohorts, limited data were available for eGFR categories above 74 ml/min per 1.73 m^2; hence, these results are not shown. Cox proportional hazards models were used to obtain adjusted HRs for each category of eGFR relative to the reference group of 45–74 ml/min per 1.73 m^2, and for each category of ACR/PCR/dipstick proteinuria (using the lowest category for each as the reference) (Supplementary Appendix S2 online). A broad eGFR reference group was chosen because several studies had no events or few events in the narrower ranges of eGFR 60–74 or 45–59 ml/min per 1.73 m^2. These models were adjusted for age, sex, race, history of CVD, smoking status, diabetes mellitus, systolic blood pressure, and serum total cholesterol concentration, wherever data were available. Cox proportional hazards models were also constructed with log ACR or log PCR, and eGFR, modeled as continuous variables, adjusted for all the covariates in the categorical analysis. When log ACR or log PCR are modeled as linear terms, results are presented for an eightfold higher ACR or PCR. eGFR was modeled as a linear spline with knots at 45, 60, 75, 90, and 105 ml/min per 1.73 m^2. As data were limited at the higher eGFR ranges, results are presented for 15 ml/min per 1.73 m^2 lower eGFR below 45 ml/min per 1.73 m^2. Data from specific studies were excluded from specific analyses if the range of values included in the study did not allow HRs to be estimated (for example, all ACR values >300 mg/g) or if the study had no events in the reference category.

Pooled estimates of the HR and 95% CI were obtained from a random effects meta-analysis. Heterogeneity was estimated using the χ^2-test for heterogeneity and the I^2 statistic.[22] Meta-analyses were conducted separately for studies with ACR and PCR. The Grampian cohort

included ACR data on some participants and PCR data on other participants. These were treated as two separate studies in the analyses.

DISCLOSURE

The authors declared no conflict of interest. A variety of institutions supported the cohorts contributing to the CKD Prognosis Consortium, as described in publications on these cohorts.

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CONTRIBUTORS

All members of the writing committee contributed to the collection and analysis of the data, and to the preparation of the report. All collaborators were given a copy of the paper as prepared for submission and given the opportunity to comment on the draft manuscript. The writing committee accepts full responsibility for the content of this paper.

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SUPPLEMENTARY MATERIAL

Appendix S1. Analytic notes for specific studies.

Appendix S2. Statistical models used in this study.

Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

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