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# Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts

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Screening for chronic kidney disease is recommended in people at high risk, but data on the independent and combined associations of estimated glomerular filtration rate (eGFR) and albuminuria with all-cause and cardiovascular mortality are limited. To clarify this, we performed a collaborative meta-analysis of 10 cohorts with 266,975 patients selected because of increased risk for chronic kidney disease, defined as a history of hypertension, diabetes, or cardiovascular disease. Risk for all-cause mortality was not associated with eGFR between 60–105 ml/min per 1.73 m<sup>2</sup>, but increased at lower levels. Hazard ratios at eGFRs of 60, 45, and 15 ml/min per 1.73 m<sup>2</sup> were 1.03, 1.38 and 3.11, respectively, compared to an eGFR of 95, after adjustment for albuminuria and cardiovascular risk factors. Log albuminuria was linearly associated with log risk for all-cause mortality without thresholds. Adjusted hazard ratios at albumin-to-creatinine ratios of 10, 30 and 300 mg/g were 1.08, 1.38, and 2.16, respectively compared to a ratio of five. Albuminuria and eGFR were multiplicatively associated with all-cause mortality, without evidence for interaction. Similar associations were observed for cardiovascular mortality. Findings in cohorts with dipstick data were generally comparable to those in cohorts measuring albumin-to-creatinine ratios. Thus, lower eGFR and higher albuminuria are risk factors for all-cause and cardiovascular mortality in high-risk populations, independent of each other and of cardiovascular risk factors.

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KEYWORDS: albumin-to-creatinine ratio (albuminuria); all-cause mortality; cardiovascular mortality; eGFR (kidney function); high-risk cohorts; meta-analysis

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The definition and classification of chronic kidney disease was proposed by Kidney Disease Outcomes Quality Initiative (KDOQI) in 2002, and endorsed by Kidney Disease Improving Global Outcomes (KDIGO) in 2004.<sup>1–3</sup> Widespread implementation of the definition and classification has promoted increased attention to chronic kidney disease in clinical practice, research, and public health.<sup>4</sup> It has also generated substantial debate about the appropriateness of recommending the same glomerular filtration rate (GFR) thresholds for people of all ages, the optimal level of albuminuria as a marker of kidney damage, and about the value of the 5-stage classification system based on estimated GFR (eGFR) without consideration of albuminuria.<sup>5–8</sup>

In October 2009, KDIGO sponsored a Controversies Conference to examine the validity of the existing system as well as to evaluate proposed alternatives.<sup>9</sup> The report of the Consensus Conference is included in this issue of *Kidney International*.<sup>10</sup> As part of the process, the CKD Prognosis Collaboration was formed to undertake a comprehensive analysis of mortality and kidney outcomes according to estimated GFR and albuminuria, to answer key questions underlying the debate.

This paper is the second in a series of four papers to report the results of collaborative meta-analyses undertaken by the CKD Prognosis Consortium. The first paper in this series deals with all-cause and cardiovascular mortality in general population cohorts.<sup>11</sup> The present report describes all-cause and cardiovascular mortality in cohorts at high risk for chronic kidney disease. Other manuscripts report kidney outcomes from general population and high-risk cohorts,<sup>12</sup> and mortality and kidney outcomes in chronic kidney disease cohorts.<sup>13</sup>

Chronic kidney disease is now recognized as a risk factor for all-cause and cardiovascular mortality.<sup>14</sup> Our meta-analysis of 21 general population cohorts showed the independent and joint associations of reduced estimated GFR and higher levels of albuminuria on these outcomes.<sup>11</sup>

**Table 1 | Characteristics of included studies**

	N	Age (year)	Male (%)	Black (%)	CVD (%)	HT (%)	HC (%)	DM (%)	Smoking (%)	eGFR (ml/min per 1.73 m <sup>2</sup> )	ACR (mg/g)	FU (Year)	ACM (n)	CVM (N)
<i>Cohorts with ACR data</i>														
ADVANCE	11,140	65.8	57.5	NA	32.2	82.2	33.0	100	15.1	78.2	15.9	4.8	1031	542
AKDN	67,406	55.8	56.8	NA	5.0	46.8	NA	49.0	NA	76.8	11.1	2.3	2371	—
ONTARGET	25,620	66.4	73.3	2.5	92	NA*	NA*	37.5	12.6	73.6	52.2	4.5	3068	1821
Pima	6341	26.4	45.4	0	NA	12.9	4.2	20.4	27.8	14.4	11.9	13.5	1083	170
TRANSCEND	5926	66.9	57	1.8	92.5	NA*	NA*	35.7	9.8	71.7	25.3	4.6	713	450
ZODIAC	1067	67.9	43.4	0	34.9	83.3	40	100	18.6	63.8	19.6	7.8	440	188
Total	117,500												8706	3171
Weighted mean		58.0	59.2	1.9	32.7	49.3	23.6	49.6	14.9	79.5	21.4	3.8		
<i>Cohorts with dipstick data</i>														
CARE	4098	58.6	86.2	3.2	100	82.9	79.0	14.2	16.1	71.9	—	4.8	371	211
KEEP	92,316	54.8	31.7	31.3	13.0	57.3	23.0	30.5	11.1	81.2	—	2.4	568	—
KP Hawaii	40,210	59.0	50.4	NA	17.0	NA	NA	48.0	13.6	71.5	—	2.4	1706	—
MRFIT	12,851	46.2	100	7.2	0.0	62.3	57.1	3.1	63.7	79.7	—	21.6	4658	2274
Total	149,475												7303	2485
Weighted mean		55.3	44.1	27.4	15.3	58.8	29.1	32.4	16.4	78.2	—	4.1		

Abbreviations: ACM, all-cause mortality; ACR, albumin-to-creatinine ratio; CVD, cardiovascular disease; CVM, cardiovascular mortality; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FU, duration of follow-up; HC, hypercholesterolemia; HT, hypertension; NA, not available.

NA\* in ONTARGET and TRANSCEND, respectively, a history of hypertension was reported by 69 and 76%, and statin use by 62 and 55%.

Presently, screening for chronic kidney disease is recommended in people at high risk for chronic kidney disease including patients with cardiovascular disease risk factors.<sup>4</sup> However, the associations between eGFR and albuminuria with mortality may differ in high-risk populations as compared with the general population. As a comprehensive analysis of the associations between eGFR and albuminuria with all-cause and cardiovascular mortality in high-risk populations has not been reported, we studied these associations in a collaborative meta-analysis. *A priori* we hypothesized 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.

## RESULTS

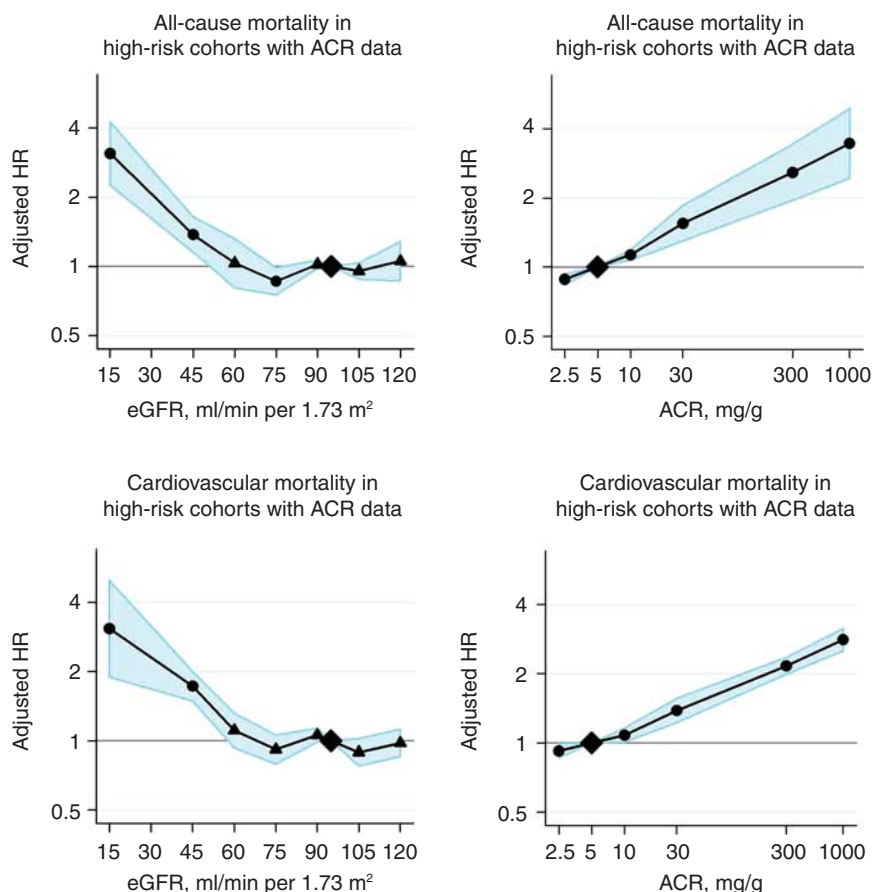
### Study characteristics

Of 10 high-risk cohorts (266,975 subjects), 6 had data on albumin-to-creatinine ratio (117,500 subjects) and 4 on dipstick proteinuria (149,475 subjects) (Table 1). Acronyms and abbreviations for studies included in the current report are given in Supplementary Table S1 online. By definition, the study participants have a high prevalence of cardiovascular disease risk factors. The characteristics of the dipstick cohorts are, in general, comparable to those of the albumin-to-creatinine ratio cohorts, with the albumin-to-creatinine ratio cohorts having a higher percentage of males and subjects with diabetes and a history of cardiovascular disease, and a lower percentage of Blacks. In the cohorts with information on albumin-to-creatinine ratio, there were 8706 all-cause deaths and 3171 cardiovascular disease deaths

during follow-up. In the subjects with dipstick data, these figures are 7303 and 2485, respectively. A total of 36.7% of the subjects in the pooled study population with measurements of albumin-to-creatinine ratio had chronic kidney disease according to the current definition (eGFR <60 ml/min per 1.73 m<sup>2</sup> or albumin-to-creatinine ratio ≥30 mg/g) (Supplementary Tables S2 and S3 online). This subgroup accounted for 58.6% of all-cause mortality events (Supplementary Table S4 online) and 59.4% of cardiovascular mortality events (Supplementary Table S5 online). Data on cardiovascular mortality were available in only two of the dipstick cohorts, which differed greatly in sample size and duration of follow-up.

### Independent continuous associations of eGFR and albuminuria with mortality risk

Pooled adjusted hazard ratios of all-cause mortality and cardiovascular mortality according to eGFR and albumin-to-creatinine ratio are shown in Figure 1. The association between eGFR and relative risk for all-cause mortality and cardiovascular mortality was relatively constant between 60 and 105 ml/min per 1.73 m<sup>2</sup>, and steadily increased at eGFR below 60 ml/min per 1.73 m<sup>2</sup> (Figure 1, left panels). For all-cause mortality, adjusted hazard ratios at eGFR 60, 45, and 15 ml/min per 1.73 m<sup>2</sup> were 1.03 (0.81–1.33), 1.38 (1.15–1.65), and 3.11 (2.26–4.27), respectively, whereas for cardiovascular mortality, the adjusted hazard ratios were 1.11 (0.93–1.32), 1.73 (1.49–2.00), and 3.08 (1.89–5.01), respectively. The pattern for all-cause mortality was comparable in the dipstick cohorts (Supplementary Figure S1 online), except there was a tendency for a U-shaped relationship



**Figure 1 | Pooled adjusted hazard ratios (95% confidence interval) for all-cause (upper panels) and cardiovascular (lower panels) mortality in high-risk cohorts with albumin-to-creatinine ratio data, according to spline eGFR (left panels) and albumin-to-creatinine ratio (right panels), adjusted for each other and for age, sex, race, cardiovascular disease history, systolic blood pressure, diabetes, smoking, and total cholesterol (continuous analyses).** Reference categories are eGFR 95 ml/min per 1.73 m<sup>2</sup> and albumin-to-creatinine ratio 5 mg/g, respectively. Dots represent statistical significance, triangles represent non-significance, and shaded areas are 95% confidence interval. ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

with significantly decreased risk at eGFR 75 ml/min per 1.73 m<sup>2</sup> (hazard ratio 0.83 (0.77–0.91)) and a significantly increased risk at eGFR below 45 ml/min per 1.73 m<sup>2</sup> (hazard ratio at 15 ml/min per 1.73 m<sup>2</sup> 1.93 (1.46–2.56)).

In contrast, the relationship of albumin-to-creatinine ratio to the relative risk of all-cause mortality and cardiovascular mortality was monotonic with log hazard ratios increasing linearly with increasing log albumin-to-creatinine ratio, without threshold effects (Figure 1, right panels). As compared with an albumin-to-creatinine ratio of 5 mg/g, hazard ratios for all-cause mortality at albumin-to-creatinine ratios of 10, 30, and 300 mg/g were 1.08 (1.01–1.16), 1.38 (1.23–1.56), and 2.16 (1.99–2.35), respectively, and for cardiovascular mortality 1.13 (1.07–1.20), 1.55 (1.30–1.86), and 2.59 (1.95–3.44), respectively.

### Interactions

The interaction between eGFR and albuminuria was significant for all-cause mortality in only 4 of 10 cohorts, and for cardiovascular mortality in only 1 of 7 cohorts (Supplementary Table S6 online). Significant interaction

between eGFR and age was found in 3 of 10 cohorts for all-cause mortality, and in 2 out of 7 cohorts for cardiovascular mortality (Supplementary Table S6 online).

### Joint associations of eGFR and albuminuria with mortality risk in the overall groups

Table 2 shows unadjusted incidence rates of all-cause and cardiovascular mortality for cohorts with albumin-to-creatinine ratio data. Pooled hazard ratios for all-cause mortality and cardiovascular mortality in the 28 categories of eGFR and albuminuria show that a higher albumin-to-creatinine ratio is associated with a higher risk across all levels of eGFR and a lower eGFR is associated with a higher risk across all levels of albumin-to-creatinine ratio, indicating multiplicative independence for all-cause mortality and cardiovascular mortality (Table 3). At severely reduced eGFR values (15–29 ml/min per 1.73 m<sup>2</sup>), the risk associated with higher albuminuria was slightly attenuated. The hazard ratios for all-cause mortality were significantly increased in all eGFR categories with an albumin-to-creatinine ratio  $\geq$  30 mg/g, whereas the hazard ratios for lower eGFR at an

albumin-to-creatinine ratio <30 mg/g were significantly increased only for eGFR categories <45 ml/min per 1.73 m<sup>2</sup>. In contrast, the hazard ratios for cardiovascular mortality were significantly increased in all albumin-to-creatinine ratio ≥10 mg/g categories, even when eGFR was >60 ml/min per 1.73 m<sup>2</sup> and for all eGFR <60 ml/min per

1.73 m<sup>2</sup> categories, even when the albumin-to-creatinine ratio was <10 mg/g.

For cohorts with dipstick data, unadjusted incidence rates for all-cause and cardiovascular mortality are shown in Table 4, and pooled hazard ratios for these end points in Table 5. This latter table shows that pooled hazard ratios for all-cause mortality were similarly increased for a higher dipstick category across all eGFR levels and for a lower eGFR across all dipstick categories. However, because of the U-shaped relationship, these hazard ratios were significantly higher than the reference group only at an eGFR level of 30–45 ml/min per 1.73 m<sup>2</sup> and below, and hazard ratios were not significantly increased in the eGFR 45–59 ml/min per 1.73 m<sup>2</sup> category with a negative or trace positive dipstick test.

Figure 2 shows the continuous analyses (allowing interaction) of the hazard ratios of eGFR and albuminuria for all-cause mortality and cardiovascular mortality of cohorts with albumin-to-creatinine ratio and dipstick data. These figures suggest that eGFR and albuminuria are independently associated with all-cause mortality and cardiovascular mortality, with a tendency towards a weaker association between albumin-to-creatinine ratio and these outcomes at severely reduced eGFR values. The two cohorts with dipstick data that reported on cardiovascular mortality included very few persons with lower eGFR. Interpretation of these data is therefore difficult.

### Joint associations of eGFR and albuminuria with mortality risk per age group

The overall incidence rates for all-cause mortality and cardiovascular mortality were four- and twofold higher,

**Table 2 | Unadjusted incidence rates (per 1000 patient-years) for ACM and cardiovascular mortality in the high-risk cohorts with ACR ratio data**

	ACR (mg/g)				All
	<10	10–29	30–299	≥300	
<b>ACR</b>					
<i>eGFR (ml/min per 1.73 m<sup>2</sup>)</i>					
>105	11.7	10.8	13.0	26.8	12.4
90–104	9.4	11.9	16.8	26.5	11.9
75–89	9.4	11.5	20.9	32.2	12.5
60–74	11.1	17.0	26.2	42.9	16.6
45–59	19.6	27.4	43.0	65.9	30.1
30–44	37.1	48.7	68.7	84.8	56.6
15–29	105.8	105.4	118.3	123.8	112.0
All	12.4	17.6	29.8	54.3	19.2
<b>Cardiovascular mortality</b>					
<i>eGFR (ml/min per 1.73 m<sup>2</sup>)</i>					
>105	8.9	10.0	12.6	19.4	10.3
90–104	8.2	11.5	14.1	29.9	10.4
75–89	8.9	10.6	16.0	40.0	11.0
60–74	9.3	12.9	19.2	37.3	12.4
45–59	14.5	20.4	26.3	46.3	19.8
30–44	27.5	35.6	45.0	66.1	38.6
15–29	45.7	58.3	68.7	76.2	61.7
All	10.5	14.4	20.8	44.4	14.4

Abbreviations: ACM, all-cause mortality; ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate. Shaded areas make up the combined reference groups.

**Table 3 | Pooled adjusted hazard ratios (95% CI) for ACM and cardiovascular mortality in the high-risk cohorts with ACR data**

	ACR (mg/g)				All
	<10	10–29	30–299	≥300	
<b>ACM</b>					
<i>eGFR (ml/min per 1.73 m<sup>2</sup>)</i>					
>105	1.26 (0.97–1.64)	1.31 (1.07–1.60)	1.51 (1.23–1.84)	2.97 (2.19–4.04)	1.10 (0.96–1.26)
90–104	Ref	1.26 (1.05–1.51)	1.63 (1.37–1.95)	2.72 (2.08–3.56)	Ref
75–89	0.88 (0.70–1.11)	1.12 (0.85–1.48)	1.58 (1.36–1.84)	2.91 (2.28–3.73)	0.93 (0.77–1.12)
60–74	0.82 (0.64–1.05)	1.18 (0.89–1.56)	1.63 (1.28–2.07)	2.67 (1.76–4.04)	0.98 (0.75–1.27)
45–59	1.16 (0.77–1.73)	1.39 (0.97–1.98)	1.96 (1.57–2.43)	3.58 (2.54–5.05)	1.37 (1.00–1.88)
30–44	1.54 (1.11–2.13)	2.06 (1.42–2.97)	2.84 (1.98–4.06)	3.99 (2.73–5.83)	2.01 (1.47–2.75)
15–29	2.73 (1.87–3.97)	3.52 (2.18–5.69)	3.73 (2.90–4.80)	5.43 (3.94–7.49)	3.21 (2.58–4.01)
All	Ref	1.28 (1.17–1.39)	1.79 (1.60–2.00)	3.29 (3.04–3.56)	
<b>Cardiovascular mortality</b>					
<i>eGFR (ml/min per 1.73 m<sup>2</sup>)</i>					
>105	1.20 (0.89–1.62)	1.62 (1.10–2.39)	2.04 (1.40–2.95)	3.55 (1.80–7.01)	1.03 (0.86–1.24)
90–104	Ref	1.56 (1.12–2.17)	1.95 (1.44–2.65)	4.12 (2.50–6.77)	Ref
75–89	1.02 (0.82–1.26)	1.34 (1.03–1.76)	1.82 (1.42–2.34)	4.76 (3.32–6.81)	0.98 (0.85–1.13)
60–74	1.00 (0.81–1.23)	1.54 (1.16–2.04)	2.01 (1.55–2.59)	4.00 (2.83–5.66)	1.01 (0.80–1.28)
45–59	1.42 (1.14–1.77)	2.06 (1.60–2.66)	2.56 (2.03–3.22)	5.58 (3.19–9.79)	1.63 (1.22–2.18)
30–44	2.27 (1.72–3.01)	3.74 (2.06–6.78)	3.95 (3.02–5.18)	6.00 (4.40–8.18)	2.50 (2.10–2.97)
15–29	3.93 (2.10–7.35)	5.60 (2.34–13.43)	6.06 (3.89–9.45)	7.21 (4.33–11.99)	3.98 (3.02–5.24)
All	Ref	1.46 (1.32–1.62)	2.09 (1.73–2.53)	4.02 (3.50–4.62)	

Abbreviations: ACM, all-cause mortality; ACR, albumin-to-creatinine ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; Ref, reference cell. Shaded areas are the reference groups.

respectively, in the subgroup of subjects with age  $\geq 65$  years compared with the subgroup with age  $< 65$  years (Supplementary Tables S7 and S8 online). For albumin-to-creatinine ratio cohorts, pooled hazard ratios for all-cause mortality and

cardiovascular mortality of the 28 categories of eGFR and albumin-to-creatinine ratio according to age group are shown in Tables 6 and 7, respectively. For higher albumin-to-creatinine ratios, younger and older subjects showed a similar pattern for all-cause mortality and cardiovascular mortality. However, the patterns for eGFR were less steep among older subjects when compared with younger subjects. For all-cause mortality in dipstick cohorts, these patterns were generally similar to those in albumin-to-creatinine ratio cohorts (Table 8). Only one of the two dipstick cohorts that reported on cardiovascular mortality included subjects  $\geq 65$  years of age. For this reason, no data are shown for risk for cardiovascular mortality according to age group in dipstick cohorts.

**Table 4 | Unadjusted incidence rates (per 1000 patient-years) for ACM and cardiovascular mortality in the high-risk cohorts with dipstick data**

	ACR ratio (mg/g)				All
	< 10	10–29	30–299	$\geq 300$	
<b>ACM</b>					
<i>eGFR (ml/min per 1.73 m<sup>2</sup>)</i>					
> 105	3.8	2.0	6.7	8.7	3.8
90–104	6.0	4.2	8.2	24.3	6.1
75–89	6.9	6.8	10.9	28.3	7.8
60–74	8.0	9.1	18.2	32.5	10.5
45–59	10.1	14.5	30.7	52.9	18.0
30–44	18.3	26.2	40.8	69.9	35.9
15–29	32.4	55.1	49.8	113.2	75.5
All	7.7	8.5	20.5	53.3	11.9
<b>Cardiovascular mortality</b>					
<i>eGFR (ml/min per 1.73 m<sup>2</sup>)</i>					
> 105	7.1	9.2	23.8	9.2	8.2
90–104	8.2	9.9	19.1	17.7	8.9
75–89	7.2	8.2	8.5	25.6	7.6
60–74	8.6	10.8	12.9	22.3	9.3
45–59	10.1	10.1	35.3	21.8	12.7
30–44	4.6	20.7	27.5	48.1	16.3
15–29	<sup>a</sup>	<sup>a</sup>	<sup>a</sup>	<sup>a</sup>	<sup>a</sup>
All	8.0	9.6	15.9	23.3	8.8

Abbreviations: ACM, all-cause mortality; ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate.

Shaded areas make up the combined reference groups.

<sup>a</sup>Insufficient number of events for reliable estimates.

### Heterogeneity

For the categorical analyses, we found modest but statistically significant heterogeneity in pooled adjusted hazard ratios within some eGFR  $\times$  albuminuria categories. For all-cause mortality, heterogeneity was significant in 9 of 28 categories in the albumin-to-creatinine ratio cohorts, and in 6 of 28 categories in the dipstick cohorts (Supplementary Table S9 online). For cardiovascular mortality, heterogeneity was significant in 2 of 28 categories in the albumin-to-creatinine ratio cohorts (Supplementary Table S10 online). Qualitatively, however, the direction of the associations was the same in all cohorts—increased risk with lower eGFR categories and with higher albuminuria categories. Significant heterogeneity was, in nearly all cases, limited to the lowest eGFR and the highest albuminuria categories. Significant heterogeneity for all-cause mortality and cardiovascular mortality was observed in only very few of the eGFR  $\times$  albuminuria categories of most

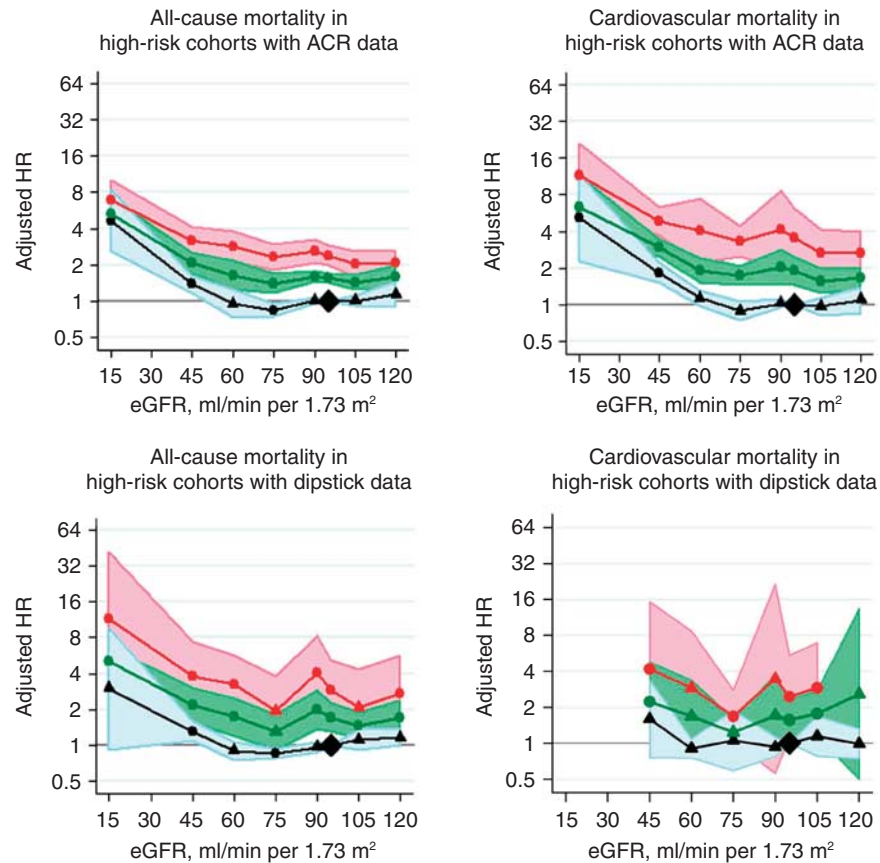
**Table 5 | Pooled adjusted hazard ratios (95% CI) for ACM and cardiovascular mortality in high-risk cohorts with dipstick data**

	Dipstick (classes)				All
	Negative	Trace	1+	$\geq 2+$	
<b>ACM</b>					
<i>eGFR (ml/min per 1.73 m<sup>2</sup>)</i>					
> 105	1.08 (0.91–1.27)	1.16 (0.69–1.97)	2.10 (1.33–3.32)	1.86 (0.63–5.46)	1.06 (0.93–1.22)
90–104	Ref	1.09 (0.90–1.32)	1.63 (1.20–2.21)	3.86 (1.44–10.36)	Ref
75–89	0.82 (0.75–0.90)	1.02 (0.86–1.20)	1.35 (0.88–2.05)	3.22 (1.59–6.52)	0.85 (0.76–0.95)
60–74	0.81 (0.73–0.89)	0.93 (0.79–1.11)	1.41 (0.85–2.35)	2.29 (1.32–3.98)	0.85 (0.74–0.97)
45–59	0.88 (0.75–1.03)	1.05 (0.82–1.36)	2.25 (1.55–3.25)	2.40 (1.13–5.12)	1.07 (0.84–1.35)
30–44	1.18 (0.68–2.06)	1.87 (1.30–2.68)	2.51 (1.78–3.54)	5.50 (3.56–8.50)	1.69 (1.34–2.12)
15–29	3.12 (1.53–6.37)	4.25 (2.11–8.58)	3.49 (2.26–5.41)	7.14 (4.64–10.99)	3.40 (2.70–4.29)
All	Ref	1.24 (1.09–1.41)	1.93 (1.38–2.70)	3.48 (1.75–6.92)	
<b>Cardiovascular mortality</b>					
<i>eGFR (ml/min per 1.73 m<sup>2</sup>)</i>					
> 105	0.96 (0.73–1.26)	1.07 (0.62–1.83)	3.05 (0.60–15.40)	1.18 (0.29–4.75)	0.96 (0.76–1.21)
90–104	Ref	1.10 (0.81–1.50)	2.07 (1.24–3.46)	2.28 (1.07–4.86)	Ref
75–89	0.87 (0.75–1.00)	1.03 (0.85–1.26)	1.03 (0.72–1.48)	2.82 (1.03–7.70)	0.86 (0.76–0.98)
60–74	0.86 (0.75–1.00)	1.05 (0.72–1.54)	1.29 (0.91–1.82)	1.91 (0.96–3.79)	0.86 (0.76–0.98)
45–59	0.89 (0.79–1.15)	1.04 (0.65–1.66)	2.70 (1.29–5.68)	1.62 (0.80–3.31)	0.94 (0.76–1.16)
30–44	0.55 (0.13–2.31)	1.07 (0.23–5.05)	3.06 (0.81–11.56)	3.45 (1.01–11.76)	1.07 (0.51–2.22)
15–29	<sup>a</sup>	<sup>a</sup>	<sup>a</sup>	<sup>a</sup>	<sup>a</sup>
All	Ref	1.15 (1.03–1.29)	1.57 (1.27–1.93)	2.30 (1.52–3.50)	

Abbreviations: ACM, all-cause mortality; CI, confidence interval; eGFR, estimated glomerular filtration rate; Ref, reference cell.

Shaded areas are the reference groups.

<sup>a</sup>Insufficient number of events for reliable estimates.



**Figure 2 | Pooled adjusted hazard ratios (95% confidence interval) for all-cause (left panels) and cardiovascular (right panels) mortality according to eGFR and albuminuria based on continuous models with eGFR (splines), albuminuria (log-linear albumin-to-creatinine ratio or categorical dipstick), and their interaction terms.** Upper panels show data for high-risk cohorts with albumin-to-creatinine ratio data, and lower panels for high-risk cohorts with dipstick data. Hazard ratios are adjusted for age, sex, race, cardiovascular disease history, systolic blood pressure, diabetes, smoking, and total cholesterol. Dots represent statistical significance, triangles represent non-significance, and shaded areas are 95% confidence interval. In this figure, albuminuria is treated categorically. Black lines and blue shading represent an albumin-to-creatinine ratio < 30 mg/g or dipstick negative or trace; green lines and green shading an albumin-to-creatinine ratio 30–299 mg/g or dipstick 1+; and red lines and red shading an albumin-to-creatinine ratio  $\geq$  300 mg/g or dipstick  $\geq$  2+. ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

clinical interest (eGFR of 45–60 ml/min per 1.73 m<sup>2</sup> and albumin-to-creatinine ratio 30–300 mg/g or dipstick 1+).

For the continuous analyses, forest plots are shown for the eGFR and albumin-to-creatinine ratio knots of most clinical interest (eGFR 45 ml/min per 1.73 m<sup>2</sup> and albumin-to-creatinine ratio 30 mg/g) (Supplementary Figure S2 online). For all-cause mortality, significant heterogeneity was found, whereas for cardiovascular mortality, this was not observed. Meta-regression analysis was conducted for all-cause mortality and cardiovascular mortality at these knots to explore sources of heterogeneity, taking into account all variables listed in Table 1. Only two (near) significant associations were found: duration of follow-up and baseline eGFR was negatively associated with relative risk for all-cause mortality at an albumin-to-creatinine ratio 30 mg/g when compared with 5 mg/g (Supplementary Figure S3 online). However, both meta-regressions are, for a large part, explained by 1 outlier (Pima Indian study), characterized by a high baseline eGFR (144 ml/min per 1.73 m<sup>2</sup>). Without this outlier, no significant associations were noted ( $P = 0.33$  and  $P = 0.20$ , respectively).

## DISCUSSION

In this collaborative meta-analysis of 10 high-risk cohorts, including 267,275 subjects, we found that a lower eGFR and a higher albuminuria were associated with a higher risk for all-cause mortality, independent of each other and independent of traditional cardiovascular disease risk factors. A similar association of eGFR and albuminuria was found with the risk for cardiovascular mortality.

The risk for all-cause mortality and cardiovascular mortality based on eGFR and albuminuria has been reported in a limited number of high-risk cohorts.<sup>15–17</sup> The current meta-analysis confirms these studies and extends the generalizability of these data to other populations worldwide. Furthermore, our collaborative meta-analysis includes 16,702 all-cause mortality and 5656 cardiovascular mortality events, substantially more than the number of events in reports of individual studies, allowing more precise evaluation of the independent and joint associations of these measures with these outcomes.

We observed an exponential increase in risk for both all-cause mortality and cardiovascular mortality risk at low

**Table 6 | Pooled adjusted hazard ratios (95% CI) for ACM in the high-risk cohorts with ACR data, by age group**

	ACR (mg/g)				All
	< 10	10–29	30–299	≥ 300	
ACM, younger than 65 years of age eGFR (ml/min per 1.73 m <sup>2</sup> )					
> 105	1.43 (1.13–1.80)	1.33 (1.04–1.72)	1.45 (1.12–1.88)	3.10 (2.20–4.38)	1.12 (0.94–1.33)
90–104	Ref	1.45 (1.07–1.97)	1.58 (1.24–2.01)	2.79 (1.98–3.95)	Ref
75–89	0.90 (0.69–1.19)	1.30 (0.77–2.20)	1.77 (1.31–2.38)	2.92 (2.11–4.03)	1.00 (0.76–1.32)
60–74	0.80 (0.62–1.04)	1.32 (0.88–1.97)	1.77 (1.22–2.56)	3.60 (2.48–5.21)	1.04 (0.77–1.40)
45–59	1.21 (0.79–1.84)	1.60 (1.04–2.45)	2.21 (1.41–3.46)	4.88 (3.47–6.88)	1.72 (1.10–2.69)
30–44	2.03 (1.26–3.27)	2.96 (0.88–10.03)	3.67 (1.77–7.61)	6.22 (4.54–8.51)	2.73 (1.78–4.20)
15–29	9.27 (2.92–29.45)	9.16 (4.19–20.00)	5.79 (3.03–11.08)	6.42 (4.12–10.02)	4.69 (3.42–6.42)
All	Ref	1.34 (1.08–1.66)	1.73 (1.44–2.07)	3.40 (2.77–4.16)	
ACM, aged 65 years or older eGFR (ml/min per 1.73 m <sup>2</sup> )					
> 105	1.03 (0.71–1.49)	1.30 (0.92–1.85)	1.59 (1.15–2.18)	2.54 (1.24–5.17)	0.99 (0.79–1.24)
90–104	Ref	1.09 (0.82–1.45)	1.66 (1.27–2.16)	2.62 (1.68–4.07)	Ref
75–89	0.87 (0.66–1.14)	1.00 (0.74–1.36)	1.51 (1.22–1.86)	2.81 (1.86–4.26)	0.82 (0.65–1.03)
60–74	0.81 (0.60–1.09)	1.02 (0.71–1.46)	1.43 (1.03–1.99)	2.04 (1.20–3.46)	0.86 (0.67–1.09)
45–59	0.98 (0.69–1.38)	1.23 (0.80–1.90)	1.90 (1.47–2.44)	3.01 (2.22–4.09)	1.14 (0.89–1.46)
30–44	1.46 (0.98–2.17)	1.89 (1.32–2.69)	2.45 (1.62–3.69)	3.10 (2.08–4.61)	1.71 (1.27–2.31)
15–29	2.67 (1.71–4.18)	2.92 (1.77–4.82)	3.46 (2.52–4.75)	5.22 (3.36–8.10)	2.81 (2.27–3.49)
All	Ref	1.31 (1.22–1.41)	1.85 (1.73–1.98)	3.18 (2.87–3.51)	

Abbreviations: ACM, all-cause mortality; ACR, albumin-to-creatinine ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; Ref, reference cell. Shaded areas are the reference groups.

**Table 7 | Pooled adjusted hazard ratios (95% CI) for cardiovascular mortality in the high-risk cohorts with ACR data, by age group**

	ACR (mg/g)				All
	< 10	10–29	30–299	≥ 300	
Cardiovascular cause mortality, younger than 65 years of age eGFR (ml/min per 1.73 m <sup>2</sup> )					
> 105	1.27 (0.84–1.94)	1.78 (0.95–3.34)	2.05 (0.89–4.71)	4.55 (1.92–10.82)	0.96 (0.74–1.24)
90–104	Ref	2.09 (0.99–4.44)	2.20 (1.35–3.59)	6.24 (3.35–11.64)	Ref
75–89	1.11 (0.81–1.52)	2.06 (0.88–4.84)	2.22 (1.53–3.23)	5.35 (2.96–9.66)	1.04 (0.85–1.29)
60–74	1.00 (0.64–1.56)	1.65 (1.07–2.53)	2.72 (1.43–5.18)	6.71 (2.01–22.46)	1.11 (0.71–1.73)
45–59	1.57 (1.09–2.26)	2.83 (1.49–5.38)	3.00 (1.33–6.74)	7.48 (2.24–24.96)	2.09 (1.09–3.98)
30–44	3.06 (1.69–5.52)	9.89 (2.15–45.45)	4.55 (1.64–12.62)	9.12 (5.63–14.76)	3.26 (1.85–5.73)
15–29	13.12 (1.80–95.72)	17.52 (4.59–66.81)	13.00 (3.19–53.02)	13.60 (5.11–36.16)	6.11 (3.49–10.70)
All	Ref	1.53 (1.15–2.04)	2.07 (1.60–2.68)	4.54 (3.59–5.73)	
Cardiovascular mortality, aged 65 years or older eGFR (ml/min per 1.73 m <sup>2</sup> )					
> 105	1.22 (0.78–1.90)	1.63 (0.92–2.89)	2.38 (1.52–3.75)	5.62 (1.35–23.47)	1.21 (0.91–1.60)
90–104	Ref	1.39 (0.89–2.15)	1.83 (1.18–2.84)	2.97 (1.25–7.02)	Ref
75–89	0.98 (0.73–1.32)	1.22 (0.77–1.92)	1.72 (1.23–2.40)	4.70 (2.92–7.58)	0.94 (0.74–1.19)
60–74	1.02 (0.76–1.36)	1.39 (0.95–2.02)	1.69 (1.01–2.85)	3.87 (2.55–5.90)	1.00 (0.77–1.32)
45–59	1.31 (0.91–1.91)	1.94 (1.41–2.66)	2.62 (1.94–3.55)	4.73 (3.21–6.96)	1.50 (1.24–1.82)
30–44	2.08 (1.36–3.16)	2.95 (2.02–4.33)	4.03 (2.89–5.62)	5.20 (3.41–7.92)	2.44 (1.97–3.03)
15–29	3.96 (1.99–7.87)	4.39 (1.94–9.93)	5.85 (3.53–9.68)	6.24 (3.33–11.72)	3.72 (2.67–5.19)
All	Ref	1.47 (1.30–1.66)	2.07 (1.69–2.53)	3.78 (3.18–4.49)	

Abbreviations: ACR, albumin-to-creatinine ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; Ref, reference cell. Shaded areas are the reference groups.

eGFR. In the cohorts with albumin-to-creatinine ratio data, increased hazard ratios became statistically significant around eGFR 60 ml/min per 1.73 m<sup>2</sup>, and were two- and threefold higher at eGFR 45 and 15 ml/min per 1.73 m<sup>2</sup>, respectively, compared with optimal eGFR, independent of albuminuria and potential confounders. In the cohorts with dipstick data, we observed a U-shaped relationship, and the increased

hazard ratio with lower eGFR became significant only below eGFR 45 ml/min per 1.73 m<sup>2</sup>. We also observed the U-shaped relationship with all-cause mortality in the general population cohorts,<sup>11</sup> and it has been observed by others.<sup>18</sup> This U-shaped relationship can make it more difficult to interpret the eGFR threshold for increased risk. Of note, the Modification of Diet in Renal Disease Study equation is

**Table 8 | Pooled adjusted hazard ratios (95% CI) for ACM in the cohorts with dipstick data, by age group**

	Dipstick (classes)				All
	Negative	Trace	1+	≥2+	
ACM, younger than 65 years of age eGFR (ml/min per 1.73 m <sup>2</sup> )					
> 105	1.06 (0.89–1.26)	1.16 (0.64–2.08)	2.09 (1.09–3.99)	1.59 (0.63–3.99)	1.07 (0.92–1.24)
90–104	Ref	1.06 (0.86–1.29)	1.55 (1.09–2.20)	3.06 (1.17–8.04)	Ref
75–89	0.87 (0.56–1.35)	0.98 (0.85–1.12)	1.19 (0.93–1.53)	2.94 (1.41–6.13)	0.83 (0.72–0.97)
60–74	0.81 (0.73–0.89)	0.88 (0.76–1.02)	1.50 (0.79–2.84)	2.61 (1.24–5.49)	0.90 (0.72–1.12)
45–59	0.87 (0.73–1.04)	0.93 (0.65–1.31)	2.75 (1.10–6.87)	3.22 (1.25–8.29)	1.47 (0.83–2.59)
30–44	2.26 (0.91–5.57)	1.82 (0.79–4.20)	3.16 (1.59–6.27)	6.11 (3.34–11.18)	2.08 (1.25–3.46)
15–29	6.62 (1.54–28.44)	10.84 (1.41–83.19)	4.06 (1.58–10.44)	12.06 (5.28–27.53)	6.26 (3.96–9.90)
All	Ref	1.13 (1.04–1.21)	1.95 (1.26–3.01)	3.85 (1.64–9.08)	
ACM, aged 65 years or older eGFR (ml/min per 1.73 m <sup>2</sup> )					
> 105	1.53 (0.74–3.17)	0.98 (0.36–2.69)	2.52 (0.86–7.39)	3.70 (1.02–13.46)	1.12 (0.66–1.91)
90–104	Ref	1.35 (0.74–2.46)	1.75 (0.92–3.34)	6.70 (3.02–14.87)	Ref
75–89	0.79 (0.49–1.30)	1.44 (0.88–2.34)	1.97 (1.19–3.27)	4.40 (2.30–8.43)	0.91 (0.70–1.19)
60–74	0.77 (0.49–1.21)	1.11 (0.70–1.76)	1.70 (1.07–2.71)	2.62 (1.45–4.76)	0.83 (0.55–1.25)
45–59	0.93 (0.59–1.47)	1.12 (0.70–1.78)	2.05 (1.29–3.24)	2.90 (1.38–6.07)	0.90 (0.71–1.15)
30–44	1.20 (0.72–1.99)	1.74 (1.07–2.82)	2.45 (1.53–3.93)	5.30 (2.89–9.70)	1.51 (1.00–2.27)
15–29	2.57 (1.05–6.33)	3.53 (1.75–7.12)	3.03 (1.76–5.24)	5.68 (3.26–9.88)	2.58 (1.96–3.41)
All	Ref	1.43 (1.24–1.64)	2.31 (2.02–2.64)	4.56 (3.18–6.54)	

Abbreviations: ACM, all-cause mortality; CI, confidence interval; eGFR, estimated glomerular filtration rate; Ref, reference cell. Shaded areas are the reference groups.

known to underestimate measured GFR at the range of GFR  $\geq 60$  ml/min per 1.73 m<sup>2</sup> in healthy individuals, and to have more variability among racial groups, such as Blacks and Pima Indians.<sup>19</sup> Furthermore, the Modification of Diet in Renal Disease equation overestimates measured GFR in individuals with reduced muscle mass because of ill health, the latter potentially contributing to the U-shaped association of GFR with mortality.

The association of albuminuria with mortality was linear on the log-log scale, with a 1.5- and 2.5-fold higher risk at albumin-to-creatinine ratio 30 and 300 mg/g (corresponding to thresholds for microalbuminuria and macroalbuminuria), respectively, compared with an optimal albumin-to-creatinine ratio level (5 mg/g), independent of eGFR and conventional cardiovascular disease risk factors. Of note, the risk for cardiovascular mortality was statistically significant at an albumin-to-creatinine ratio of 10 mg/g compared with 5 mg/g. These findings are in agreement with previous reports that the association of albuminuria with all-cause mortality and cardiovascular mortality appears continuous with increased risk at levels below 30 mg/g.<sup>15,20–22</sup> Our findings of an increased relative risk of lower eGFR and of higher albuminuria were, in general, comparable for cohort studies with data on dipstick and cohort studies with data on albumin-to-creatinine ratio. These findings suggest that measurement of dipstick proteinuria is useful for risk stratification, despite being a less precise measure of albuminuria.

The statistical code that was sent to the participating cohorts rendered output that did not permit computation of a meta-analytic result for interactions. However, the general pattern of a graded increase in risk with lower eGFR and

higher albuminuria was present for subjects younger as well as older than 65 years of age. Moreover, the hazard ratios for higher albuminuria for both all-cause mortality and cardiovascular mortality increase to a similar extent in older and younger subjects, and in cohorts with albumin-to-creatinine ratio data as well as in cohorts with dipstick data. In contrast, the pattern of higher relative hazards of a lower eGFR for all-cause mortality and cardiovascular mortality is less steep in the subgroups older than 65 years of age than in those younger than 65 years of age (Tables 4 and 5). This less steep relationship with lower eGFR may be a reflection of the increased incidence rates for these outcomes in the older subgroup (Supplementary Table S3 online). Similar findings have been reported for traditional cardiovascular risk factors.<sup>23</sup> Of note, tests for interaction between eGFR and age for all-cause mortality and cardiovascular mortality were not significant in the majority of studies (Supplementary Table S9 online).

The pattern of an increased risk for all-cause mortality and cardiovascular mortality for both a lower eGFR and a higher albuminuria in these high-risk cohorts is comparable to that observed in the general population cohorts.<sup>11</sup> This is an important observation in the context of the recommendations for screening for chronic kidney disease. Current recommendations limit screening to subjects at increased risk.<sup>1–4</sup> The similar relative risks for mortality of lower eGFR and higher albuminuria in general population and high-risk population cohorts suggest that the potential benefit of detecting a case of chronic kidney disease would be similar in both populations. However, the yield from screening would be expected to be higher in the high-risk population because

of the higher prevalence of chronic kidney disease. Further study of the benefit of case detection and yield of screening for chronic kidney disease is required to inform public health policies.

We acknowledge that this meta-analysis has limitations. First, we did not perform a systematic literature search to identify all potential 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. To our knowledge, the present analysis is the largest and most comprehensive assessment of the relationship between eGFR and albuminuria in high-risk populations. Second, the data analysis we used provides superior consistency of results compared with a review of the literature, but falls short of having a uniform study protocol and centralized laboratories across all cohorts. Measurements of creatinine and albuminuria were not comparable across all cohorts. Third, no data could be taken into account on 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 all-cause and cardiovascular mortality, as is expected for cardiovascular disease risk reduction, then it would be expected to lead to an underestimation of the true relative risk of low eGFR and high albuminuria for these outcomes. Fourth, our results showing residual statistical heterogeneity imply that the relationships of eGFR with all-cause mortality and of albumin-to-creatinine ratio with all-cause mortality (and their level of statistical significance) may differ across various subpopulations, although what characterizes these subpopulation differences could not be determined using meta-regression.

Strengths of our study are the large sample size and large number of well-defined outcomes. Moreover, the consistency of our findings in both continuous as well as categorical analyses, in cohorts with albumin-to-creatinine ratio data as well as in cohorts with dipstick data, with respect to both all-cause mortality as well as to cardiovascular mortality, shows the robustness of our findings and makes likely that bias would not have had a major role. Finally, the similarity between our present findings in high-risk cohorts and previous findings in general population cohorts<sup>11</sup> and cohorts including only subjects with known chronic kidney disease<sup>13</sup> strengthens the validity of our findings that both eGFR and albuminuria are independently associated with outcome. These considerations, together with the fact that the presently studied cohorts originate from all over the world (Supplementary Table S1 online), suggest that the results are generalizable to a broad population.

Altogether the relative risks in this analysis are consistent with the current KDOQI thresholds for eGFR <60 ml per min per 1.73 m<sup>2</sup> and albumin-to-creatinine ratio ≥30 mg/g for the definition of chronic kidney disease as indicative of increased mortality risk. They also suggest that the addition

of albuminuria stages in chronic kidney disease staging independent of GFR would be helpful in predicting mortality risk. The finding that mortality risk is substantially higher in subjects with an eGFR 30–45 when compared with 45–60 ml/min per 1.73 m<sup>2</sup> supports the proposed subdivision of the present stage 3 chronic kidney disease into two stages. Some have suggested age-specific thresholds, arguing that lower eGFR at older age is a reflection of ageing<sup>24</sup> and associated with lower risk for adverse outcomes than at younger age.<sup>25,26</sup> We indeed found a less steep pattern of relative risk of all-cause mortality with lower eGFR in older subjects compared with younger subjects. However, absolute mortality risk is higher in older versus younger subjects, and relative risks for cardiovascular mortality were more similar in older versus younger subjects. Therefore, these data do not provide evidence for the use of age-specific eGFR thresholds to define chronic kidney disease. In general, decisions regarding which levels of eGFR and albuminuria to be used for the definition and staging of chronic kidney disease and guide clinical management should incorporate a wide range of considerations, including not only relative risk, but also prevalence, absolute risk, risk classification, and the cost-effectiveness of preventive measures.

In conclusion, our data show that both albuminuria and eGFR are associated with all-cause and cardiovascular mortality, independent of each other and independent of cardiovascular risk factors. These findings provide a quantitative basis for including these two kidney measures for risk stratification, and chronic kidney disease definition and staging.

## MATERIALS AND METHODS

### Study selection

Studies were identified by the planning committee and analytic team, and by discussion between collaborators. This was enhanced by a call for participation at the World Congress of Nephrology in Milan, 2009, a published position statement of KDOQI and KDIGO,<sup>9</sup> and an announcement on the KDIGO website (<http://www.KDIGO.org>). To be eligible for inclusion, studies had to meet the following criteria: (1) prospective cohort study; (2) including subjects referred for evaluation of chronic kidney disease risk factors or subjects known to have at least one risk factor defined as a history of cardiovascular disease, diabetes, hypertension, hypercholesterolemia, or family history of cardiovascular disease; (3) information at baseline on eGFR as well as on albuminuria; (4) at least 1000 subjects included; (5) information on mortality; and (6) a minimum of 50 events for all-cause mortality or cardiovascular mortality. The reason to require a minimum sample size is to ensure sufficient outcomes in the reference cell. This process identified 12 cohorts that met the inclusion criteria. The investigators of 10 eligible studies were willing to participate in this meta-analysis.<sup>15–17,27–33</sup>

### Study variables

In each cohort, subjects were subdivided according to eGFR and albuminuria. GFR was estimated using the Modification of Diet in Renal Disease Study equation.<sup>34</sup> Each participating study was asked to standardize their serum creatinine to isotope dilution mass spectrometry-traceable methods, but calibration methods were not uniform. As recommended in clinical practice guidelines,<sup>1,35–37</sup>

albuminuria was assessed as the albumin-to-creatinine ratio. 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 testing for proteinuria were collected.<sup>17,27–29</sup>

Besides eGFR and albuminuria, information on demographic factors and cardiovascular risk factors were obtained to compare baseline characteristics of the different cohort studies and to adjust for confounding in multivariable models. Cardiovascular disease history was defined as a history of myocardial infarction, bypass grafting, percutaneous coronary intervention, heart failure, or stroke. Hypertension was defined as systolic blood pressure  $\geq 140$  mm Hg or diastolic blood pressure  $\geq 90$  mm Hg or use of antihypertensive medication. Hypercholesterolemia was defined as total cholesterol  $> 5.0$  mmol/l in the case of a positive history of cardiovascular disease and as  $> 6.0$  mmol/l in the case of a negative history of cardiovascular disease. Diabetes mellitus was defined as fasting glucose  $\geq 7.0$  mmol/l or non-fasting glucose  $\geq 11.1$  mmol/l or use of glucose-lowering drugs. Smoking habit was dichotomised as current versus not current smoking.

Outcome measures for this meta-analysis were all-cause mortality and cardiovascular mortality, with the latter defined as death due to myocardial infarction, heart failure, sudden cardiac death, or stroke. Cardiovascular mortality was chosen as a specific cause of death, as it is the leading cause of death in individuals with chronic kidney disease.<sup>14</sup>

### Statistical analysis

Our primary objective was to evaluate the associations of eGFR and albuminuria, independently and jointly on all-cause mortality and cardiovascular mortality. To maximize uniformity and minimize bias, investigators from the cohort studies were invited to collaborate in a pooled analysis following an *a priori* analytic plan using standard statistical code provided by the analytic team of the CKD Prognosis Consortium. All analyses were conducted using Stata version 10 or 11 (Stata Corp, College Station, TX, SAS version 9 (SAS Institute, Cary, NC), or R version 2.9.2 (R Foundation for Statistical Computing, Vienna, Austria). All data classification was performed separately by analytic teams at the John Hopkins Bloomberg School of Public Health, Baltimore, USA (KM, JC, and BCA) and the University Medical Center Groningen, Groningen, the Netherlands (MvdV, PEDJ), and differences were resolved by consensus.

Some of the included cohorts consisted of participants of randomised controlled trials.<sup>15,17,29–31</sup> All participants in these trials met our inclusion criteria (high risk for chronic kidney disease). Of these cohorts, only data were used that were obtained during the trial, thus no follow-up data beyond the duration of the actual trials were taken into account. In multivariable regression analysis, we adjusted for treatment allocation, enhancing generalizability of these trial populations to the observational cohorts in our pooled analysis.

For each study, a table was generated providing baseline study characteristics. Cox proportional hazard models were used to estimate the hazard ratios for all-cause mortality and cardiovascular mortality. These analyses were adjusted for age, sex, race, cardiovascular disease history, smoking status, diabetes mellitus, systolic blood pressure, and serum total cholesterol, and for randomized controlled trials also for treatment arm. The independent continuous association of eGFR and albuminuria with risk for all-cause and cardiovascular mortality was evaluated after adjusting

for each other and for cardiovascular disease risk factors. eGFR and albumin-to-creatinine ratio were modeled using linear splines with knots at 45, 60, 75, 90, and 105 ml/min per  $1.73 \text{ m}^2$ , and 10, 30, and 300 mg/g, respectively. eGFR 95 ml/min per  $1.73 \text{ m}^2$  and an albumin-to-creatinine ratio 5 mg/g were treated as the reference points. These points were chosen, as they reflect the anticipated low-risk groups. Interactions between eGFR and both albuminuria and age were evaluated by likelihood-ratio tests in individual studies, with albuminuria and age treated as continuous variables.

For each outcome variable, information was generated for the joint association of eGFR and albuminuria with kidney outcomes. Eight eGFR categories were defined:  $< 15$ , 15–29, 30–44, 45–59, 60–74, 75–89, 90–104, and  $\geq 105$  ml/min per  $1.73 \text{ m}^2$ . These 15 ml/min per  $1.73 \text{ m}^2$  categories were chosen to correspond to current chronic kidney disease stages 1–5, and to evaluate whether these stages should be subdivided. For albumin-to-creatinine ratio, we defined four categories:  $< 10$ , 10–29, 30–299, and  $\geq 300$  mg/g. These categories were chosen to correspond to current definitions for microalbuminuria and macroalbuminuria, and to evaluate whether the normoalbuminuria category should be subdivided. When information on albumin-to-creatinine ratio was lacking, we used information on dipstick proteinuria. As it has been shown that the majority of subjects with a dipstick trace have high-normal albuminuria, dipstick 1+ microalbuminuria, and dipstick  $\geq 2+$  macroalbuminuria,<sup>37</sup> we defined four dipstick categories: negative, trace, 1+, and  $\geq 2+$ , respectively. *A priori*, the reference categories of eGFR 90–104 ml/min per  $1.73 \text{ m}^2$  and an albumin-to-creatinine ratio  $< 10$  mg/g or dipstick negative were chosen, as they were considered to represent subjects with the lowest risk. For all of the 32 eGFR  $\times$  albuminuria categories, information was obtained on the distribution of subjects and the distribution of incident events. For each study, the unadjusted incidence rate per 1000 person-years was calculated for each category. Hazard ratios were estimated with adjustment for the aforementioned cardiovascular risk factors. We conducted complementary analyses where eGFR and albumin-to-creatinine ratio were modeled continuously using the same statistical models and adjustments. These models were parameterized with eGFR of 95 ml/min per  $1.73 \text{ m}^2$ , albumin-to-creatinine ratio of 5 mg/g or dipstick negative/trace as the reference point (hazard ratio = 1.0).

Pooled unadjusted incidence rates were obtained by weighting the individual studies by the number of subjects per category. Pooled estimates of the adjusted hazard ratios, with 95% confidence intervals, were obtained from random effects meta-analyses. Heterogeneity was estimated using the  $\chi^2$ -test for heterogeneity and the  $I^2$  statistic.<sup>38</sup> Meta-analyses were conducted separately for cohorts with albumin-to-creatinine ratio data and cohorts with dipstick data. As there were few participants (0.2%) with eGFR  $< 15$  ml/min per  $1.73 \text{ m}^2$ , we only report results for participants with eGFR  $\geq 15$  ml/min/ per  $1.73 \text{ m}^2$ . *A priori*, it was considered that age could be an important effect modifier, and hence results were also produced for age  $< 65$  and  $\geq 65$  years. As statistical heterogeneity in the associations under study was anticipated, we *a priori* defined systematic exploration of possible source heterogeneity. This was done by meta-regression analysis, using the continuous analyses with a random effects model, in the eGFR and albumin-to-creatinine ratio knots of most clinical interest (eGFR 45 ml/min per  $1.73 \text{ m}^2$  and albumin-to-creatinine ratio 30 mg/g). As possible sources of heterogeneity all variables listed in Table 1 were investigated, some being known risk factors for all-cause and

cardiovascular mortality (for example, blood pressure, cholesterol, and diabetes), others being effect modifiers (age and follow-up duration).

In all analyses, a  $P$ -value  $<0.05$  was considered to indicate statistical significance.

#### DISCLOSURE

All the authors declared no competing interests.

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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 are responsible for the collection and analysis of their individual data, and were sent the paper as prepared for submission and given the opportunity to comment on the draft manuscript. The writing committee and all collaborators accept responsibility for the content of this paper.

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#### SUPPLEMENTARY MATERIAL

**Figure S1.** Pooled adjusted hazard ratios for all-cause mortality in high-risk cohorts with dipstick data, according to spline eGFR.

**Figure S2.** Forest plots of adjusted hazard ratios at eGFR 45 ml/min per 1.73 m<sup>2</sup> and albumin-to-creatinine ratio 30 mg/g.

**Figure S3.** Meta-regression of all-cause mortality for albumin-to-creatinine ratio 30 mg/g on duration of follow-up and baseline eGFR.

**Table S1.** Acronyms/abbreviations for individual studies.

**Table S2.** Distribution of subjects for analysis of all-cause mortality.

**Table S3.** Distribution of subjects for analysis of cardiovascular mortality.

**Table S4.** Distribution of all-cause mortality.

**Table S5.** Distribution of cardiovascular mortality.

**Table S6.** Statistical significance for interaction between eGFR and age, and between eGFR and albuminuria for all-cause and cardiovascular mortality.

**Table S7.** Incidence rate for all-cause mortality.

**Table S8.** Incidence rate for cardiovascular mortality.

**Table S9.** Adjusted hazard ratios for all-cause mortality.

**Table S10.** Adjusted hazard ratios for cardiovascular mortality.

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

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