Table 2 | Patient characteristics and BP values according to the BP classification by gender

	Women (n=142,293)					Men (n=89,732)				
	Optimal BP (n=51,715)	Prehypertension with normal BP (n=36,182)	Prehypertension with high-normal BP (n=27,348)	Hypertension (n=27,048)	P-value	Optimal BP (n=23,759)	Prehypertension with normal BP (n=23,012)	Prehypertension with high-normal BP (n=19,199)	Hypertension (n=23,762)	P-value
Age, years	58.8 ± 10.2	62.7 ± 8.4	64.4 ± 7.5	64.8 ± 7.2	<0.001	59.0 ± 10.7	61.0 ± 10.1	62.9 ± 9.3	63.0 ± 8.8	<0.001
Body mass index, kg/m^2	21.4 ± 2.9	22.2 ± 3.1	22.7 ± 3.2	23.2 ± 3.5	<0.001	22.5 ± 2.8	23.3 ± 2.9	23.6 ± 3.0	24.0 ± 3.1	<0.001
Obesity, n (%)	6775 (13.1)	7349 (20.3)	6863 (25.1)	8371 (30.9)	<0.001	5256 (22.1)	7168 (31.1)	6689 (34.8)	9590 (40.4)	<0.001
Current smoker, n (%)	4852 (9.4)	2234 (6.2)	1488 (5.4)	1338 (4.9)	<0.001	7953 (33.5)	6562 (28.5)	5071 (26.4)	6560 (27.6)	<0.001
Daily drinker, n (%)	4594 (8.9)	3120 (8.6)	2350 (8.6)	2407 (8.9)	0.33	8059 (33.9)	9428 (41.0)	8713 (45.4)	11,824 (49.8)	<0.001
eGFR, ml/min per 1.73m^2	77.8 ± 15.9	76.9 ± 15.9	76.1 ± 15.7	75.8 ± 15.8	<0.001	78.1 ± 16.5	77.0 ± 16.1	76.1 ± 16.0	76.0 ± 16.4	<0.001
CKD, n (%)	5619 (10.9)	4204 (11.6)	3540 (12.9)	4046 (15.0)	<0.001	3303 (13.9)	3582 (15.6)	3475 (18.1)	4923 (20.7)	<0.001
Stage 1 and 2, n (%)	864 (1.7)	672 (1.9)	650 (2.4)	1046 (3.9)	<0.001	729 (3.1)	799 (3.5)	814 (4.2)	1467 (6.2)	<0.001
Stage 3, n (%)	4774 (9.2)	3516 (9.7)	2874 (10.5)	2983 (11.0)	<0.001	2565 (10.8)	2775 (12.1)	2652 (13.8)	3438 (14.5)	<0.001
Stage 4, n (%)	11 (0.02)	16 (0.04)	16 (0.05)	17 (0.06)	<0.001	9 (0.03)	8 (0.03)	9 (0.04)	18 (0.07)	<0.001
Proteinuria (⩾1+), n (%)	1040 (2.0)	812 (2.2)	796 (2.9)	1300 (4.8)	<0.001	872 (3.7)	1003 (4.4)	1013 (5.3)	1915 (8.1)	<0.001
BP measurement										
Systolic BP, mm Hg	107 ± 8	123 ± 4	133 ± 4	149 ± 12	<0.001	109 ± 7	123 ± 4	132 ± 4	148 ± 13	<0.001
Diastolic BP, mm Hg	65 ± 7	73 ± 7	77 ± 7	85 ± 10	<0.001	67 ± 7	75 ± 6	79 ± 7	88 ± 10	<0.001

Abbreviations: BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.
Data are expressed as the means ± SD or percentage. Obesity was defined as body mass index (BMI) ⩾25 kg/m^2, and CKD was defined as eGFR <60 ml/min per 1.73 m^2 and/or presence of proteinuria (⩾1+). The proteinuria number in each column includes all stage 1/2 patients plus a few in stage 3/4.

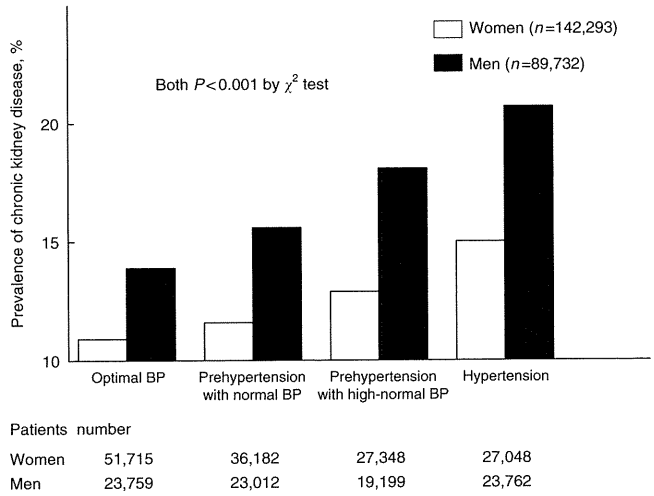

Figure 1 | Prevalence of chronic kidney disease according to the blood pressure (BP) classification in women (white bar) and men (black bar). The gender difference in the prevalence of chronic kidney disease increased in accordance with the severity of BP classification. Chronic kidney disease was defined as estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73 m^2 and/or the presence of proteinuria (⩾1+).

The prevalence of CKD and/or proteinuria (⩾1+) paralleled the severity of BP classification in both genders (Figure 1). The gender difference of CKD became greater and more prominent with increasing severity of BP classification.

Using multiple logistic regression analysis, the odds ratio for the presence of CKD was estimated. Hypertension was significantly associated with CKD in both genders. In contrast, only in men, but not in women, prehypertension with high-normal BP was significantly associated with an increased risk of CKD even after adjustment for confounders, such as age, obesity, current smoking, and daily drinking (Table 3). We also reanalyzed the results of Table 3 after adjusting for serum glucose, triglyceride, high-density lipoprotein, and low-density lipoprotein levels: these factors had no influence on the association between prehypertension with high-normal BP and CKD in men (data not shown).

Lifestyle factors, obesity, and CKD

Obesity was positively associated with CKD in both genders, and eGFR was significantly decreased in the subjects with obesity compared with those without obesity (76.1 ± 16.2 versus 77.1 ± 16.0 ml/min per 1.73 m^2; P<0.001). When we reanalyzed the risk of CKD conferred by obesity in either the subjects with low eGFR (<60 ml/min per 1.73 m^2) or the subjects with proteinuria (⩾1+), the conclusion remained unchanged (data not shown). In contrast, daily drinking was inversely associated with CKD in both genders. Additional analysis of the subgroup of subjects for whom daily alcohol intake data were available (n=70,416 men and n=75,416 women) revealed that the inverse association between daily drinking and CKD was consistent regardless of the amount of daily intake (⩾23 g of ethanol or <23 g of ethanol) in men (odds ratio (95% confidence interval, CI): 0.77 (0.73–0.80) and 0.89 (0.84–0.95), respectively; both P<0.001); in women, the inverse association between daily drinking and CKD was found only in those with a daily intake of <23 g of ethanol (odds ratio (95% CI): 0.91 (0.84–0.99); P=0.03).

In women, current smoking status was positively associated with CKD. In contrast, among men, current smoking was inversely associated with CKD; that is, male current smokers had a significantly higher level of eGFR than current non-smokers (mean (95% CI) of eGFR: 79.0 (78.8–79.2) versus 75.9 (75.8–76.1) ml/min per 1.73 m^2; P<0.001). In contrast, there was no significant difference in eGFR between female current smokers and non-smokers (mean (95% CI) of eGFR: 77.0 (76.7–77.3) versus 76.9 (76.8–77.0) ml/min per 1.73 m^2; P=0.45). When we reanalyzed the association of current smoking with the presence

Table 3 | Odds ratio (95% confidence interval) for CKD by gender

	Women (n=142,293)		Men (n=89,732)	
	Odds ratio (95% confidence interval)	P-value	Odds ratio (95% confidence interval)	P-value
Age, 10 years	1.39 (1.37:1.42)	<0.001	1.82 (1.78:1.87)	<0.001
Obesity (0=no, 1=yes)	1.26 (1.22:1.31)	<0.001	1.43 (1.38:1.49)	<0.001
Current smoker (0=no, 1=yes)	1.34 (1.26:1.43)	<0.001	0.90 (0.86:0.94)	<0.001
Daily drinker (0=no, 1=yes)	0.92 (0.86:0.98)	0.006	0.78 (0.76:0.81)	<0.001
BP classification[a]				
Optimal BP	1 (Reference)		1 (Reference)	
Prehypertension with normal BP	0.95 (0.91:1.00)	0.03	1.01 (0.96:1.07)	0.60
Prehypertension with high-normal BP	1.02 (0.97:1.06)	0.54	1.11 (1.05:1.17)	<0.001
Hypertension	1.17 (1.12:1.23)	<0.001	1.32 (1.25:1.38)	<0.001

Abbreviations: BP, blood pressure; CKD, chronic kidney disease.
Obesity was defined as body mass index (BMI) ≥25 kg/m^2. BP classification was defined as follows: optimal BP, systolic blood pressure (SBP) <120 mm Hg and diastolic blood pressure (DBP) <80 mm Hg; prehypertension with normal BP, SBP 120–129 mm Hg and/or 80–84 mm Hg; prehypertension with high-normal BP, SBP 130–139 mm Hg and/or DBP 85–89 mm Hg; hypertension, SBP ≥140 mm Hg and/or DBP ≥90 mm Hg. Statistical significance was defined as $P<0.05$.
[a]BP classification: Odds ratio was adjusted for age, obesity, current smoking, and daily drinking.

of proteinuria, there was a positive association between current smoking and proteinuria in both genders (odds ratio (95% CI): 1.47 (1.38–1.56) in men and odds ratio (95% CI): 1.89 (1.15–3.11) in women; both $P<0.001$).

Effect of obesity on the association between CKD and BP classification

Among subjects without hypertension ($n=181,215$), the risk of CKD conferred by prehypertension with high-normal BP increased when these conditions were accompanied by obesity (≥25 kg/m^2) in men (Figure 2a), but not in women (Figure 2b). Accordingly, we examined whether or not there was an interaction between obesity and prehypertension with high-normal BP on CKD risk among subjects without hypertension. Using a multivariable logistic regression analysis, we showed that there was an additive effect, but not a synergistic one, of obesity and prehypertension with high-normal BP on CKD risk in men (data not shown). Furthermore, we also examined whether there was an interaction between obesity and hypertension (≥140/90 mm Hg) on CKD risk among all subjects ($n=232,025$). The results showed that there was no synergistic interaction in either gender (data not shown).

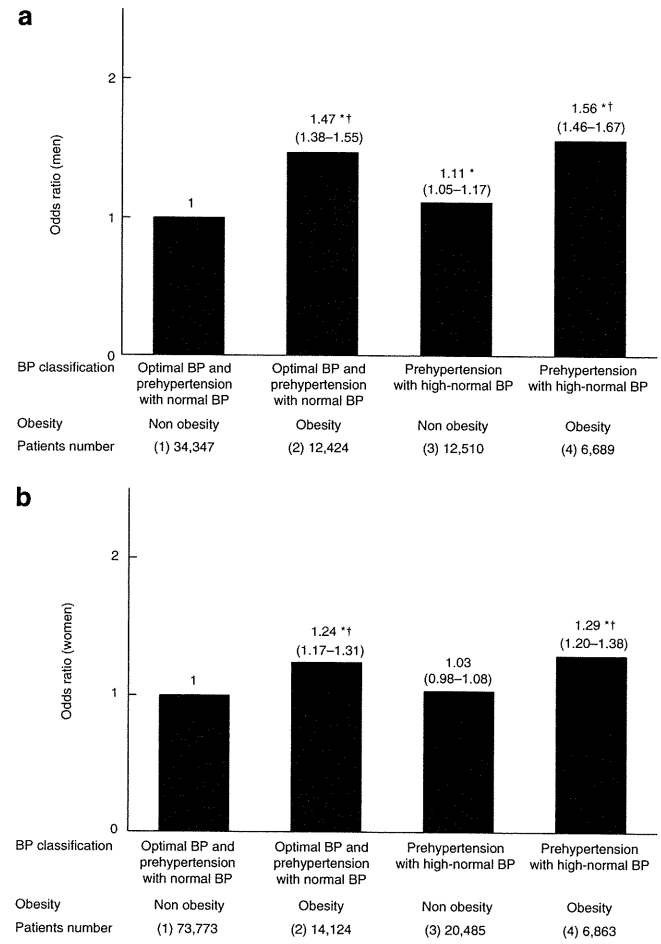

Figure 2 | Logistic regression analysis of chronic kidney disease risk among subjects without hypertension. The odds ratio (95% confidence interval) of chronic kidney disease risk in subjects with or without obesity and/or prehypertension with high-normal blood pressure (BP) is shown in men (**a**) and women (**b**). The analysis was adjusted for age, current smoking, and daily drinking. Chronic kidney disease was defined as estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73 m^2 and/or the presence of proteinuria (≥1+). *$P<0.001$ versus group (1) and †$P<0.001$ versus group (3).

DISCUSSION

Prehypertension and CKD

In this nationwide study of 232,025 Japanese aged 20 years or older, we have demonstrated the prevalence of CKD across the diagnostic spectrum of BP classification. In the present study, the prevalence of CKD was 17.0% in men and 12.2% in women. The prevalence was lower than a previous Japanese report,[5] because the present study excluded treated hypertensive patients. In particular, we focused on the prevalence of CKD among subjects with prehypertension (16.7% in men and 12.2% in women). The prevalence of CKD among subjects with prehypertension with high-normal BP was greater in men than in women (18.1% versus 12.9%), and prehypertension with high-normal BP was an

independent risk factor for CKD in men, but not in women, even after adjustment for confounders.

Evidence is accumulating that prehypertension, and particularly a high-normal BP range, is associated with a variety of cardiovascular diseases and cardiovascular-associated and all-cause mortality;[15–17] however, information about the association of prehypertension with CKD is scarce in Japan.[18] Much as in other previous reports worldwide,[14–16] older age, higher prevalence of men, and obesity or obesity-related metabolic abnormalities were more prevalent in subjects with prehypertension than those with optimal BP (Table 2). These characteristics could partly explain the cardiovascular risk of prehypertesion;[15–17] however, our data show that the association between CKD and prehypertension with high-normal BP in men is independent of these confounders.

The increased risk of CKD among prehypertensive subjects with high-normal BP was recognized only in men; this means that the parallel increase of CKD in accordance with the level of severity of BP begins at an earlier phase in men than in women. This gender difference cannot be fully explained by the gender differences in metabolic factors or BP itself. It is speculated that it may be related to gender-specific differences in glomerular structure, hemodynamic condition, activity of local cytokines and hormones, gene expression, and/or the effects of sex hormones on kidney cells.[9,19]

As shown in several previous reports,[10–12] hypertension ($\geqslant$140/90 mm Hg) is a clear risk factor for CKD in both the genders. In the present study, we excluded 84,854 subjects who had been treated with anti-hypertensive medication, and included 50,810 subjects who had never been treated with anti-hypertensive medication. This exclusion rate suggests that about a quarter of hypertensive subjects have not been treated for their condition. This proportion is substantially improved as compared with a previous report,[20] but more health promotion to increase awareness and treatment of hypertension is still considered necessary.

Obesity, BP, and CKD

Obesity is an independent risk factor for CKD both in men and women (Table 3). Intriguingly, our data indicate that the risk of CKD conferred by prehypertension with high-normal BP in men increased when these conditions were accompanied by obesity (Figure 2a). There was an additive effect of obesity and prehypertension with high-normal BP on CKD risk in men.

Obesity-associated glucose and lipid abnormalities could partly explain the increased risk of CKD in obesity.[21,22] However, our data show that the increased risk of CKD conferred by obesity was independent of these confounders, although there was some lack of data on glucose and lipid parameters. There remain several other possible explanations for the risk of obesity. First, unmeasured obesity-associated factors, such as insulin resistance, inflammatory and oxidative stress, and abnormal adipocytokine production, may be involved in the increased risk of CKD in obesity.[22,23] Second, obesity has a fairly consistent effect on renal hemodynamics, suggestive of glomerular hypertension.[24,25] At an early phase, obesity is associated with an elevated GFR with a less pronounced increase, or even a decrease, in effective renal plasma flow, resulting in an increased filtration rate. This alteration, that is, a predominant decrease in afferent rather than efferent glomerular tone in obese subjects, may confer enhanced renal susceptibility toward damage when BP increase is superimposed.[24,25] Obesity-induced hyperfiltration, if continued for a certain period, can cause a decline in GFR, which may be one of the reasons why our data showed that obese subjects had a lower eGFR than nonobese subjects in both genders.

Lifestyle factors and CKD

Lifestyle factors, such as smoking and drinking, are also important contributors to CKD.[26] In the present study, an inverse association between CKD and current smoking was found (Table 3), despite the fact that several previous studies have identified smoking as an important risk factor in the promotion and progression of renal dysfunction in healthy subjects or those with complications.[27,28] Our study is a cross-sectional study, and thus there may have been artifacts due to the observation of sick subjects after they have changed their lifestyles. However, the effects of smoking on eGFR are still controversial.[27,29,30] In fact, we observed that male current smokers had a higher eGFR than male non-smokers, whereas no such association was found in women. On the other hand, our present results agree with previous reports;[27,29] in that we found a positive association between smoking and proteinuria in both genders, suggesting the possibility that smoking causes endothelial dysfunction, partly through an inflammatory or oxidative pathway.[28,29] It was also unexpected that there was an inverse association between the BP increase and the prevalence of current smoking (Table 2); this may have been attributable to one of the following: (1) Some of the smokers in the hypertensive group may have had knowledge that they were hypertensive, and may have ceased to smoke on the advice of their physicians. (2) There may have been a so-called survival effect, as smokers who develop hypertension were more likely to have died and thus not to have been included in the cross-sectional study. (3) Daytime BP under daily activity would likely be more elevated in smokers compared with non-smokers, even when there is no difference in the clinical or office BP between them (i.e., masked hypertension is more prevalent in smokers).[31]

Evidence on the association between CKD and alcohol intake has been scarce. We found that subjects with a daily drinking habit had a lower likelihood of CKD compared with those who had no alcohol intake. We could not assess the kinds or total amount of alcohol; therefore, to discuss this issue is beyond the scope of the present research. Further investigation with prospective or lifestyle interventional studies, such as smoking cessation studies, are warranted to better elucidate the impact of smoking or drinking on renal outcomes.

Several limitations of our study should be mentioned. First, we cannot infer a cause–effect relationship based on our cross-sectional data. Second, only a single measurement of serum creatinine, as well as only a single assessment of proteinuria, is not fully accurate, and thus there may be an underestimation of the true association between CKD and BP level. Third, subjects who participated in the present survey were generally healthy individuals who were interested in their health; therefore, the prevalence of prehypertension/hypertension or CKD may have been underestimated. Finally, little is known about the cost-effectiveness of screening male subjects with prehypertension and high-normal BP range for CKD; therefore, an additional study is needed to identify the most appropriate populations to undergo CKD screening.

CONCLUSION

Using a nationwide Japanese database, we show an increased prevalence of CKD across the diagnostic spectrum of hypertension. Among men, even in the state of prehypertension, high-normal BP, particularly when in conjunction with obesity, was an independent risk factor for CKD. Considering the fact that the prevalence of CKD and the incidence of end-stage renal disease are increasing in Japanese men,[5,8,9] these data have important clinical implications; as CKD is often asymptomatic but progressive, more attention must be paid to men and women with hypertension or obesity and to men even with high-normal BP for the early detection and prevention of CKD, or to delay the progression to renal failure.

MATERIALS AND METHODS

Study population

The methods of the study are detailed in the Supplementary Information section online. Briefly, based on a recent survey that showed that obesity and metabolic syndrome are not uncommon in Japan (http://www-bm.mhlw.go.jp/houdou/2008/04/h0430-2.html), the Japanese government started a new health-care strategy that targeted early diagnosis and intervention for metabolic syndrome from 2008 (Specific Health Checkups and Guidance System (Tokutei-Kensin)). In this new health-care system, people diagnosed with metabolic syndrome are obligated to receive repeated lifestyle guidance over a 6-month period after an annual health examination.

Thirteen of the prefectures participating in this nationwide project (Yamagata, Miyagi, Fukushima, Niigata, Tokyo, Kanagawa, Ibaraki, Osaka, Okayama, Kochi, Fukuoka, Miyazaki, and Okinawa) agreed on our study purpose and were included in the present analysis. The population surveyed included a total of 346,942 subjects (41% ($n = 141{,}938$) were men) above 20 years of age, for whom all the data necessary for our research purposes were available—namely, information about age, gender, BP, body mass index, habitual smoking or drinking, use of anti-hypertensive drugs, previous history of cardiovascular diseases (i.e., cardiac disease and stroke), and data about the serum creatinine level and dipstick urine test for proteinuria. This study was granted ethics approval from the respective institutional review boards. Data were sent to an independent data center called the NPO Japan Clinical Research Support Unit, and verified by trained staff.

Baseline measurement

At the baseline examination, all subjects completed a self-administered questionnaire about lifestyle factors (current smoking status, daily drinking), and provided medical information on treatment with anti-hypertensive drugs and a previous history of cardiac disease or stroke. The study physicians performed a physical examination of each subject and rechecked their medical history to improve the precision of the information.

According to the recommendations of the Ministry of Health, Labor and Welfare (http://www.mhlw.go.jp/bunya/shakaihosho/iryouseido01/info03a.html), BP was measured by trained observers using a standard sphygmomanometer or an automated device on the right arm after resting for 5 min in a seated position with the legs not crossed. Conversation and alcohol/caffeine consumption should also be avoided before measurement. Subjects were classified according to their BP level as follows: optimal BP (systolic BP/diastolic BP $< 120/80$ mm Hg), prehypertension[32] that comprises normal BP (systolic BP 120–129 mm Hg, diastolic BP 80–84 mm Hg or both) and high-normal BP (systolic BP 130–139 mm Hg, diastolic BP 85–89 mm Hg or both), and treated or untreated hypertension (systolic BP/diastolic BP $\geqslant 140/90$ mm Hg or usage of anti-hypertensive medication).[33]

Body height and weight were measured in light clothing without shoes, and the body mass index was calculated (kg/m^2). According to the Japan Society for the Study of Obesity,[34] obesity was defined as a body mass index $\geqslant 25$ kg/m^2.

Blood samples were collected after an overnight fast and were assayed within 24 h. For the purpose of our study, there were no missing data on the serum creatinine level, but there was a substantial lack of data on the glucose and lipid parameters (Supplementary Table S1 online). Freshly voided urine samples were tested by the dipstick methods in all subjects. Proteinuria was defined as 1+ or more.

Definition of CKD

Serum creatinine was assayed by an enzymatic method. eGFR was derived using the following equation:

$$\text{eGFR (ml/min per 1.73 m}^2) = 194 \times \text{age (years)}^{-0.287} \times \text{serum creatinine (mg/dl)}^{-1.094} \text{ (if women } \times 0.739).[35]$$

Details about this equation are also shown in the Supplementary Information section. CKD was defined as either the presence of proteinuria or eGFR < 60 ml/min per 1.73 m^2. The clinical stages of CKD were classified according to the recommendations of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines[36]: Stage 1 or 2 (eGFR $\geqslant 60$ ml/min per 1.73 m^2 and the presence of proteinuria), Stage 3 (eGFR 30–59 ml/min per 1.73 m^2), Stage 4 (eGFR 15–29 ml/min per 1.73 m^2), and Stage 5 (eGFR < 15 ml/min per 1.73 m^2).

Statistical analysis

All statistical analyses were performed with the SPSS version 18.0J software (SPSS, Chicago, IL). The differences of patient characteristics and BP values according to the BP classification were assessed using analysis of variance, and categorical parameters were compared with the χ^2-test. As there is a significant gender difference in the prevalence of CKD, we examined the association between CKD and the severity of BP classification separately in men and women. The odds ratio and 95% CI of each BP classification group (optimal BP group (reference) versus prehypertension with normal BP, prehypertension with high-normal BP, and untreated hypertension group) were calculated for the presence of CKD by multiple

logistic regression analysis. Finally, we used a multivariable logistic regression analysis to examine the effect of obesity on the association between CKD and BP classification, as well as whether or not there was an interaction between obesity and prehypertension with high-normal BP on CKD risk. Statistical significance was defined as $P<0.05$.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Table S1. Glucose and lipid parameters according the BP classification by gender.

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

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Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts

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Both a low estimated glomerular filtration rate (eGFR) and albuminuria are known risk factors for end-stage renal disease (ESRD). To determine their joint contribution to ESRD and other kidney outcomes, we performed a meta-analysis of nine general population cohorts with 845,125 participants and an additional eight cohorts with 173,892 patients, the latter selected because of their high risk for chronic kidney disease (CKD). In the general population, the risk for ESRD was unrelated to eGFR at values between 75 and 105 ml/min per 1.73 m^2 but increased exponentially at lower levels. Hazard ratios for eGFRs averaging 60, 45, and 15 were 4, 29, and 454, respectively, compared with an eGFR of 95, after adjustment for albuminuria and cardiovascular risk factors. Log albuminuria was linearly associated with log ESRD risk without thresholds. Adjusted hazard ratios at albumin-to-creatinine ratios of 30, 300, and 1000 mg/g were 5, 13, and 28, respectively, compared with an albumin-to-creatinine ratio of 5. Albuminuria and eGFR were associated with ESRD, without evidence for multiplicative interaction. Similar associations were found for acute kidney injury and progressive CKD. In high-risk cohorts, the findings were generally comparable. Thus, lower eGFR and higher albuminuria are risk factors for ESRD, acute kidney injury and progressive CKD in both general and high-risk populations, independent of each other and of cardiovascular risk factors.

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KEYWORDS: acute kidney injury; albumin-to-creatinine ratio (albuminuria); dipstick (proteinuria); eGFR (kidney function); ESRD (end-stage renal disease); meta-analysis

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This is the third in a series of four manuscripts to report the results of collaborative meta-analyses of estimated GFR (eGFR) and albuminuria on outcomes of chronic kidney disease (CKD) undertaken by the CKD Prognosis Consortium. These analyses were undertaken in conjunction with the 2009 Controversies Conference sponsored by Kidney Disease Improving Global Outcomes (KDIGO) to evaluate the current definition and classification of CKD and proposed alternatives.[1] The report of the Consensus Conference is included in this issue of Kidney International.[2]

Widespread implementation of the definition and classification of CKD, as proposed by Kidney Disease Outcomes Quality Initiative (KDOQI) in 2002 and subsequently endorsed by KDIGO in 2004, has promoted increased attention to CKD in clinical practice, research, and public health.[3–6] It has also generated substantial debate about the appropriateness of recommending the same GFR thresholds for people of all ages, the optimal level of albuminuria for diagnosing kidney damage, and about the value of the 5-stage classification system based on eGFR without consideration of albuminuria.[7–11] It was the position of KDOQI and KDIGO that a comprehensive analysis of mortality and kidney outcomes according to eGFR and albuminuria was needed to answer key questions underlying the debate.[1,2]

Until recently, most of the data on kidney outcomes were from studies of patients with later stages of CKD rather than from general population cohorts or cohorts at increased risk for CKD.[12–14] Reports from the general population and high-risk cohorts focused mainly on all-cause and cardiovascular mortality,[15–20] with fewer data available on kidney outcomes.[19–22] In this manuscript, we describe a collaborative meta-analysis of nine general population and eight high-risk cohorts. The outcomes reported in this manuscript include kidney failure treated by dialysis or transplantation (end-stage renal disease (ESRD)) or coded on the death certificate. In addition, we also included acute kidney injury, because it is

increasingly recognized as a major cause for[23] and consequence of CKD,[24] and kidney disease progression, based on fast eGFR decline (progressive CKD), because of its clinical importance and potential to lead to ESRD or other complications.

Other papers in this series deal with all-cause and cardiovascular mortality in general population cohorts and high-risk cohorts.[25,26] This report describes the kidney outcomes from these cohorts. A fourth manuscript reports mortality and kidney outcomes in CKD cohorts.[27] *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 and population characteristics

Of the nine general population cohorts (845,125 subjects), five had data on albumin-to-creatinine ratio and four on dipstick. Of the eight high-risk cohorts (173,892 subjects), five had data on albumin-to-creatinine ratio and three on dipstick (Table 1). Acronyms and abbreviations for studies included in the current report are given in Supplementary Web appendix Table S1 online. Subjects in the high-risk cohorts were more often male, and these cohorts had a higher prevalence of cardiovascular risk factors than did the general population cohorts. Moreover, the high-risk cohorts generally had a lower eGFR and higher albumin-to-creatinine ratio. Not all cohorts had data on all kidney outcomes. There were a total of 2179, 4939, and 11,144 participants who developed ESRD, acute kidney injury, and progressive CKD, respectively. The incidence rates for the kidney outcomes were two- to sixfold higher in the high-risk cohorts compared with the general population cohorts (1.83 versus 0.31 for ESRD, 4.88 versus 2.21 for acute kidney injury, and 18.44 versus 7.55 events per 1000 person-years for progressive CKD, respectively) (Supplementary Web appendix Tables S1–4 online, respectively). A total of 13.7% of the subjects of general population cohorts with albumin-to-creatinine ratio data had CKD according to the current definition (eGFR <60 ml/min per 1.73 m^2 or albumin-to-creatinine ratio $\geqslant 30$ mg/g) (Supplementary Web appendix Table S5 online). This subgroup accounted for 88.6% of ESRD events (Supplementary Web appendix Table S6 online), 61.5% of acute kidney injury events (Supplementary Web appendix Table S7 online), and 76.7% of subjects with progressive CKD (Supplementary Web appendix Table S8 online).

Independent continuous associations of eGFR and albuminuria with kidney outcomes

Pooled hazard ratios of ESRD according to eGFR and albuminuria adjusted for each other and covariates in the general population cohorts and the high-risk cohorts are shown in Figure 1. ESRD risk was relatively constant between an eGFR of 75 and 120 ml/min per 1.73 m^2, and was exponentially greater at lower eGFR. In the general population cohorts, eGFR risk association with ESRD showed hazard ratios at eGFR 60, 45, and 15 ml/min per 1.73 m^2 of 3.69 (2.36–5.76), 29.3 (19.5–44.1), and 454.9 (112.4–1840.2), respectively. The relationship of albumin-to-creatinine ratio to the relative risk of ESRD was monotonic on the log–log scale, without threshold effects. As compared with albumin-to-creatinine ratio 5 mg/g, hazard ratios for ESRD at albumin-to-

Table 1 | Characteristics of included studies

	N	Age, year	Male, %	Black, %	CVD, %	HT, %	HC, %	DM, %	Smoking, %	eGFR, ml/min per 1.73 m^2	ACR, mg/g	FU, Year	ESRD, *n*	AKI, *n*	pCKD, *n*
General population cohorts with ACR data													**147**	**427**	**173**
ARIC	11,408	62.8	44.2	22.2	8.6	47.6	34.5	16.7	14.9	82.5	3.7	8.0	92	363	—
AusDiab	11,240	51.5	44.9	0	8.3	32.7	70.6	8.4	15.5	78.9	4.9	5.0	—	—	72
CHS	3230	78.0	40.2	15.9	29.3	50.1	31.0	14.7	7.6	79.4	8.8	7.6	—	64	—
HUNT2	9525	62.0	44.8	0	22.5	82.5	61.3	17.6	19.7	83.8	7.5	10.5	55	—	—
MESA	6728	62.2	47.2	27.5	0.0	44.8	9.0	12.6	13.0	81.2	5.3	4.7	—		101
General population cohorts with dipstick data													**713**	**3438**	**4624**
AKDN UDIP	690,680	47.4	45.1	NA	1.8	20.2	NA	6.1	NA	80.9	—	2.3	478	3438	4475
Beaver Dam	4926	62.0	43.9	0	14.8	50.5	53.9	10.3	19.7	76.2	—	11.6	—	—	149
Okinawa 83	6659	51.9	39.5	NA	NA	NA	NA	3.8	NA	73.9	—	16.8	61	—	—
Okinawa 93	93,234	54.6	43.6	NA	NA	NA	NA	4.7	NA	77.3	—	6.9	174	—	—
High-risk cohorts with ACR data													**740**	**1074**	**4935**
ADVANCE	11,140	65.8	57.5	NA	32.2	82.2	33.0	100	15.1	78.2	15.9	4.8	59	—	822
AKDN ACR	67,406	55.5	56.8	NA	5.0	46.8	NA	49.0	NA	76.8	11.1	2.3	191	1013	1572
ONTARGET	25,620	66.4	73.3	2.5	92	NA*	NA*	37.5	12.6	73.6	52.2	4.5	162	61	1914
Pima	6341	26.4	45.4	0	NA	12.9	4.2	20.4	27.8	144	11.9	13.5	328	—	273
TRANSCEND	5926	66.9	57	1.8	92.5	NA*	NA*	35.7	9.8	71.7	25.3	4.6	—	—	354
High-risk cohorts with dipstick data													**579**	—	**1412**
CARE	4098	58.6	87.2	3.2	100	82.9	79.0	14.2	16.1	71.9	—	4.8	—	—	124
Hawaii	40,210	59.0	50.4	NA	17.0	NA	NA	48.0	13.6	71.5	—	2.4	331	—	1288
MRFIT	12,851	46.2	100	31.3	0.0	62.3	57.1	3.1	63.7	79.7	—	21.6	248	—	—

Abbreviations: ACR, albumin-to-creatinine ratio; AKI, acute kidney injury; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; FU, duration of follow-up; HC, hypercholesterolemia; HT, hypertension; NA, not available; pCKD, progressive chronic kidney disease.
NA* in ONTARGET and TRANSCEND, respectively, a history of hypertension was reported by 69 and 76%, and statin use by 62 and 55%.

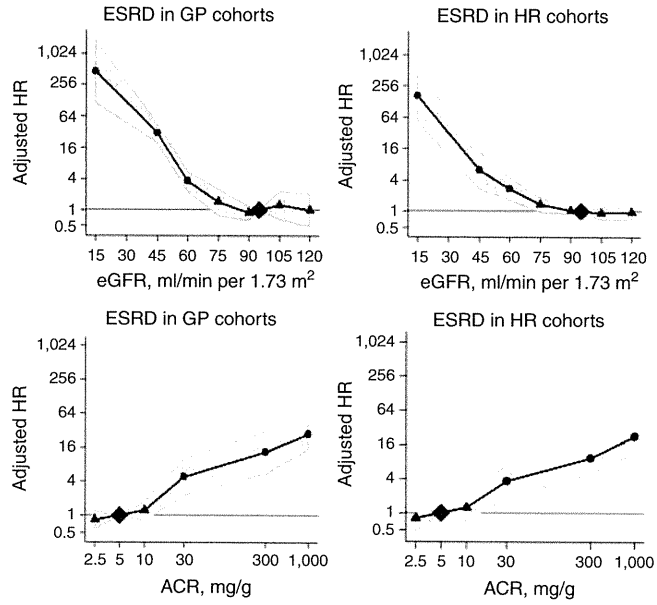

Figure 1 | Pooled hazard ratios (95% confidence interval) for ESRD according to spline eGFR (upper panels) and albumin-to-creatinine ratio (lower panels), adjusted for each other and for age, sex, and cardiovascular risk factors (continuous analyses). Reference categories are eGFR 95 ml/min per 1.73 m^2 and albumin-to-creatinine ratio 5 mg/g or dipstick negative or trace. Left panels show results for general population cohorts, and right panels for high-risk cohorts. Dots represent statistical significance, triangles represent non-significance, and shaded areas are 95% confidence interval. ACR, albumin-to-creatinine ratio; AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GP cohorts, general population cohorts; HR, hazard ratio; HR cohorts, high-risk cohorts.

creatinine ratios of 30, 300 and 1000 mg/g were 4.87 (2.30–10.3), 13.4 (5.49–32.7), and 28.4 (14.9–54.2), respectively. These patterns for ESRD in the high-risk cohorts were similar to the general population cohorts (Figure 1). The patterns for acute kidney injury and progressive CKD were generally similar to the patterns for ESRD, although less steep (Supplementary Web appendix Figures S1, S2 online).

Interactions

The multiplicative interaction between eGFR and albuminuria was significant for ESRD in only 1 out of 8 cohorts, for acute kidney injury in 3 out of 5 cohorts, and for progressive CKD in 4 out of 11 cohorts (Supplementary Web appendix Table S9 online). Significant interaction between eGFR and age was found for ESRD in only 1 out of 9 cohorts, for acute kidney injury in 3 out 5 cohorts, and for progressive CKD in 4 out of 11 cohorts (Supplementary Web appendix Table S9 online). Age interactions tended to show lower hazard ratios at older age, but a similar pattern of the associations of eGFR and albumin-to-creatinine ratio with the various kidney outcomes (Supplementary Web appendix Tables S10–12 online). The eGFR × albumin-to-creatinine ratio interaction can be visually assessed in graph 2. At low eGFR, the hazard ratio of higher albumin-to-creatinine ratio tended to be less than at high eGFR for ESRD as well as for acute kidney injury, but not for progressive CKD.

Table 2 | General population cohorts

	Albumin-to-creatinine ratio (mg/g) or dipstick (classes)				
	<10 Negative	10–29 Trace	30–299 (1+)	⩾300 (⩾2+)	All
ESRD					
eGFR ml/min per 1.73 m^2					
>105			0.13	0.75	
90–104	0.04		0.05	0.57	0.06
75–89			0.11	2.35	
60–74			0.27	2.66	
45–59	0.12	0.77	1.44	5.13	0.34
30–44	1.03	1.55	9.15	27.07	4.02
15–29	9.05	19.50	37.69	128.4	42.99
All	0.09		1.61	14.9	0.31
Acute kidney injury					
eGFR ml/min per 1.73 m^2					
>105			3.55	7.57	
90–104	0.98		3.04	5.73	1.14
75–89			3.45	5.86	
60–74			6.46	13.77	
45–59	4.73	13.10	21.40	36.08	6.48
30–44	24.49	42.53	52.09	76.62	32.65
15–29	69.66	65.82	92.93	109.6	81.37
All	1.69		10.15	26.26	2.21
Progressive CKD					
eGFR ml/min per 1.73 m^2					
>105			1.56	12.60	
90–104	2.02		2.72	7.02	2.48
75–89			5.25	25.21	
60–74			16.80	47.50	
45–59	23.91	31.91	63.61	135.1	28.78
30–44	37.53	54.60	82.27	177.5	55.37
15–29	33.12	55.36	82.08	178.9	77.14
All	5.62		25.93	89.59	7.55

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease.
Unadjusted incidence rates (per 1000 patient-years) for ESRD, acute kidney injury, and progressive CKD. Shaded areas make up the combined reference groups.

Joint associations of eGFR and albuminuria with kidney outcomes

As the albumin-to-creatinine ratio and the dipstick cohorts showed similar relationships between eGFR and albuminuria with ESRD, these two type of cohorts were combined to increase power for investigation of the joint associations of eGFR and albuminuria with kidney outcomes, both in general population and in high-risk cohorts (Supplementary Web appendix Figure S3 online). Table 2 shows unadjusted incidence rates of the three kidney outcomes for general population cohorts. Pooled hazard ratios/odds ratios for ESRD, acute kidney injury, and progressive CKD of the 21 categories of eGFR and albuminuria for the general population cohorts are shown in Tables 3 and 4. Low eGFR showed a similar association with risk across all levels of albuminuria, and high albuminuria showed a similar association with risk across all levels of eGFR, indicating multiplicative independent risk for kidney outcomes. At severely reduced eGFR values (15–29 ml/min per 1.73 m^2),

Table 3 | General population cohorts

	Albumin-to-creatinine ratio (mg/g) or dipstick (classes)				
	<10 Negative	10–29 Trace	30–299 (1+)	⩾300 (⩾2+)	All
ESRD					
eGFR ml/min per 1.73 m²					
>105	Ref		7.8 (1.7–35.9)	18.1 (4.3–75.9)	Ref
90–104			11.3 (2.7–47.7)	19.7 (5.8–66.5)	
75–89			3.8 (1.2–12.3)	48.1 (28.1–82.3)	
60–74			7.4 (3.6–15.2)	67.2 (40.1–113)	
45–59	5.2 (3.3–8.0)	21.8 (12.0–39.6)	40.3 (23.5–69.2)	147 (98.7–219)	9.6 (7.0–13.2)
30–44	55.5 (36.0–85.6)	74.1 (29.3–187)	293 (199–433)	763 (563–1035)	98.1 (61.8–156)
15–29	433 (239–787)	1044 (524–2077)	1056 (572–1948)	2286 (1114–4695)	573 (241–1362)
All	Ref		12.0 (7.9–18.1)	72.1 (43.0–121)	
Acute kidney injury					
eGFR ml/min per 1.73 m²					
>105	Ref		2.7 (0.9–8.5)	8.4 (5.1–13.8)	Ref
90–104			2.4 (1.1–5.2)	5.8 (3.7–9.2)	
75–89			2.5 (1.9–3.4)	4.1 (2.8–5.9)	
60–74			3.3 (2.6–4.1)	6.4 (5.0–8.2)	
45–59	2.2 (2.0–2.5)	4.9 (3.3–7.3)	6.3 (4.8–8.4)	5.9 (2.4–14.5)	2.6 (2.2–3.1)
30–44	7.3 (6.5–8.2)	10.2 (5.9–17.5)	12.4 (10.2–15.2)	19.6 (16.5–23.2)	7.9 (7.1–8.7)
15–29	16.8 (14.0–20.2)	16.8 (11.3–25.1)	21.4 (16.5–27.8)	28.8 (23.7–35.1)	16.7 (14.7–18.9)
All	Ref		2.5 (1.7–3.7)	6.0 (4.5–8.0)	
Progressive CKD					
eGFR ml/min per 1.73 m²					
>105	Ref		0.7 (0.7–0.8)	3.0 (0.4–23.7)	Ref
90–104			0.9 (0.4–2.1)	3.3 (0.5–23.3)	
75–89			1.9 (0.6–5.6)	5.0 (0.9–27.1)	
60–74			3.2 (1.4–7.5)	8.1 (5.2–12.8)	
45–59	3.1 (1.6–6.0)	4.0 (1.9–8.8)	9.4 (3.7–23.7)	56.6 (4.2–767.6)	3.9 (1.9–7.8)
30–44	3.0 (1.2–7.5)	19.1 (19.0–19.2)	14.9 (2.8–78.5)	22.2 (4.8–103.6)	3.7 (1.1–12.3)
15–29	4.0 (3.9–4.0)	11.7 (11.6–11.9)	21.0 (4.5–99.5)	7.7 (2.9–20.6)	7.9 (3.0–21.2)
All	Ref		3.1 (2.5–3.8)	11.2 (5.8–21.5)	

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; Ref, reference.
Pooled adjusted hazard ratios (95% confidence interval) for ESRD and acute kidney injury, and pooled adjusted odds ratios (95% confidence interval) for progressive CKD. Shaded areas make up the combined reference groups.

Table 4 | General population cohorts

	Albumin-to-creatinine ratio (mg/g) or dipstick (classes)				
	<10 Negative	10–29 Trace	30–299 (1+)	⩾300 (⩾2+)	All
ESRD, younger than 65 years of age					
eGFR ml/min per 1.73 m²					
>105	Ref		12.4 (2.3–66.8)	28.6 (6.5–127)	Ref
90–104			14.2 (3.3–61.0)	13.8 (1.9–101.2)	
75–89			5.8 (1.4–24.2)	65.2 (37.3–114)	
60–74			5.6 (2.0–15.7)	87.3 (32.3–236)	
45–59	3.1 (1.1–8.3)	31.8 (14.3–70.5)	55.4 (29.6–103)	261 (112–610)	9.5 (5.6–15.9)
30–44	101 (54.8–187)	293 (69.3–1236)	272 (107–693)	828 (443–1545)	110 (49.6–245)
15–29	999 (493–2023)	3897 (1717–8845)	2398 (1247–4609)	5081 (2736–9435)	1281 (556–2952)
All	Ref		13.7 (8.8–21.3)	124 (60.2–257)	
ESRD, older than 65 years of age					
eGFR ml/min per 1.73 m²					
>105	Ref		0.0 (0.0–∞)	0.0 (0.0–∞)	Ref
90–104			0.0 (0.0–∞)	0.0 (0.0–∞)	
75–89			0.0 (0.0–∞)	0.0 (0.0–∞)	
60–74			6.6 (1.6–27.2)	18.8 (5.3–67.1)	
45–59	3.4 (1.6–7.2)	9.6 (3.8–24.4)	16.4 (5.9–45.9)	41.4 (8.0–215)	4.5 (3.0–6.8)
30–44	11.5 (6.0–22.1)	18.1 (3.83–85.9)	90.8 (48.3–171)	268 (157–458)	42.1 (28.7–61.7)
15–29	131 (62.7–274)	115 (33.8–389)	413 (222–768)	1071 (645–1779)	186 (92.9–372)
All	Ref		10.3 (6.0–17.8)	47.5 (27.2–82.9)	

Abbreviations: eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; Ref, reference.
Pooled adjusted hazard ratios (95% confidence interval) for ESRD subdivided for age groups <65 and >65 years of age. Shaded areas make up the combined reference groups.

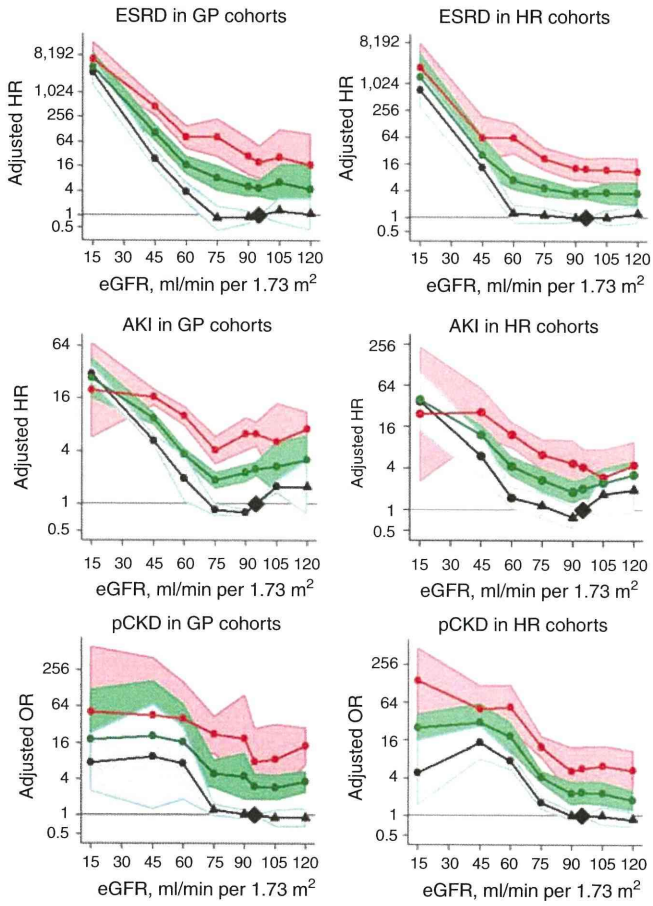

Figure 2 | Pooled adjusted hazard ratios or odds ratios (95% confidence interval) for ESRD (upper panels), acute kidney injury (middle panels), and progressive chronic kidney disease (lower panels) according to eGFR and albuminuria based on continuous models with eGFR (splines), albuminuria (log-linear albumin-to-creatinine ratio or categorical dipstick), and their interaction terms. Hazard ratios are adjusted for age, sex, and cardiovascular risk factors. Reference category is eGFR 95 ml/min per 1.73 m^2 plus albumin-to-creatinine ratio 5 mg/g or dipstick negative or trace. Left panels shows results for general population cohorts, and right panels for high-risk cohorts. 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 ⩾300 mg/g or dipstick ⩾2+. AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GP cohorts, general population cohorts; HR, hazard ratio; HR cohorts, high-risk cohorts; OR, odds ratio; pCKD, progressive chronic kidney disease.

the risk associated with higher albuminuria was attenuated. The patterns were much steeper (that is, risk increased more rapidly with increasing albuminuria) for ESRD than for acute kidney injury and progressive CKD (Tables 3 and 4). Figure 2 shows the continuous analyses (allowing interaction) of the hazard ratios/odds ratios of eGFR and albuminuria for ESRD, acute kidney injury, and progressive CKD, respectively.

Table 5 | High-risk cohorts

	Albumin-to-creatinine ratio (mg/g) or dipstick (classes)				
	<10 Negative	10–29 Trace	30–299 (1+)	⩾300 (⩾2+)	All
ESRD					
eGFR ml/min per 1.73 m^2					
>105			1.22	6.52	
90–104	0.22		0.39	5.00	0.45
75–89			0.30	4.56	
60–74			0.36	7.77	
45–59	0.25	0.36	1.65	13.38	1.44
30–44	1.56	2.42	4.33	29.80	7.35
15–29	1.57	12.78	20.93	133.0	60.98
All	0.31		1.41	25.72	1.83
Acute kidney injury					
eGFR ml/min per 1.73 m^2					
>105			2.99	5.54	
90–104	1.41		3.35	5.43	2.25
75–89			3.09	9.92	
60–74			6.06	13.73	
45–59	2.28	8.00	13.42	29.03	8.07
30–44	11.20	17.76	36.70	52.09	27.63
15–29	25.74	48.66	69.90	104.7	73.94
All	2.33		9.08	26.59	4.88
Progressive CKD					
eGFR ml/min per 1.73 m^2					
>105			4.43	27.52	
90–104	5.51		5.75	14.44	7.97
75–89			8.59	30.90	
60–74			19.01	68.77	
45–59	23.75	37.88	57.67	147.1	43.84
30–44	33.55	35.35	64.99	160.3	65.65
15–29	12.44	43.16	58.43	209.3	103.3
All	10.40		25.96	105.0	18.44

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease.
Unadjusted incidence rates (per 1000 patient-years) for ESRD, acute kidney injury, and progressive CKD. Shaded areas make up the combined reference groups.

Similar data are given for cohorts at high risk for CKD (Tables 5, 6 and 7). The patterns for ESRD were less steep in the high-risk cohorts (Table 6) compared with the general population cohorts (Table 3), whereas the patterns for acute kidney injury and progressive CKD were similar in the general population cohorts and high-risk cohorts.

Joint associations of eGFR and albuminuria with kidney outcomes per age group

The overall incidence rates for the kidney outcomes were three- to ninefold higher in the subgroup of subjects with age ⩾65 years compared with the subgroup with age <65 years (Supplementary Web appendix Tables S2–4 online, respectively). Pooled hazard ratios for ESRD of the 21 categories of eGFR and albuminuria according to age group are shown in Table 4 for the general population cohorts and in Table 5 for the high-risk cohorts. The general pattern of higher risk for a lower eGFR independent of albuminuria level and of a higher albuminuria independent of eGFR level was observed in both age groups. However, in general, relative hazards were smaller among participants ⩾65 years of age than among participants <65

Table 6 | High-risk cohorts

	Albumin-to-creatinine ratio (mg/g) or dipstick (classes)				
	<10 Negative	10–29 Trace	30–299 (1+)	⩾300 (⩾2+)	All
ESRD					
eGFR ml/min per 1.73 m²					
>105	Ref		1.1 (0.8–1.6)	2.0 (0.9–4.5)	Ref
90–104			2.3 (1.0–5.4)	10.0 (2.1–47.2)	
75–89			1.7 (0.9–3.3)	17.3 (4.0–74.9)	
60–74			3.1 (1.8–5.3)	32.2 (11.8–87.8)	
45–59	2.7 (1.7–4.3)	3.8 (1.9–7.5)	14.5 (6.3–33.1)	55.5 (17.9–173)	5.7 (1.7–4.3)
30–44	23.4 (11.0–49.5)	33.4 (12.9–86.4)	56.0 (20.0–157)	139.8 (35.6–549)	27.4 (11.0–49.5)
15–29	32.6 (4.3–249)	308 (97.0–979)	387 (86.9–1725)	462.7 (31.6–6780)	166 (52.4–524)
All	Ref		4.3 (2.6–7.1)	38.1 (15.6–93.5)	
Acute kidney injury					
eGFR ml/min per 1.73 m²					
>105	Ref		2.2 (1.2–4.2)	3.8 (1.2–12.0)	Ref
90–104			2.1 (1.3–3.4)	3.4 (1.4–8.3)	
75–89			1.8 (1.3–2.5)	5.2 (3.2–8.6)	
60–74			2.8 (1.4–5.6)	6.3 (4.3–9.2)	
45–59	1.7 (1.2–2.5)	3.5 (2.6–4.7)	6.6 (5.2–8.5)	13.0 (9.7–17.3)	3.0 (2.5–3.5)
30–44	8.0 (5.4–11.8)	7.5 (5.3–10.6)	14.3 (11.2–18.3)	26.9 (12.3–58.8)	10.6 (5.2–21.9)
15–29	12.3 (5.4–27.8)	1.6 (0.0–∞)	25.3 (18.2–35.3)	13.7 (0.0–∞)	16.8 (13.5–20.9)
All	Ref		2.7 (2.2–3.4)	7.4 (5.5–9.8)	
Progressive CKD					
eGFR ml/min per 1.73 m²					
>105	Ref		0.6 (0.5–0.8)	4.7 (0.3–69.4)	Ref
90–104			0.9 (0.7–1.2)	3.5 (0.5–26.0)	
75–89			1.0 (0.8–1.1)	3.5 (2.5–5.0)	
60–74			2.8 (1.3–6.1)	9.3 (6.0–14.4)	
45–59	3.0 (2.1–4.4)	4.8 (3.7–6.2)	10.1 (4.9–20.8)	31.4 (16.1–61.5)	4.7 (3.3–6.8)
30–44	3.3 (2.7–4.1)	3.4 (2.5–4.7)	9.8 (6.3–15.3)	68.7 (57.6–81.9)	6.4 (4.3–9.7)
15–29	0.5 (0.4–0.7)	3.1 (1.2–7.7)	9.4 (5.3–16.6)	38.6 (15.7–94.8)	8.9 (4.8–16.7)
All	Ref		2.2 (1.9–2.7)	9.9 (6.7–14.5)	

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; Ref, reference.
Pooled adjusted hazard ratios (95% confidence interval) for ESRD and acute kidney injury, and pooled adjusted odds ratios (95% confidence interval) for progressive CKD. Shaded areas make up the combined reference groups.

Table 7 | High-risk cohorts

	Albumin-to-creatinine ratio (mg/g) or dipstick (classes)				
	<10 Negative	10–29 Trace	30–299 (1+)	⩾300 (⩾2+)	All
ESRD, younger than 65 years of age					
eGFR ml/min per 1.73 m²					
>105	Ref		1.1 (0.8–1.7)	1.4 (0.9–3.6)	Ref
90–104			2.6 (1.0–6.9)	10.5 (2.0–55.3)	
75–89			1.7 (0.8–3.8)	16.3 (2.3–119)	
60–74			4.0 (2.0–7.7)	39.0 (10.3–148)	
45–59	2.4 (1.4–4.2)	5.3 (2.3–12.2)	16.9 (4.7–60.5)	66.9 (20.1–222)	7.0 (4.3–11.6)
30–44	15.9 (1.9–133)	73.6 (20.5–264)	90.9 (27.6–299)	161 (26.3–989)	33.9 (14.6–78.9)
15–29	#	656 (172–2507)	792 (210–2982)	998 (105–9455)	223 (69.9–709)
All	Ref		4.5 (2.4–8.5)	43.8 (16.4–117)	
ESRD, older than 65 years of age					
eGFR ml/min per 1.73 m²					
>105	Ref		0.0 (0.0–∞)	20.6 (2.4–173)	Ref
90–104			0.0 (0.0–∞)	15.5 (2.0–122)	
75–89			1.9 (0.6–5.9)	16.2 (3.1–84.6)	
60–74			1.7 (0.6–4.7)	20.7 (9.4–45.8)	
45–59	2.8 (1.1–7.2)	1.8 (0.5–6.4)	10.0 (5.5–18.1)	31.2 (10.9–89.5)	3.8 (2.5–5.8)
30–44	16.1 (6.7–38.8)	18.1 (7.5–43.6)	24.3 (9.3–63.4)	92.7 (46.3–186)	20.7 (14.0–30.6)
15–29	25.0 (3.2–196)	175 (42.5–718)	125 (43.0–363)	506 (158–1620)	146.6 (46.3–464)
All	Ref		4.1 (2.5–6.8)	43.3 (13.0–145)	

Abbreviations: #, insufficient number of events for reliable estimates; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; Ref, reference.
Pooled adjusted hazard ratios (95% confidence interval) for ESRD subdivided for age groups <65 and >65 years of age. Shaded areas make up the combined reference groups.

years of age (Supplementary Web appendix Table S10 online). Similar findings were obtained for acute kidney injury (Supplementary Web appendix Table S11 online) and progressive CKD (Supplementary Web appendix Table S12 online).

Heterogeneity

eGFR × albumin-to-creatinine ratio categories with significant heterogeneity are shown in the Supplementary Web appendix Table S10–12 online. Quantitative heterogeneity, rather than qualitative heterogeneity, was observed in several categories, reflecting numerical differences in the hazard ratios between cohorts, but the direction of the risk was similar in all cohorts (increased risk with lower eGFR categories and with higher albuminuria categories). However, in all cohorts, the direction of the risk was similar (increased risk with lower eGFR categories and with higher albuminuria categories). Moreover, significant heterogeneity was limited to the lowest eGFR and the highest albuminuria categories. There was no significant heterogeneity in the groups with eGFR of 45–60 ml/min per 1.73 m^2 and in the groups with microalbuminuria (albumin-to-creatinine ratio 30–299 mg/g or dipstick 1+), either in the general population or in the high-risk population.

Meta-regression analysis was performed to test whether the association between eGFR and albumin-to-creatinine ratio with outcomes differed by the proportion of diabetic participants within each high-risk cohort. The proportion of diabetic participants was not significantly associated with the hazard ratio for ESRD associated with eGFR (45 versus 95 ml/min per 1.73 m^2; $P=0.58$) or albumin-to-creatinine ratio (30 versus 5 mg/g; $P=0.31$). Likewise, the proportion of diabetic participants was not significantly associated with the hazard ratio for progressive CKD associated with eGFR ($P=0.57$) or albumin-to-creatinine ratio ($P=0.96$). There were too few cohorts with sufficient events to allow similar meta-regression models for acute kidney injury.

DISCUSSION

In this collaborative meta-analysis of nine general population and eight high-risk cohorts, including a total of more than 1 million subjects, we found that lower eGFR and higher albuminuria were associated with a higher risk for ESRD, independent of each other and independent of traditional CVD risk factors. A similar association of eGFR and albuminuria was found with the risk for acute kidney injury and for progressive CKD, although the relative hazards were higher for ESRD.

The risk for ESRD based on eGFR and albuminuria have been reported in a limited number of follow-up studies from general population cohorts.[20,22,28–30] The current meta-analysis confirms these studies and extends the generalizability of these data to other populations worldwide. Furthermore, our collaborative meta-analysis includes 2201 ESRD outcomes, substantially more than the number of events in reports of individual studies, thereby allowing evaluation of the independent and joint associations of eGFR and albuminuria with this outcome. In addition, we included data on acute kidney injury and progressive CKD, other kidney disease outcomes of clinical and epidemiologic interest.

We found similar patterns in studies that had data on albumin-to-creatinine ratio and in the studies that only had semiquantitative information available on dipstick proteinuria. These findings suggest that measurement of dipstick proteinuria is useful for risk stratification, despite being a less precise measure of albuminuria. This is of importance considering the lower cost of dipstick compared with albumin-to-creatinine ratio measurement. However, studies directly comparing dipstick testing with more accurate albuminuria measurements are needed to investigate sensitivity, specificity, and negative and positive predictive value to make definite recommendations for screening. Also, it is important to bear in mind that most studies had measured albuminuria only once, thus raising questions regarding reproducibility and chronicity of albuminuria. However, the finding that a single urine test has significant prognostic implication strengthens the conclusion that albuminuria is an important risk factor. In addition, a single test may underestimate rather than overestimate the risk associated with albumin-to-creatinine ratio because of regression dilution bias.[31]

The general pattern of a graded increase in relative risk for the various kidney outcomes with higher albuminuria and lower eGFR was observed in both cohorts at high risk for CKD as well as cohorts derived from the general population. Although the absolute incidence of ESRD was higher in the high-risk population compared with the general population, the increase in relative hazards for a lower eGFR and a higher albuminuria was more pronounced in the general population than the high-risk population. The consistency of our findings in both cohorts with albumin-to-creatinine ratio and dipstick proteinuria data, in both general population and high-risk cohorts, and in both continuous and categorical models for eGFR and albumin-to-creatinine ratio, demonstrates the robustness of our findings. The finding of only quantitative, but not qualitative heterogeneity, and that heterogeneity was not observed in the categories of most clinical interest, that is, eGFR 45–60 ml/min per 1.73 m^2 and albumin-to-creatinine ratio 30–299 mg/g or dipstick >1+, further underscores the strengths of our observations. Of note, our meta-regression analyses showed that the associations of eGFR and albuminuria with adjusted hazard rates for ESRD and acute kidney injury outcomes were not related to the proportion of diabetic subjects included in the various high-risk cohorts. This provides no evidence for the assumption of some investigators that diabetic and non-diabetic kidney disease should be regarded as separate entities.

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, Tables 3 and 4 show that the pattern of higher relative hazards for ESRD for a lower eGFR and for a higher albuminuria is less steep in subgroups older than ⩾65 than in those <65 years of

age. The relationship of higher albuminuria with higher unadjusted incidence rate of ESRD is comparable for both age groups, but less steep with lower eGFR in the elderly when compared with the young (Supplementary Web appendix Table S3 online). The less steep relationship with lower eGFR needs to be balanced against the higher incidence rates in the older subgroup. Although in elderly the increase in adjusted relative risk with lower eGFR is less than in the young, the increase in unadjusted incidence rates is higher. The age–eGFR interaction will be studied in depth in later analyses by the CKD Prognosis Consortium.

The observed relative risk increase for ESRD with lower eGFR is more pronounced than the relative risk increase for all-cause and cardiovascular mortality, as described separately.[24] The hazard ratios for ESRD at eGFR 60, 45, and 15 ml/min per 1.73 m^2 were 3.69 (2.36–5.76), 29.3 (19.5–44.1), and 454.9 (112.4–1840.2), respectively, compared with 1.16 (1.04–1.30), 1.49 (1.28–1.72), and 3.18 (2.45–4.14), respectively, for all-cause mortality.[25] Interestingly, the increase in relative risk for higher albuminuria is also substantially higher for ESRD compared with all-cause mortality, with hazard ratios for ESRD at albumin-to-creatinine ratio 30, 300, and 1000 mg/g of 4.87 (2.30–10.3), 13.4 (5.49–32.72), and 28.4 (14.9–54.2), respectively, compared with 1.16 (1.08–1.25), 1.51 (1.34–1.70), and 2.15 (1.80–2.58), respectively, for all-cause mortality.[25] For kidney outcomes, eGFR and albumin-to-creatinine ratios were the strongest risk factors examined, often stronger than age, which differs from all-cause mortality and cardiovascular mortality where age is the dominant factor. The higher relative risks for kidney outcomes than for mortality likely reflect a greater specificity of association of eGFR and albumin-to-creatinine ratio with these outcomes. The implications of the more steep relationship of low eGFR and high albuminuria with relative risk for ESRD than for mortality should be considered in view of the relative low incidence rates of the kidney outcomes. Lastly, these data are not consistent with the suggestion by others that microalbuminuria is only a marker for increased CVD risk,[11] as it also indicates substantially increased risk for all kidney outcomes examined.

A strength of this pooled analysis is that it includes data on acute kidney injury and progressive CKD as well as on ESRD. A disadvantage of limiting study of kidney outcomes to only ESRD is that it will predispose to identification of low eGFR values as the most important risk predictor, as the decision to start renal replacement therapy is for a large part based on eGFR. For clinical practice, however, it is also important to identify risk predictors in subjects with relatively preserved renal function, who may benefit from early initiation of therapies to slow progression of CKD, thereby delaying or even preventing ESRD and other complications. Therefore, incident acute kidney injury and progressive CKD were studied as earlier kidney outcomes than ESRD. For acute kidney injury, the International Classification of Diseases hospital discharge code 584 was adopted as defining criterion. For progressive CKD, different definitions have been used in the literature. Our definition required loss of eGFR of more than 2.5 ml/min per 1.73 m^2 per year (~3–5 times faster than the rate of renal function decline in the general population[21,30]) and a final eGFR during follow-up of $\leqslant$45 ml/min per 1.73 m^2 (as it is widely acknowledged that this threshold is of clinical significance). Such a combination of a relative decrease and an absolute threshold has been used before in epidemiological studies[32] to increase specificity with a recognized loss of sensitivity. Of note, the weaker associations of eGFR and albuminuria for progressive CKD in comparison with the two other kidney outcomes can be partially explained by misclassification of the outcome and regression to the mean.

Some limitations of this meta-analysis should be mentioned. First, we included only a relatively limited number of cohorts, and measurements of serum creatinine and albuminuria were not centrally standardized across these cohorts. The present analysis, however, is to the best of our knowledge the largest and most comprehensive assessment of the relation between eGFR, albuminuria, and kidney outcomes yet performed. Second, no data on treatment effects could be taken into account. Thus, it cannot be excluded that the observed associations are influenced by the start of specific treatments. However, if such treatment were effective in preventing kidney disease progression, then it would be expected to lead to an underestimation of the true relative risk of low eGFR and high albuminuria for these outcomes. Finally, we used a restrictive definition of progressive CKD, and alternative definitions should be explored.

What do these findings mean for the current debate on the definition and classification of CKD? First, as albuminuria is a risk factor for kidney outcomes independent of eGFR and conventional cardiovascular risk factors, this suggests that albuminuria could be used for risk stratification at each level of eGFR. A lack of multiplicative interaction means that albuminuria has a similar relative risk at normal and low eGFR. However, the baseline risk is higher at lower eGFR, and hence the attributable risk will be higher at lower eGFR for the same relative risk. Furthermore, as the risk for kidney outcomes is higher for subjects with macroalbuminuria ($\geqslant$300 mg/g) than for subjects with microalbuminuria (30–299 mg/g), it seems prudent to define not only one, but several thresholds for albuminuria to indicate increased risk for kidney outcomes. Second, our finding that risk for kidney outcomes is substantially higher in subjects with eGFR 30–45 ml/min per 1.73 m^2 as compared with 45–60 ml/min per 1.73 m^2 suggests that it may be appropriate to subdivide the present stage 3 CKD into two stages, as has been proposed by others.[33] Our finding of increased relative risk for all three kidney outcomes for eGFR below 60 ml/min per 1.73 m^2 and albuminuria (albumin-to-creatinine ratio >30 mg/g or dipstick >trace) are consistent with the current thresholds for the definition of CKD. Some have suggested age-specific thresholds, arguing that lower eGFR at older age is a reflection of ageing[11] and less associated with

risk for adverse outcomes.[34,35] Although we found a less steep pattern of risk for kidney outcomes with lower eGFR in older subjects compared with younger subjects, the pattern of incidence rates was similar in older and younger subjects. These data do not provide clear-cut evidence for the use of age-specific eGFR thresholds to define CKD. In general, decisions about the threshold levels for decreased GFR and albuminuria to define and classify CKD should consider the prevalence and absolute risk of decreased eGFR and albuminuria, as well as relative risk.

In conclusion, our data show that both albuminuria and eGFR are associated with all three kidney outcomes, independent of each other and cardiovascular risk factors. There was no evidence of multiplicative interaction between eGFR and albuminuria. These findings provide a quantitative basis for including these two kidney measures for risk stratification, and CKD definition and staging.

MATERIALS and METHODS

Search strategy and study selection

In August 2009, we performed a systematic review of the available literature to retrieve all general population cohorts that might have information on the relation between eGFR and/or albuminuria versus kidney outcomes. Details of the search strategy can be found elsewhere.[25] To be eligible for inclusion, studies had to meet the following criteria: (1) prospective, general population-based cohort study, (2) information at baseline on eGFR as well as albuminuria levels, (3) at least 1000 subjects included, (4) information on at least one of the three kidney outcome measures, and (5) a minimum of 50 events for that outcome measure. The reason to require a minimum sample size is to ensure sufficient out comes in the reference cell. Ultimately, 21 general population cohorts met these eligibility criteria and were willing to cooperate, of which 9 had data on kidney outcomes.[20,28,36–42]

We also included cohorts of individuals selected because of high risk of CKD, including patients with cardiovascular disease risk factors (such as hypertension and diabetes) or a history of cardiovascular disease, because screening for CKD is recommended in these groups. However, the associations between eGFR and/or albuminuria and kidney outcomes may differ between high-risk populations and the general population. We analyzed eight high-risk cohorts that met the same eligibility criteria as the general population cohorts.[20,29,31,43–47]

Study variables

In each cohort, subjects were subdivided according to eGFR and albuminuria. GFR was estimated using the abbreviated Modification of Diet in Renal Disease Study equation.[48] 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,[3,33] albuminuria was assessed as the urine 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 urine protein-to-creatinine ratio[47] or dipstick testing for proteinuria[20] were collected. eGFR and albuminuria were measured at the onset of cohort studies.

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 $\geqslant 140$ mm Hg or diastolic blood pressure $\geqslant 90$ 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 $\geqslant 7.0$ mmol/l or non-fasting glucose $\geqslant 11.1$ mmol/l or use of glucose-lowering drugs. Smoking habit was dichotomized as current versus not current smoking.

Definition of kidney outcome measures

ESRD was defined as start of renal replacement therapy or death coded as because of kidney disease other than acute kidney injury. Acute kidney injury was defined as ICD-9 code 584 as primary or additional discharge code. Progressive CKD was defined as an average annual decline in eGFR during follow-up of at least 2.5 ml/min per 1.73 m^2 per year and a last eGFR value being less than 45 ml/min per 1.73 m^2, independent of the level of baseline eGFR. The average annual decline in eGFR was calculated as last available eGFR minus baseline eGFR divided by follow-up time (in years, minimum two) between the two observations.

Statistical analysis

Our primary objective was to evaluate the associations of eGFR and albuminuria, independently and jointly, on kidney outcome measures. 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 that was 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 Institute for Public Health, Baltimore, USA (KM, JC, and BCA) and the University Medical Center Groningen, Groningen, the Netherlands (MvdV, PEdJ, and RTG), and differences were resolved by consensus.

For each study, a table was generated providing baseline study characteristics. Cox proportional hazard models were used to estimate the hazard ratios for ESRD and acute kidney injury, and logistic regression analysis to estimate odds ratios

for progressive CKD. These analyses were adjusted for age, sex, race, and cardiovascular risk factors. Cardiovascular risk factors taken into account were cardiovascular disease history, smoking status, diabetes mellitus, systolic blood pressure, and serum total cholesterol. The independent continuous association of eGFR and of albuminuria with risk for kidney outcomes was evaluated after adjusting for each other and for CVD 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 m^2 and 10, 30, and 300 mg/g, respectively. eGFR splines were also adjusted for albuminuria (adjusted to an albumin-to-creatinine ratio of 5 mg/g and dipstick negative), whereas albuminuria splines were also adjusted for eGFR. For the continuous albuminuria splines, only cohorts that had albumin-to-creatinine ratio data were taken into account. eGFR 95 ml/min per 1.73 m^2 and 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 $\geqslant 105$ ml/min per 1.73 m^2. These 15 ml/min per 1.73 m^2 categories were chosen to correspond to current CKD stages 1–5 and to evaluate whether these stages require subdivision. For albumin-to-creatinine ratio, we defined four categories: <10, 10–29, 30–299, and $\geqslant 300$ 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 $\geqslant 2+$ macroalbuminuria,[49] we defined four dipstick categories as: negative, trace, 1+, and $\geqslant 2+$. We tested whether combining cohorts with data on albumin-to-creatinine ratio and cohorts with data on dipstick proteinuria were valid. Unlike the mortality analyses,[24,25] there were insufficient kidney outcomes in the 'optimal' reference cell (eGFR 90–104 ml/min per 1.73 m^2 and albumin-to-creatinine ratio <10 mg/g) for the current analyses. Therefore, eGFR $\geqslant 60$ ml/min per 1.73 m^2 and albumin-to-creatinine ratio <30 mg/g or dipstick negative/trace were chosen as the reference cell, as present guidelines classify this group as being free of CKD. For all of the 25 eGFR $\times$ albumin-to-creatinine ratio 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 or odds ratios were estimated with adjustment for the aforementioned cardiovascular risk factors. We conducted complementary analyses where eGFR and albumin-to-creatinine ratio were modelled continuously using the same statistical models and adjustments. These models were parameterized with eGFR = 95 ml/min per 1.73 m^2 and albumin-to-creatinine ratio = 5 mg/g or eGFR = 95 ml/min per 1.73 m^2 and dipstick = negative/trace as the reference point (hazard ratio or odds 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 and odds ratios, with 95% confidence interval, were obtained from meta-analyses of random effects. Heterogeneity was estimated using the χ^2-test for heterogeneity and the I^2 statistic.[50] Meta-analyses were conducted separately for general population cohorts and high-risk cohorts. As there were few participants (0.1%) with eGFR <15 ml/min per 1.73 m^2, we only report results for participants with eGFR $\geqslant 15$ ml/min per 1.73 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 $\geqslant 65$ years. This age subdivision was chosen, as guidelines advise to screen for CKD in subjects $\geqslant 65$ years of age.

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

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Table S1. Acronyms/abbreviations for individual studies.
Table S2. Incidence rate for end-stage renal disease.
Table S3. Incidence rate for acute kidney injury.
Table S4. Incidence rate for progressive chronic kidney disease.
Table S5. Distribution of subjects for analysis of incident end-stage renal disease.
Table S6. Distribution of incident end-stage renal disease events.
Table S7. Distribution of incident acute kidney injury events.
Table S8. Distribution of incident progressive chronic kidney disease events.
Table S9. Statistical significance for interaction between eGFR and age, and between eGFR and albuminuria for end-stage renal disease, acute kidney injury, and progressive chronic kidney disease.
Table S10. Hazard ratios for incident end-stage renal disease.
Table S11. Hazard ratios for incident acute kidney injury.
Table S12. Odds ratios for incident progressive chronic kidney disease.
Figure S1. Pooled adjusted hazard ratios for acute kidney injury according to spline eGFR and albumin-to-creatinine ratio adjusted for each other and for age, sex, and cardiovascular risk factors.
Figure S2. Pooled adjusted hazard ratios for progressive chronic kidney disease according to spline eGFR and albumin-to-creatinine ratio adjusted for each other and for age, sex, and cardiovascular risk factors.
Figure S3. Pooled adjusted hazard ratios for end-stage renal disease according to eGFR and albuminuria for four groups (general population cohorts with albumin-to-creatinine ratio data, general population cohorts with dipstick data, high-risk cohorts with albumin-to-creatinine ratio data, and high-risk cohorts with dipstick data).
Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

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REVIEW ARTICLE

Role of chronic kidney disease in cardiovascular disease: are we different from others?

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Abstract The incidence and prevalence of chronic dialysis patients in Japan is increasing linearly and is currently as high as 300 and 2300 per million population, respectively. The incidence of end-stage renal disease is closely related to that of chronic dialysis; findings which are captured in detail in the Japanese Society for Dialysis Therapy registry. Life expectancy of dialysis patients is poor compared to the age- and sex-matched general population, and is equivalent to that of an 80-year-old man or an 87-year-old woman, i.e., dialysis patients seem 15–18 years older than their actual age. Cardiac death is the leading cause of death; however, death due to stroke and acute myocardial infarction is decreasing. The annual mortality rate is 6.5% among the dialysis population. For the past 10 years, the mortality risk has remained high despite the avoidance of blood transfusions by the administration of erythropoiesis-stimulating agents, the use of renin–angiotensin system inhibitors, and improvements in general medical care. Several studies have confirmed the significance of chronic kidney disease (CKD) on the development of cardiovascular disease (CVD) and mortality; the lower the estimated glomerular filtration rate (eGFR), the higher the incidence of CVD. The cut-off levels for eGFR are not yet clear. CKD is an important predictor of CVD in Japan, similar to other parts of the world. Strategies for early detection of CKD are needed because, in many cases, CKD remains asymptomatic until late stages. Timely treatment for CKD is necessary to minimize costs for unnecessary care and testing. Unless CDK is properly managed, it will not be possible to maintain quality and longevity of life. The Japanese population is rapidly aging and will have the largest proportion of elderly people in the world. A systematic strategy for managing CKD patients is warranted.

Keywords Proteinuria · Glomerular filtration rate (GFR) · Chronic kidney disease (CKD) · Cardiovascular disease (CVD) · Screening

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Introduction

In Japan, the incidence and prevalence of chronic dialysis is increasing linearly and is as high as 300 and 2,300 per million population, respectively [1]. According to the annual report of the Japanese Society for Dialysis Therapy (JSDT), the number of dialysis patients and facilities increased to 290,675 and 4,125, respectively, in 2009. There are 114,000 dialysis beds which can accommodate 340,000 patients. It is also noteworthy that the mean age at the start of dialysis is increasing, which may reflect the increase in the elderly population. In addition, preventive strategies such as universal screening including urine tests and treatment of hypertension may have prolonged the onset of end-stage renal disease (ESRD). As Japan has a long history of universal screening early detection of CKD might be possible [2]. Dipstick proteinuria has been used in a community-based screening [3]. However, many patients are diagnosed and are inevitably started on dialysis soon after their first visit to a nephrology clinic.

The preliminary results of the JSDT support the notion that the longer the duration of pre-ESRD treatment, the better the survival. Survival of dialysis patients was better in those treated for >6 months (up to <12 months) and >48 months in referral facilities compared to those with the shortest duration after referral (<1 month) (Fig. 1).

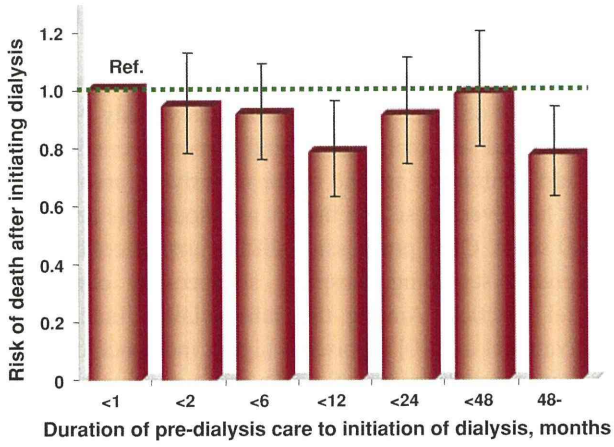

Fig. 1 Survival based on the duration of predialysis care (JSDT data)

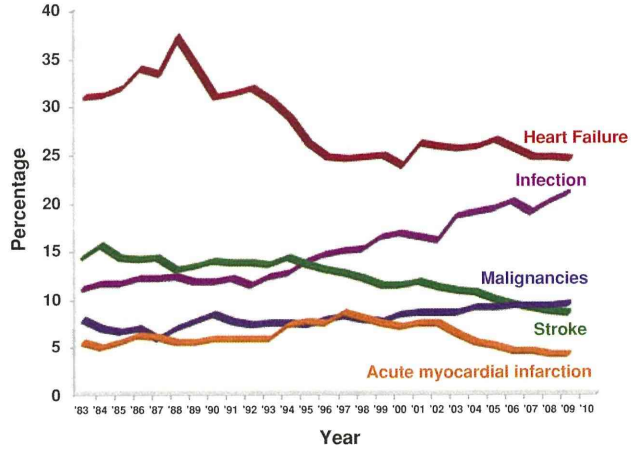

Fig. 2 Causes of death in prevalent dialysis patients in Japan (JSDT data)

Malnutrition is a strong predictor of survival of prevalent dialysis patients, but it often begins before starting dialysis therapy. Differences in the control of hypertension, nutritional status, and comorbid conditions might play a role. Only limited information is available on the course of CKD progression. Outcomes likely differ between screened cohorts in the CKD clinic and hospital patients. ESRD patients are those who have survived and been accepted for dialysis therapy. Because the acceptance policy is quite open in Japan, the incidence of ESRD is closely related to that of acceptance to dialysis therapy; findings which are captured in detail in the JSDT registry.

The present study reviews the role of CKD in the development of CVD in the Japanese population, both pre-ESRD and with ESRD. The Japanese society is rapidly aging and the proportion of elderly people in the total population will be the largest in the world. The Japanese dietary habits and lifestyle are unique. Managing CKD is essential for maintaining quality and longevity of life. Strategies for early detection and proper treatment for CKD are needed because many people remain asymptomatic until the late stages of CKD.

CVD in dialysis population

The causes of death in prevalent dialysis patients are summarized in Fig. 2. Cardiac death is a leading cause and remains high; however, death due to stroke and acute myocardial infarction is decreasing while deaths due to infection and malignancies are increasing. Among incident dialysis patients, infection has become the leading cause of death since 2006. This is partly due to the rapid increase in mean age of incident dialysis patients, 67.3 years in 2009 (up from 63.4 years in 1999), and prevalent patients, 65.8 years in 2009 (up from 59.9 years in 1999). The precise nature of cardiac death is difficult to investigate further. Most deaths are believed to be due to congestive heart failure related to volume overload, hypertensive heart disease, valvular heart disease, and other 'uremic' cardiomyopathies. Sudden death and/or death due to hyperkalemia comprise less than 5% which is quite different from the United States Renal Data System (USRDS) [4]. At the 2010 Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference, the role of CKD in CVD mortality was discussed and the lack of pertinent data recognized. Volume overload remains a big problem in dialysis patients.

Causes of death in dialysis patients are different from those in the general population (Fig. 3). The leading cause of death in the general population in Japan is malignancy; however, malignancy as a cause of death in the dialysis population is small, which is probably because patients with malignancies are not accepted for dialysis therapy even if they are uremic. There are no definite criteria for

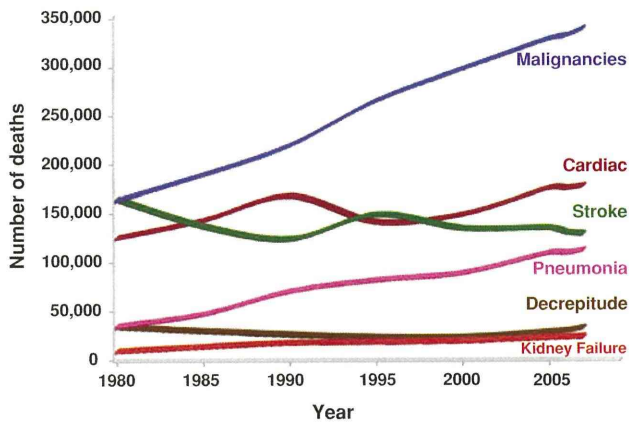

Fig. 3 Number of deaths in the general population in Japan (National data)

initiating dialysis, although we have been using the Japanese Ministry of Health, Welfare and Labor (MHWL) research group criteria [5]. In this recommendation, uremic symptoms are required in addition to impaired kidney function based on creatinine clearance or serum creatinine. Others use only a cut-off level of serum creatinine of at least 8.0 mg/dl.

In the JSDT 2005 cohort, the prevalence of a history of acute myocardial infarction, cerebral hemorrhage, cerebral infarction, and amputation was 6.1, 3.7, 11.8, and 2.4%, respectively [6]. Mean body mass index (BMI) was 21.1 kg/m^2 which was significantly lower than that of the USRDS [7]. Body size difference is crucial if the target fluid removal is defined as 5% of the dry weight. The amount of fluid to be removed by one dialysis session in most Japanese dialysis patients (body weight (BW) 60 kg) is 3.0 liters, whereas that of patients in the USRDS (BW $\geq$75 kg) is 3.75 liters. Rapid removal of fluid in a short dialysis time is often associated with hypotension during dialysis and eventually leads to chronic volume overload. Obesity is often associated with sleep apnea and risk of CVD. CKD patients have a higher incidence of sleep apnea and dialysis patients have a much higher prevalence of sleep apnea [8].

Life expectancy of dialysis patients is poor compared to the age- and sex-matched general population. The annual mortality rate is 6.5% among the dialysis population (Fig. 4), which is equivalent to 80 years in men and 87 years in women, i.e., dialysis patients seem older by 15–18 years than their actual real age. For the past 10 years, the mortality risk has remained high despite the avoidance of blood transfusion by the administration of erythropoiesis-stimulating agents, the use of renin–angiotensin system inhibitors, and improved general medical care. In contrast to the USRDS, dialysis patients are dialyzed mostly via an arteriovenous fistula and each dialysis session lasts at least 4 h.

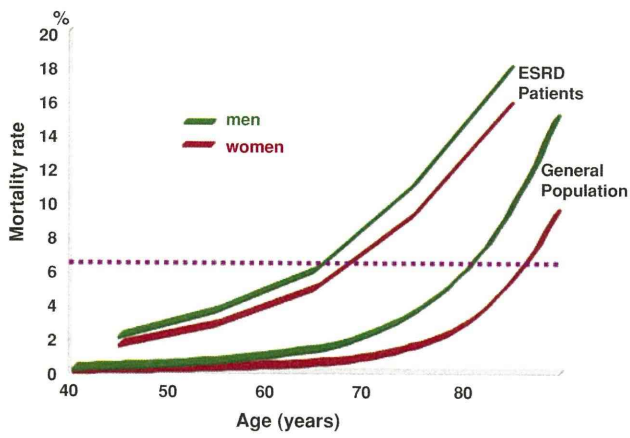

Fig. 4 Comparison of annual mortality rate between dialysis patients and general population (JSDT and National data)

Factors related to survival, studied in our own cohort and those of others, were summarized previously [9]. Other than age and sex, malnutrition and comorbid conditions at the start of dialysis are the major underlying predictors of death; however, these two factors are modifiable at the pre-ESRD stage. CKD progression differs among cohorts such as general screening, hospital, subspecialty clinic, and general practice. Among the subspecialty clinic cohort, Nakayama et al. [10] reported a higher incidence of ESRD but lower development of CVD and very few mortality cases. Currently, a large nationwide prospective study is underway [11]. In this study, registered CKD patients are cared for by general practitioners (Kakarituke-I, i.e., family or near-by doctor) according to the Japanese Society of Nephrology (JSN) CKD Practice Guidebook and Guidelines [12]. Forty-nine regional doctors' associations were randomized into two groups. CKD patients seeing doctors in Group B are cared for intensively with the aid of a dietician and nurses, who check for compliance with doctors' orders, and are instructed in diet and lifestyle modifications. Such pre-HD care may improve life expectancy, despite eventual entrance into an ESRD program.

CVD in the non-dialysis population

The glomerular filtration rate (GFR) estimation formula needs to be refined to examine the progression of CKD in each ethnic group. In Japan, this was made possible by the JSN task force [13]. Methods of serum creatinine measurement should be clarified and standardized. The formulas for estimating GFR were developed using CKD patients; therefore, they are not applicable to a healthy population. In particular, underestimation is possible in those with an estimated GFR (eGFR) of >60 ml/min/1.73 m^2 [14]. Serum creatinine concentration is affected not only by GFR, but also by various other factors, such as muscle mass, sex, race, diet, drugs, and tubular function. Ideally, the clearance of exogenous GFR markers, such as inulin, should be measured for GFR estimation, but the method is time-consuming and difficult and therefore not feasible for community-based screening.

Geographic differences in CKD prevalence in Japan

Japan has a long history of universal screening. Based on such nationwide screening data, the JSN estimated the prevalence of stage 3 CKD to be 10.4% [15]; GFR in 7.6% of these subjects was in the range of 50–59 ml/min/1.73 m^2. Geographic differences in ESRD prevalence have been noted, but there is little data on CKD prevalence.