

RESEARCH

Associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex: a meta-analysis

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Dorothea Nitsch *clinical senior lecturer*¹, Morgan Grams *assistant professor*², Yingying Sang *biostatistician*³, Corri Black *senior clinical lecturer*⁴, Massimo Cirillo *associate professor*⁵, Ognjenka Djurdjev *corporate director*⁶, Kunitoshi Iseki *director*⁸, Simerjot K Jassal *clinical professor*⁹, Heejin Kimm *assistant professor*¹⁰, Florian Kronenberg *professor*¹¹, Cecilia M Øien *associate professor*¹², Andrew S Levey *professor*¹³, Adeera Levin *professor*⁷, Mark Woodward *professor*¹⁴, Brenda R Hemmelgarn *associate professor*¹⁵, for the Chronic Kidney Disease Prognosis Consortium

¹Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK; ²Department of Medicine, Division of Nephrology, Johns Hopkins University School of Medicine, Baltimore MD, USA; ³Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore MD, USA; ⁴Chronic Disease Research Group, Medical School, Aberdeen, UK; ⁵Department of Medicine (Nephrology), University of Salerno, Baronissi (SA), Italy; ⁶Provincial Health Services Authority, Vancouver BC, Canada; ⁷Division of Nephrology UBC, St. Pauls Hospital, Vancouver BC, Canada; ⁸Dialysis Unit, University Hospital of the Ryukyus, Okinawa, Japan; ⁹VA San Diego Healthcare System, Division of GIM/G, San Diego CA, USA; ¹⁰Institute for Health Promotion, Department of Epidemiology and Health Promotion, Graduate School of Public Health, Yonsei University, Seoul, Korea; ¹¹Division of Genetic Epidemiology, Department of Medical Genetics, Molecular and Clinical Pharmacology, Innsbruck Medical University, Innsbruck, Austria; ¹²St Olavs Hospital, Department of Medicine, Section of Nephrology, Trondheim, Norway; ¹³Division of Nephrology, Department of Medicine, Tufts Medical Center, Boston MA, USA; ¹⁴George Institute for Global Health, Camperdown NSW, Australia; ¹⁵Division of Nephrology, Foothills Medical Centre, Calgary AB, Canada

Abstract

Objective To assess for the presence of a sex interaction in the associations of estimated glomerular filtration rate and albuminuria with all-cause mortality, cardiovascular mortality, and end stage renal disease.

Design Random effects meta-analysis using pooled individual participant data.

Setting 46 cohorts from Europe, North and South America, Asia, and Australasia.

Participants 2 051 158 participants (54% women) from general population cohorts (n=1 861 052), high risk cohorts (n=151 494), and chronic kidney disease cohorts (n=38 612). Eligible cohorts (except chronic kidney disease cohorts) had at least 1000 participants, outcomes of either mortality or end stage renal disease of ≥50 events, and baseline

measurements of estimated glomerular filtration rate according to the Chronic Kidney Disease Epidemiology Collaboration equation (mL/min/1.73 m²) and urinary albumin-creatinine ratio (mg/g).

Results Risks of all-cause mortality and cardiovascular mortality were higher in men at all levels of estimated glomerular filtration rate and albumin-creatinine ratio. While higher risk was associated with lower estimated glomerular filtration rate and higher albumin-creatinine ratio in both sexes, the slope of the risk relationship for all-cause mortality and for cardiovascular mortality were steeper in women than in men. Compared with an estimated glomerular filtration rate of 95, the adjusted hazard ratio for all-cause mortality at estimated glomerular filtration rate 45 was 1.32 (95% CI 1.08 to 1.61) in women and 1.22 (1.00 to 1.48) in men ($P_{\text{interaction}} < 0.01$). Compared with a urinary albumin-creatinine ratio

Correspondence to: A S Levey, Chronic Kidney Disease Prognosis Consortium, 615 N Wolfe Street, Baltimore, MD 21205, USA ckdpc@jhmi.edu

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Appendix 1: Acronyms or abbreviations for studies included in study. Appendix 2: Data analysis overview and analytical notes for some of the individual studies. Appendix 3: Acknowledgements and funding for collaborating cohorts.

Supplementary table: Numbers of adverse events and length of follow-up for studies included in the general population and high risk cohorts. Supplementary figures: Hazard ratios according to estimated glomerular filtration rate and albuminuria of (fig 1) all-cause mortality in chronic kidney disease cohorts; (fig 2) cardiovascular mortality in general and high risk population cohorts; (fig 3) cardiovascular mortality in chronic kidney disease cohorts; and (fig 4) end stage renal disease in general and high risk population cohorts. Hazard ratios according to estimated glomerular filtration rate of (fig 5) all-cause mortality and (fig 6) cardiovascular mortality in age categories <65 and ≥65 years in general and high risk population cohorts

of 5, the adjusted hazard ratio for all-cause mortality at urinary albumin-creatinine ratio 30 was 1.69 (1.54 to 1.84) in women and 1.43 (1.31 to 1.57) in men ($P_{\text{interaction}} < 0.01$). Conversely, there was no evidence of a sex difference in associations of estimated glomerular filtration rate and urinary albumin-creatinine ratio with end stage renal disease risk.

Conclusions Both sexes face increased risk of all-cause mortality, cardiovascular mortality, and end stage renal disease with lower estimated glomerular filtration rates and higher albuminuria. These findings were robust across a large global consortium.

Introduction

Chronic kidney disease affects 10–16% of the general adult population in Asia, Europe, Australia, and the United States.^{1–6} Chronic kidney disease, typically defined by reduced estimated glomerular filtration rate and/or albuminuria, is independently associated with an increased risk of all-cause mortality and cardiovascular mortality and progression to end stage renal disease.^{7–9} Go and colleagues found in administrative healthcare data that estimated glomerular filtration rates < 60 mL/min/1.73m² were independently associated with hospitalisations, cardiovascular events, and death.¹⁰ In a collaborative meta-analysis of general population cohorts we found that mortality rises exponentially with decreasing estimated glomerular filtration rate below 60 mL/min/1.73 m², while albuminuria shows linear association across its entire measurement range.⁸ Recent data indicate that the risk associated with estimated glomerular filtration rate is even stronger when glomerular filtration rate is estimated using the more accurate equation developed by the Chronic Kidney Disease Epidemiology Collaboration.^{11 12}

Existing data regarding potential sex differences in the risk of chronic kidney disease suggest that women have a lower incidence of end stage renal disease,^{13 14} lower cardiovascular risk,¹⁵ and (in countries with low maternal mortality) lower risk of all-cause mortality than men.¹⁶ Whether sex differences exist with respect to estimated glomerular filtration rate and albuminuria levels and adverse outcomes, and in particular whether such differences exist based on the combined effect of estimated glomerular filtration rate and albuminuria, is largely unknown.

Given the clinical uncertainty, we sought to determine if sex modifies the association between estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortalities and end stage renal disease, using a global consortium of 46 cohorts and more than two million participants.

Methods

Chronic Kidney Disease Prognosis Consortium study design

The Chronic Kidney Disease Prognosis Consortium study^{7–9 17} includes data from general population cohorts, cohorts at high risk of cardiovascular events, and cohorts with chronic kidney disease. These cohorts are described in appendices 1–3 on bmj.com. Eligible cohorts contained at least 1000 participants (except chronic kidney disease cohorts), outcomes of either mortality or end stage renal disease with a minimum of 50 events, and baseline information on estimated glomerular filtration rate and albuminuria. Measures of albuminuria included the albumin-creatinine ratio (the preferred measure),^{17–19} protein-creatinine ratio, and qualitative measures using dipstick proteinuria. Adult participants (aged ≥ 18 years) were included.

Study covariates

The equation developed by the Chronic Kidney Disease Epidemiology Collaboration was used to estimate glomerular filtration rate in mL/min/1.73 m².^{12 20} In general population and high risk cohorts, estimated glomerular filtration rate was categorised as < 15 , 15–29, 30–44, 45–59, 60–74, 75–89, 90–104, or ≥ 105 mL/min/1.73 m², according to current clinical guidelines.^{8 21} Albuminuria was categorised as “negative,” “high normal,” “mild,” or “heavy” depending on whether urinary albumin-creatinine ratio or urinary dipstick tests were available (urinary albumin-creatinine ratio < 10 , 10–29, 30–299, ≥ 300 mg/g; dipstick proteinuria negative, trace, 1+, 2+ or more). These categories were adapted for chronic kidney disease cohorts to reflect the lower levels of estimated glomerular filtration rate (categories < 15 , 15–29, 30–44, 45–74, ≥ 75 mL/min/1.73 m²) and higher levels of albuminuria or proteinuria (albumin-creatinine ratio < 30 , 30–299, 300–999, ≥ 1000 mg/g; protein-creatinine ratio < 50 , 50–499, 500–1,499, $\geq 1,500$ mg/g). To derive urinary albumin-creatinine ratio or protein-creatinine ratio in mg/mmol from the mg/g cut-off values, we divided them by 8.84. For ease of reading, we have omitted units for estimated glomerular filtration rate and urinary albumin-creatinine ratio in the remainder of this manuscript.

Demographic factors included age (continuous), sex, and ethnicity (black v non-black). Comorbidities included a history of cardiovascular disease (includes previous myocardial infarction, coronary revascularisation, heart failure, or stroke) and diabetes (fasting glucose concentration ≥ 7.0 mmol/L (≥ 126 mg/dL), non-fasting glucose concentration ≥ 11.1 mmol/L (≥ 200 mg/dL), haemoglobin A_{1c} $\geq 6.5\%$ (≥ 48 mmol/mol), use of glucose lowering drugs, or self reported diabetes). Smoking was dichotomised as current versus former or never smokers, and body mass index was calculated (weight (kg)/(height (m))²). Baseline systolic blood pressure (mm Hg) was used as a continuous variable (appendix 2 on bmj.com). Serum total cholesterol (mmol/L, continuous) was available in a subset of cohorts (appendix 2).

Study outcomes

The primary study outcomes were all-cause mortality, cardiovascular mortality, and end stage renal disease. Cardiovascular mortality was defined as death due to myocardial infarction, heart failure, stroke, or sudden cardiac death. End stage renal disease was defined as initiation of renal replacement therapy or death due to kidney disease (other than acute kidney injury).

Statistical analysis

Analysis was performed in two stages: the first was a standard analysis within each cohort using centrally developed statistical code, the second pooled results in a meta-analysis (see appendix 2). Analyses were done using Stata version 11.2.

Stage 1: within-cohort analysis

For the 44 cohorts with data from both women and men, subjects with missing baseline values for estimated glomerular filtration rate or urinary albumin-creatinine ratio or dipstick tests were excluded. Cox proportional hazards models adjusted for study covariates (age, sex, ethnicity, cardiovascular disease, diabetes, smoking, body mass index, systolic blood pressure) were used to estimate the hazard ratios for outcomes associated with estimated glomerular filtration rate, urinary albumin-creatinine ratio, protein-creatinine ratio, and dipstick proteinuria. Analyses

of the risk association with estimated glomerular filtration rate were adjusted by albuminuria, and vice versa.

For continuous analyses, linear splines of estimated glomerular filtration rate (knots at each 15 mL/min/1.73 m² from 30 to 105 (to 90 in chronic kidney disease cohorts)) and their product terms with sex were fitted. Sex-specific reference points were used (estimated glomerular filtration rate of 95 in general and high risk cohorts and 50 in chronic kidney disease cohorts). From this model, the interaction was evaluated as the ratio of hazard ratios (relative hazard ratio) in women versus men at each 1 mL/min/1.73 m² of estimated glomerular filtration rate from 15 to 120 (to 60 in chronic kidney disease cohort) ("pointwise interaction"). To visually assess the main effect of sex on estimates of risk, analyses were repeated using a single reference point of estimated glomerular filtration rate of 95 in women. Because all chronic kidney disease cohorts had mean estimated glomerular filtration rates of <55 at baseline (see table 1), a reference point of 50 was chosen.

A similar approach was used in assessing the risk associations with urinary albumin-creatinine ratio. The albumin-creatinine ratio was log transformed, and linear splines were fitted with knots at 10, 30, and 300 (30, 300, 1000 in chronic kidney disease cohorts), with a reference value at 5 (100 in chronic kidney disease cohorts because many participants had an albumin-creatinine ratio >30). Pointwise interactions of the risk association of urinary albumin-creatinine ratio with sex were assessed at approximate 8% increments of the albumin-creatinine ratio. Categorical analyses were performed using estimated glomerular filtration rate and proteinuria categories as described above. Finally, a summary interaction effect of sex was defined as the inverse variance weighed average of all the individual spline relative hazard ratios for each estimated glomerular filtration rate and urinary albumin-creatinine ratio, separately.

Stage 2: pooled analyses of cohorts

Random effects meta-analysis was used to pool the individual and summary hazard ratios from all studies. Heterogeneity was estimated by the χ^2 test and the I^2 statistic.²² Given their similar risk associations, the general population and high risk cohorts were combined. Meta-regression, with log(hazard ratio) regressed on sex, was used to estimate the effect of sex on hazard ratio, comparing any specific level of estimated glomerular filtration rate or albuminuria to reference across all 46 studies, including those conducted among only men. In all analyses, we used 95% confidence intervals, and a nominal P value<0.05 was deemed significant.

Sensitivity analyses

We repeated the primary analyses among subgroups defined by: presence or absence of diabetes²³; body mass index <30 or ≥30; age categories <65 and ≥65 years; presence or absence of baseline cardiovascular disease; and in presumed premenopausal women (ages <50 years) and postmenopausal women (ages ≥65 years).²⁴

Results

Cohort characteristics

There were 26 general population cohorts (n=1 861 052), seven high risk cohorts (n=151 494 plus subsample of the AKDN study with data on albumin-creatinine ratio (n=102 639)), and 13 chronic kidney disease cohorts (n=38 612) (table 1). Cohorts represented a range of geographical areas in Asia, Europe, North

and South America, Asia, and Australasia; average mean follow-up was 5.8 years. General population cohorts had 89 595 deaths in 10 088 864 person years follow-up, and high risk and chronic kidney disease cohorts had 13 693 and 9019 deaths in 888 386 and 149 917 person years follow-up, respectively. Only a subset of cohorts had data on cardiovascular death (supplementary table on bmj.com). Overall, women comprised 54% of the general population cohorts, 50% of the high risk cohorts, and 47% of the chronic kidney disease cohorts. Mean age was lower in the general population cohorts (48 years) than the high risk cohorts (56 years) and chronic kidney disease cohorts (68 years), with no obvious sex differences. On average, women had levels of estimated glomerular filtration rate similar to those of men and a slightly lower prevalence of albuminuria (4% of women and 5% of men in general population). Fewer women had baseline hypertension, diabetes, cardiovascular disease, hypercholesterolemia, or were smokers (supplementary table).

Sex-specific associations of estimated glomerular filtration rate and albuminuria with all-cause mortality

In the combined general population and high risk cohorts, men had a 60% higher risk of all-cause mortality than women at an estimated glomerular filtration rate of 95 (adjusted hazard ratio 1.60 (95% confidence interval 1.52 to 1.69)) (fig 1A). The adjusted hazard ratio for all-cause mortality increased with lower levels of estimated glomerular filtration rate in both sexes, but the slope of the mortality risk relationship was steeper for women than men (fig 1B). For example, the risk became significant at a higher level of estimated glomerular filtration rate in women than men (52 v 44), and the relative risk was slightly higher in women at glomerular filtration rates of ≤56 (average relative hazard ratio per 15 decrease in estimated glomerular filtration rate comparing women to men, 1.04 (95% confidence interval 1.02 to 1.07), P for interaction <0.01). Compared with a reference estimated glomerular filtration rate of 95, the adjusted hazard ratio for all-cause mortality at glomerular filtration rate 45 was 1.32 (1.08 to 1.61) in women and 1.22 (1.00 to 1.48) in men (fig 2). Categorical associations for estimated glomerular filtration rate and mortality risk were similar: compared with a reference estimated glomerular filtration rate of 90–104, women with a rate <45 had a higher mortality risk than men (table 2, last column). The results for estimated glomerular filtration rate showed less heterogeneity among general population cohorts with urinary albumin-creatinine ratio data ($I^2=34.2\%$) and among high risk cohorts ($I^2=42.9\%$) than for the cohorts with urinary dipstick data ($I^2=84.1\%$).

Similar patterns were observed in the estimates of all-cause mortality risk associated with albuminuria (fig 1, panels C and D). There was statistical evidence for interaction by sex, with a steeper increase in adjusted hazard ratio among women at urinary albumin-creatinine ratio >22 (fig 1D). Compared with a reference of albumin-creatinine ratio of 5, the adjusted hazard ratio for an albumin-creatinine ratio of 30 was 1.69 (1.54 to 1.84) in women and 1.43 (1.31 to 1.57) in men (P for interaction <0.01) (fig 3). In a categorical analysis combining cohorts measuring dipstick proteinuria, urinary albumin-creatinine ratio, and protein-creatinine ratio, the risk was present in both men and women in the high-normal category compared with normal category; however, women had a higher adjusted hazard ratio than men in each of the three clinical categories (high-normal, mild, and heavy) (table 2).

In the chronic kidney disease cohorts, men had a higher adjusted all-cause mortality risk than women (hazard ratio at estimated glomerular filtration rate of 50, 1.28 (1.18 to 1.40)). As with the general population cohorts, lower estimated glomerular filtration rate and higher albuminuria were associated with increased all-cause mortality in both sexes (supplementary fig 1, panels A and C, on bmj.com). Unlike the general population cohorts, however, the pointwise interaction terms were not significant at lower levels of estimated glomerular filtration rate (supplementary fig 1, B), nor was there a significant interaction in upper levels of urinary albumin-creatinine ratio (supplementary fig 1, D).

Sex-specific associations of estimated glomerular filtration rate and albuminuria with cardiovascular mortality

In the combined general population and high risk cohorts, men had higher cardiovascular mortality at all levels of estimated glomerular filtration rate (adjusted hazard ratio at estimated glomerular filtration rate of 95, 1.66 (1.48 to 1.86)) (see supplementary fig 2, A). Similarly, a higher cardiovascular risk was seen for men in the chronic kidney disease cohorts (supplementary fig 3, A). As with all-cause mortality, the cardiovascular mortality risk relationship was steeper for women than men. For example, reduction of estimated glomerular filtration rate by 15 was associated with a 6% higher cardiovascular risk among women when compared with same association among men (average relative hazard ratio of women v men, 1.06 (1.02 to 1.09)), with minimal heterogeneity between cohorts ($I^2=5.4\%$). In categorical analysis, an increase in cardiovascular risk was apparent for the estimated glomerular filtration rate category of 75–89 among women (hazard ratio 1.11 (1.02 to 1.21)) but not men (hazard ratio 1.02 (0.95 to 1.10)). Significant interactions (with higher hazard ratios among women compared with those among men) were found for all categories of estimated glomerular filtration rate between 15 and 60 (table 2).²

Higher levels of urinary albumin-creatinine ratio were associated with increased cardiovascular risk in the combined general population and high risk cohorts (supplementary fig 2, C and D). The slope of the risk relationship was significantly steeper in women than in men. For example, a 10-fold increase of urinary albumin-creatinine ratio was associated with an 18% higher cardiovascular risk among women (average relative hazard ratio of women v men 1.18 (1.02 to 1.36)), with mild heterogeneity between cohorts ($I^2=32.3\%$). Categorical analysis showed similar associations (table 2).²

While the overall pattern of association of estimated glomerular filtration rate with cardiovascular mortality was similar in the chronic kidney disease cohorts, this analysis was based on only 896 cardiovascular deaths (supplementary table on bmj.com). Confidence intervals were wide (supplementary fig 3, A), and there was no evidence of an interaction by sex (supplementary fig 3, B). The adjusted association of urinary albumin-creatinine ratio with cardiovascular mortality seemed flat for both men and women with wide confidence intervals (supplementary fig 3, C and D).

Sex-specific associations of estimated glomerular filtration rate and urinary albumin-creatinine ratio with end stage renal disease

Results are shown for the chronic kidney disease cohorts, which provided 71% (n=5960) of all observed instances of end stage

renal disease (n=8409) (fig 4).² Lower estimated glomerular filtration rate and higher urinary albumin-creatinine ratio were associated with increased risk of end stage renal disease in both sexes (fig 4A and 4C). The associations of estimated glomerular filtration rate with end stage renal disease overlapped for men and women, with limited evidence for interaction (P for interaction=0.27) (fig 4B). For urinary albumin-creatinine ratios between 15 and 350, women showed a slightly steeper risk relationship with end stage renal disease than men (fig 4D). For example, compared with a urinary albumin-creatinine ratio of 100, the hazard ratio associated with a ratio of 300 was 1.63 (1.33 to 1.99) in women and 1.33 (1.04 to 1.69) in men (P for interaction <0.01). There was heterogeneity in the association with end stage renal disease of estimated glomerular filtration rate ($I^2=70\%$) but not in that of the urinary albumin-creatinine ratio ($I^2=0\%$).

Results were similar in the general population and high risk cohorts. Lower estimated glomerular filtration rate and higher urinary albumin-creatinine ratio were associated with higher risk of end stage renal disease (supplementary fig 4, A and C, on bmj.com), with no evidence for sex-specific associations (supplementary fig 4, B and D).

Sensitivity analyses

There was no evidence for modification of the sex interaction by diabetes, age, obesity (data not shown), or when grouped into presumed premenopausal (<50 years old) and postmenopausal age (≥ 65 years old). In the general population and high risk cohorts, the associations of estimated glomerular filtration rate with all-cause mortality and cardiovascular mortality were more “U shaped” (with higher risk in levels of estimated glomerular filtration rate >95) in the older age group (≥ 65 years old) than in the younger age groups (supplementary figs 5 and 6). Nevertheless, in both age groups the estimated glomerular filtration rate cut-off at which estimated glomerular filtration rate reached statistical significance was higher amongst women than men. In meta-regression, including the two studies comprised solely of men did not materially change results.

When stratified by age, the point estimate of the risk relationship between urinary albumin-creatinine ratio and all-cause mortality implied a steeper association for women than men (age <65 years, relative hazard ratio 1.03 (0.98 to 1.08); age ≥ 65 years, relative hazard ratio 1.05 (1.02 to 1.09)), similar to the association of urinary albumin-creatinine ratio with cardiovascular mortality (<65 years, relative hazard ratio 1.09 (0.95 to 1.23); ≥ 65 years, relative hazard ratio 1.08 (1.00 to 1.14)).

Discussion

In this pooled analysis of over two million participants in 33 general population and high cardiovascular risk cohorts, men had a higher risk than women for all-cause mortality and cardiovascular mortality at all levels of kidney function. However, the risk relationships of reduced estimated glomerular filtration rate and higher albuminuria with mortality were steeper in women than they were in men; thus, the mortality risk associated with chronic kidney disease was at least as great among women. These results strongly refute the idea that lower estimated glomerular filtration rate and higher albuminuria are less important risk factors in women than in men. Modification of mortality risk by gender was not seen in the 13 chronic kidney disease cohorts (n=38 612), where even the main effect of sex was attenuated. The risk of progression to end stage renal disease

at a given estimated glomerular filtration rate and urinary albumin-creatinine ratio seemed equivalent in men and women.

Strengths and limitations of study

Our study has several strengths, including an international consortium, comprehensive data on estimated glomerular filtration rate and albuminuria, and a large pooled study size. The data represent a wide range of cohorts in various settings, and thus our findings may apply to a wide range of clinical and general care settings. Our analysis was centrally coordinated, and adjustment for important variables was carried out in all cohorts. Our continuous analysis using splines allowed visualisation of the association curves across the entire range of urinary albumin-creatinine ratios and estimated glomerular filtration rates.

Our study also has recognised limitations. There were no studies from the African continent, and only few black participants. The analysis was based on serum creatinine measurements and urine albumin-creatinine ratio at a single time point. Albuminuria is associated with smoking, high body mass index, diabetes, and high blood pressure, and thus the variability of albuminuria prevalence across high risk cohorts is, in part, explained by the cardiovascular risk profile of the study participants at baseline. All analyses have adjusted for albuminuria and cardiovascular risk factors at baseline. Not all assays were uniform, but every attempt was made to make chronic kidney disease measures comparable across studies (appendix 2 on bmj.com). As in all observational studies, residual confounding is possible, and we were unable to adjust for several potential confounders, including C reactive protein, serum albumin, socioeconomic status, and physical activity. However, given the strength of the associations observed, it is unlikely that residual confounding would negate our results. Some of the observed heterogeneity may be due to differences in follow-up and outcome ascertainment. Causes of death may differ between men and women, and not all causes of death are associated with chronic kidney disease (for example, accidents and certain infections²⁵), which may explain the heterogeneity in all-cause mortality. In general population cohorts with available causes of deaths, about a third of deaths were cardiovascular. There was much less heterogeneity in the cardiovascular mortality associations than the all-cause mortality associations, which was otherwise broadly similar to those for all-cause mortality.

Comparison with other studies and implications

Our results contrast with previous studies suggesting that the association of estimated glomerular filtration rate with mortality is equivalent or weaker in women.²⁶⁻²⁸ Variations in the underlying populations studied may explain some of the difference: the NHANES study follows a US cohort,²⁷ and the MRC study enrolled only people aged ≥ 75 years²⁸; and all estimated glomerular filtration rate by means of the Modification of Diet in Renal Disease (MDRD) Study equation, which may have resulted in misclassification of women with an estimated glomerular filtration rate of 45–59.²⁹ Recent studies have demonstrated the superiority of the Chronic Kidney Disease Epidemiology Collaboration equation for estimating measured glomerular filtration rate and for predicting prognosis.^{11 12 30 31} In addition, the reference groups used in the previous studies were different from the ones used here. The choice of reference can affect the estimation of interaction: choosing an estimated glomerular filtration rate >60 , for example, assumes the same risk across the range of reference estimated glomerular filtration

rate, and may blunt estimates of associations (particularly when associations are U shaped).

Some investigators have suggested different thresholds of estimated glomerular filtration rate for defining chronic kidney disease in men and women, where “normal” kidney function encompasses a lower glomerular filtration rate in women than men.^{32 33} Our results strongly contradict this assertion: the risk relationship increases more steeply at lower levels of glomerular filtration rate for women than for men. We also found a smaller increase in mortality risk at higher estimated glomerular filtration rate in women than in men. Previous studies have suggested that the increased mortality at higher estimated glomerular filtration rate (resulting in a U shaped association between glomerular filtration rate and mortality) may be attributable to frailty or low muscle mass leading to decreased creatinine generation rather than high levels of kidney function.^{11 32} Our findings suggest some sex differences in the relation of frailty or muscle mass with kidney function and mortality. It was reassuring to see that the associations of mortality and of end stage renal disease with estimated glomerular filtration rate were linear in the chronic kidney disease cohorts and among the younger participants in the general population and high risk cohorts.

Similarly, because of the generally greater concentration of urine creatinine in men, sex-specific cut points to define pathological albuminuria have been proposed.³⁴ We found a stronger association between albuminuria and mortality risk (all-cause and cardiovascular) in women than men, both in the studies measuring urinary albumin-creatinine ratio and those measuring dipstick proteinuria (which is not corrected for urine creatinine). Our results are in line with a previous study³⁵ and do not support higher thresholds for urinary albumin-creatinine ratio in women.

It is well accepted that men face a higher baseline cardiovascular risk than women.¹⁶ The reason for this is not clear, nor for our finding that this difference narrows at lower levels of estimated glomerular filtration rate and higher levels of albuminuria. Speculations as to possible explanations include differences between men and women in onset, duration, and severity of some risk factors, including diabetes, hypertension, obesity, and smoking. The observed steeper associations of chronic kidney disease with mortality risk among women may reflect more advanced microvascular disease in women and relatively lower macrovascular disease and its consequent mortality in women,¹⁶ or potential complacency in the treatment and prevention of vascular disease among women. Women experience increased early mortality after acute myocardial infarction compared with men,^{36 37} particularly in younger age groups,^{38 39} a trend some attribute to delays in or lack of administration of reperfusion therapy³⁸ or drugs used in secondary prevention.⁴⁰ Similar issues of provider complacency may pertain in chronic kidney disease in the general population.

We did not find a difference between the sexes in mortality associations within the chronic kidney disease cohorts. This may be due to selection biases^{41 42} (that is, women with chronic kidney disease dying before referral or being referred later than men), or renal care being more equal for women and men than within primary care. More simply, the choice of reference may explain why an interaction was not seen in the chronic kidney disease cohorts. The fundamental question tested differs: in the general population cohorts, we asked whether the risk of mortality associated with reduced estimated glomerular filtration rate (or higher urinary albumin-creatinine ratio) compared with normal kidney function differed between men and women. In the chronic kidney disease cohorts, our comparison group

comprised those already experiencing reduced kidney function (estimated glomerular filtration rate 50 or urinary albumin-creatinine ratio 100). While there seems to be a sex difference in risk associated with chronic kidney disease when compared with normal kidney function, risk associated with further reductions in estimated glomerular filtration rate (or increases in urinary albumin-creatinine ratio) for a person already afflicted with chronic kidney disease may not differ by sex.

In both the general population and chronic kidney disease cohorts, there was no difference by sex in the risk of end stage renal disease associated with albuminuria or reduced estimated glomerular filtration rate. Future research is needed to determine why the incidence of renal replacement therapy in men exceeds that in women.^{13 14} One potential explanation could be that in our study fewer women had albuminuria, although the prevalence of reduced estimated glomerular filtration rate (as measured by the Chronic Kidney Disease Epidemiology Collaboration equation) was similar by sex. Another possible explanation could be competing mortality. We found stronger associations of urinary albumin-creatinine ratio with all-cause and cardiovascular mortality among women than men. The hazard ratio associated with end stage renal disease does not take into account the possibility of unequal rates of mortality by sex. We had too few cohorts with both mortality data and end stage renal disease events to investigate this issue further.

Conclusions

In this pooled analysis of over two million participants, there was an increased risk of all-cause and cardiovascular mortality and end stage renal disease with lower estimated glomerular filtration rate and higher albuminuria in both sexes. In stark contrast to previous assertions that kidney disease should be defined by a lower threshold for estimated glomerular filtration rate and higher threshold for urinary albumin-creatinine ratio in women, we found the association between chronic kidney disease and mortality risk to be as strong in women as in men. Low estimated glomerular filtration rate or albuminuria should be considered at least as potent a risk factor in women as it is in men.

The Chronic Kidney Disease Prognosis Consortium (CKD-PC) investigators and collaborators: AASK—Jackson Wright, Lawrence Appel, Tom Greene, Brad C Astor; ADVANCE—John Chalmers, Stephen MacMahon, Mark Woodward, Hisatomi Arima; Aichi—Hiroshi Yatsuya, Kentaro Yamashita, Hideaki Toyoshima, Koji Tamakoshi; AKDN—Marcello Tonelli, Brenda Hemmelgarn, Aminu Bello, Matt James; ARIC—Josef Coresh, Brad C Astor, Kunihiro Matsushita, Yingying Sang; AusDiab—Robert C Atkins, Kevan R Polkinghorne, Steven Chadban; Beaver Dam CKD—Anoop Shankar, Ronald Klein, Barbara EK Klein, Kristine E Lee; Beijing Cohort—Haiyan Wang, Fang Wang, Luxia Zhang, Li Zuo; British Columbia CKD—Adeera Levin, Ognjenka Djurdjev; CARE—Marcello Tonelli, Frank M Sacks, Gary C Curhan; CHS—Michael Shlipak, Carmen Peralta, Ronit Katz, Linda Fried; CIRC—Hiroyasu Iso, Akihiko Kitamura, Tetsuya Ohira, Kazumasa Yamagishi; COBRA—Tazeen H Jafar, Muhammad Islam, Juanita Hatcher, Neil Poulter, Nish Chaturvedi; CRIB—Martin J Landray, Jonathan Emberson, John N Townend, David C Wheeler; ESTHER—Dietrich Rothenbacher, Hermann Brenner, Heiko Müller, Ben Schöttker; Framingham—Caroline S Fox, Shih-Jen Hwang, James B Meigs; Geisinger—Robert M Perkins; GLOMMS-1 Study—Nick Fluck, Laura E Clark, Gordon J Prescott, Angharad Marks, Corri Black; Gubbio—Massimo Cirillo; HUNT—Stein Hallan, Knut Aasard, Cecilia M Øien, Marie Radtke; IPHS—Fujiko Irie, Hiroyasu Iso, Toshimi Sairenchi, Kazumasa Yamagishi; Kaiser Permanente NW—David H Smith, Jessica W Weiss, Eric S Johnson,

Micah L Thorp; KEEP—Allan J Collins, Joseph A Vassalotti, Suying Li, Shu-Cheng Chen; KP Hawaii—Brian J Lee; MASTERPLAN—Jack F Wetzels, Peter J Blankestijn, Arjan D van Zuijlen; MDRD—Mark Sarnak, Andrew S Levey, Vandana Menon; MESA—Michael Shlipak, Mark Sarnak, Carmen Peralta, Ronit Katz, Holly J Kramer, Ian H de Boer; MMKD—Florian Kronenberg, Barbara Kollerits, Eberhard Ritz; MRC Older People—Paul Roderick, Dorothea Nitsch, Astrid Fletcher, Christopher Bulpitt; MRFIT—Areef Ishani, James D Neaton; NephroTest—Marc Froissart, Benedicte Stengel, Marie Metzger, Jean-Philippe Haymann, Pascal Houillier, Martin Flamant; NHANES III—Brad C Astor, Josef Coresh, Kunihiro Matsushita; Ohasama—Takayoshi Ohkubo, Hirohito Metoki, Masaaki Nakayama, Masahiro Kikuya, Yutaka Imai; Okinawa 83/93—Kunitoshi Iseki; Pima Indian—Robert G Nelson, William C Knowler; PREVEND—Ron T Gansevoort, Paul E de Jong, Bakhtawar K Mahmoodi, Hans Hillege; Rancho Bernardo—Simerjot Kaur Jassal, Elizabeth Barrett-Connor, Jaclyn Bergstrom; RENAAL—Hiddo J Lambers Heerspink, Barry E Brenner, Dick de Zeeuw; Renal REGARDS—David G Warnock, Paul Muntner, Suzanne Judd, William McClellan; Severance—Sun Ha Jee, Heejin Kimm, Jaeseong Jo, Yejin Mok, Eunmi Choi; STENO—Peter Rossing, Hans-Henrik Parving; Sunnybrook—Navdeep Tangri, David Naimark; Taiwan GP—Chi-Pang Wen, Sung-Feng Wen, Chwen-Keng Tsao, Min-Kuang Tsai; ULSAM—Johan Ärnlöv, Lars Lannfelt, Anders Larsson; ZODIAC—Henk J Bilo, Hanneke Joosten, Nanno Kleefstra, Klaas H Groenier, Iefke Drion.

CKD-PC Steering Committee: Brad C Astor, Josef Coresh (chair), Ron T Gansevoort, Brenda R Hemmelgarn, Paul E de Jong, Andrew S Levey, Adeera Levin, Kunihiro Matsushita, Chi-Pang Wen, Mark Woodward.

CKD-PC Data Coordinating Center: Shoshana H Ballew (coordinator), Josef Coresh (principal investigator), Morgan Grams, Bakhtawar K Mahmoodi, Kunihiro Matsushita (director), Yingying Sang (lead programmer), Mark Woodward (senior statistician); Administrative support: Laura Camarata, Xuan Hui, Jennifer Seltzer, Heather Winegrad.

Contributors: All authors had full access to the analysis reports and tables and take responsibility for the integrity of the data and the accuracy of the data analysis. The CKD-PC contributed to all aspects of the study. Conception and design: DN, MG, BRH, ASL. Analysis and interpretation of the data: DN, MG, YS, MW, BRH. Critical revision of the article for important intellectual content, and final approval of the article: all authors. Statistical expertise: YS, MW. Obtaining of funding: J Coresh for the CKD Prognosis Consortium. Administrative, technical, or logistic support: MG, YS. Collection and assembly of data: YS.

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What is already known on this topic

Reduced estimated glomerular filtration rate and albuminuria are both independently associated with an increased risk of all-cause mortality and cardiovascular mortality and progression to end stage renal disease

In the US and the UK, women have lower incident rates of starting dialysis than men

What this study adds

Using data from a global consortium of cohort studies, we found that the risks for mortality were higher in men than in women at all levels of estimated glomerular filtration rate and albuminuria. However, the slope of the associations with lower estimated glomerular filtration rate and higher albuminuria were steeper for women than men

Thus, compared with normal levels of estimated glomerular filtration rate and urinary albumin-creatinine ratio, the mortality risk associated with chronic kidney disease was slightly higher in women than men

The risk for end stage renal disease at a given estimated glomerular filtration rate and urinary albumin-creatinine ratio was equivalent between men and women

Data sharing: CKD-PC has agreed with collaborating cohorts not to share data outside the consortium. Each participating cohort has its own policy for data sharing.

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Tables

Table 1 | Descriptive characteristics of cohorts included in meta-analysis of sex-specific associations of chronic kidney disease with mortality and end stage renal disease. Results for men and women are separated by a solidus unless stated otherwise

Study	Region	No of participants (% women)	Men/women				
			Mean (SD) age (years)	% with diabetes	% with hypertension	Mean (SD) eGFR	% with albuminuria*
General population cohorts							
Aichi	Japan	4731 (20)	49 (7)/47 (7)	7/3	28/16	96 (14)/102 (14)	3/1
AKDN (Dip)	Canada	920 686 (56)	50 (16)/48 (17)	9/6	23/21	84 (19)/86 (21)	5/4
ARIC†	USA	11 441 (56)	63 (6)/62 (6)	18/16	46/49	84 (15)/85 (16)	9/8
AusDiab†	Australia	11 179 (55)	52 (14)/51 (15)	10/7	36/29	86 (16)/86 (18)	7/7
Beaver Dam CKD Study	USA	4857 (56)	61 (11)/63 (11)	10/10	50/51	81 (17)/78 (19)	6/3
Beijing†	China	1559 (50)	62 (9)/58 (10)	29/27	60/52	83 (14)/83 (15)	5/6
CHS†	USA	2988 (59)	78 (5)/78 (5)	18/14	58/67	73 (18)/75 (17)	24/18
CIRCS	Japan	11 871 (61)	54 (9)/54 (9)	7/3	41/33	89 (14)/89 (15)	4/2
COBRA†	Pakistan	2872 (52)	52 (11)/51 (11)	19/23	35/52	101 (17)/105 (18)	9/10
ESTHER	Germany	9641 (55)	62 (7)/62 (7)	22/17	62/58	85 (20)/83 (20)	15/9
Framingham†	USA	2956 (53)	59 (10)/58 (10)	12/8	43/37	88 (19)/88 (18)	11/13
Gubbio†	Italy	1681 (55)	54 (6)/55 (6)	7/4	39/40	89 (10)/81 (11)	3/5
HUNT†	Norway	9659 (55)	61 (14)/63 (15)	19/16	83/82	87 (19)/84 (20)	15/10
IPHS	Japan	95 451 (66)	61 (10)/58 (10)	8/4	56/46	85 (13)/86 (14)	3/2
MESA†	USA	6733 (53)	62 (10)/62 (10)	14/11	43/47	83 (16)/82 (17)	10/9
MRC	UK	12 371 (61)	81 (4)/81 (5)	10/7	72/79	60 (14)/55 (15)	9/7
NHANES III†	USA	15 563 (53)	47 (20)/46 (19)	12/11	30/28	98 (24)/102 (25)	11/12
Ohasama	Japan	1956 (64)	65 (10)/62 (10)	10/10	46/37	84 (14)/83 (13)	10/6
Okinawa83	Japan	9599 (60)	47 (15)/54 (16)	NA/NA	NA/NA	79 (16)/73 (17)	21/20
Okinawa93	Japan	93 216 (57)	53 (16)/56 (15)	NA/NA	NA/NA	79 (16)/76 (18)	4/3
PREVEND†	Netherlands	8385 (50)	50 (13)/48 (12)	4/3	39/27	90 (16)/87 (15)	13/10
RanchoBernardo†	USA	1474 (60)	70 (11)/71 (12)	15/10	54/56	74 (16)/73 (18)	13/16
REGARDS†	USA	27 306 (54)	66 (9)/64 (9)	22/20	58/60	84 (19)/86 (21)	17/14
Severance	Korea	76 201 (49)	45 (12)/46 (12)	7/5	26/24	88 (14)/92 (15)	7/4
ULSAM†	Sweden	1103 (0)	71 (1)/NA	19/NA	75/NA	76 (11)/NA	16/NA
Taiwan	Taiwan	515 573 (50)	41 (14)/42 (14)	5/5	18/16	90 (17)/96 (18)	2/2
General population total		1 861 052 (54)	48/48	8/6	25/24	86/88	5/4
High cardiovascular risk cohorts							
ADVANCE†	Multiple¶	10 595 (42)	66 (7)/66 (6)	100/100	81/84	80 (16)/76 (18)	31/30
AKDN (ACR)†§	Canada	102 639 (45)	57 (14)/57 (16)	56/52	48/53	78 (20)/76 (22)	26/24
CARE	Canada	4098 (14)	58 (9)/61 (9)	13/20	84/91	77 (16)/71 (17)	13/15
KEEP	USA	77 902 (68)	55 (15)/54 (15)	31/29	69/64	84 (22)/87 (24)	13/12
KP Hawaii‡	USA	39 884 (50)	58 (15)/59 (15)	50/46	NA/NA	79 (23)/80 (24)	34/33
MRFIT	USA	12 854 (0)	46 (6)/NA	5/NA	66/NA	87 (13)/NA	4/NA
Pima†	USA	5066 (56)	33 (14)/33 (15)	26/27	24/12	120 (18)/120 (20)	18/22
ZODIAC†	Netherlands	1095 (57)	66 (12)/69 (11)	100/100	83/90	76 (18)/66 (17)	41/38
High risk total		254 133 (50)	56/56	45/43	58/59	81/82	22/12
General population and high risk total		2 012 546 (54)	49/49	10/8	28/27	86/ 88	6/5
Chronic kidney disease cohorts							
AASK‡	USA	1094 (14)	54 (11)/55 (11)	0/0	100/100	46 (15)/44 (15)	61/63

Table 1 (continued)

Study	Region	No of participants (% women)	Men/women				
			Mean (SD) age (years)	% with diabetes	% with hypertension	Mean (SD) eGFR	% with albuminuria*
BC CKD†	Canada	17 426 (45)	69 (14)/70 (14)	41/35	81/80	37 (19)/36 (19)	79/71
CRIB†	UK	308 (34)	63 (13)/60 (16)	16/19	95/94	24 (12)/19 (10)	85/89
Geisinger ACR†	USA	3361 (54)	70 (10)/70 (10)	96/96	87/89	51 (9)/51 (8)	49/38
Geisinger dipstick	USA	4509 (61)	72 (11)/72 (11)	30/25	78/75	49 (11)/49 (10)	31/22
GLOMMS-1 ACR†	Scotland	537 (51)	72 (11)/74 (10)	92/93	64/64	35 (8)/30 (7)	54 /47
GLOMMS-1 PCR‡	Scotland	470 (48)	68 (15)/72 (15)	22/22	63/58	30 (10)/28 (9)	96/95
KPNW	USA	1627 (56)	71 (10)/72 (10)	39/38	91/93	46 (11)/47 (12)	38/26
MASTERPLAN†	Netherlands	636 (31)	62 (12)/58 (14)	37/30	96/94	37 (15)/35 (13)	85/84
MDRD‡	USA	1730 (40)	52 (13)/50 (13)	7/5	NA/NA	40 (20)/41 (22)	82/82
MMKD‡	Multiple**	202 (34)	48 (12)/44 (13)	0/0	89/88	49 (29)/44 (32)	95/94
NephroTest†	France	928 (31)	60 (158)/59 (15)	27/24	94/90	42 (20)/42 (22)	65/61
RENAAL†	Multiple††	1513 (37)	60 (8)/60 (7)	100/100	96/98	44 (13)/36 (12)	100/100
STENO†	Denmark	886 (43)	43 (11)/44 (11)	100/100	65/63	89 (27)/80 (25)	53/45
Sunnybrook†	Canada	3385 (44)	71 (13)/70 (15)	55/47	86/84	38 (15)/36 (17)	85/82
Chronic kidney disease total		38 612 (47)	67/68	46/43	84/82	42/41	72/59

eGFR=estimated glomerular filtration rate. NA=not assessed. Study acronyms and abbreviations listed in appendix 1 on bmj.com.

*Albuminuria defined as urine albumin-creatinine ratio ≥ 30 mg/g or urine protein-creatinine ratio ≥ 50 mg/g or urine dipstick protein $\geq 1+$.

†Studies with urine albumin-creatinine ratio.

‡Studies with urine protein-creatinine ratio.

§All participants included in AKDN (Dip), thus not included in the general population and high risk total, and only used for albumin-creatinine ratio analysis

¶Canada, China, Czech Republic, France, Germany, Hungary, Italy, Malaysia, Netherlands, New Zealand, Russia, Slovakia, United Kingdom, Australia, Estonia, India, Ireland, Lithuania, Philippines, Poland

**German speaking Alpine regions.

††Canada, China, Czech Republic, France, Germany, Hungary, Italy, Malaysia, Netherlands, New Zealand, Russia, Slovakia, United Kingdom, Argentina, Austria, Brazil, Chile, Costa Rica, Denmark, Israel, Japan, Mexico, Peru, Portugal, Singapore, Spain, United States of America, Venezuela.

Table 2| Adjusted hazard ratios of sex-specific categorical analysis of associations of estimated glomerular filtration rate (eGFR) and albuminuria with all-cause mortality and cardiovascular mortality in general population cohorts and high risk cohorts (including the studies with available urine dipstick data). Values are hazard ratios (95% confidence intervals) relative to the reference cell category of eGFR 90–104. The marginal associations of eGFR are in the rightmost column, and those for albuminuria are in the bottom rows for the two sections, each adjusted for each other

eGFR	Albuminuria								Marginal association for eGFR	
	ACR <10, dipstick –		ACR 10–29, dipstick ±		ACR 30–299, dipstick 1+		ACR ≥300, dipstick ≥2+		Men	Women
	Men	Women	Men	Women	Men	Women	Men	Women		
All-cause mortality										
>105	1.40 (1.15 to 1.71)*	1.24 (1.08 to 1.43)*†	1.99 (1.41 to 2.82)*	1.72 (1.15 to 2.57)*†	3.02 (2.18 to 4.17)*	2.80 (1.86 to 4.22)*	5.11 (3.41 to 7.67)*	5.56 (4.07 to 7.60)*	1.34 (1.13 to 1.60)*	1.11 (0.97 to 1.28)*†
90–104	Reference		1.52 (1.27 to 1.81)*	1.61 (1.29 to 2.01)*	1.75 (1.56 to 1.98)*	2.15 (1.73 to 2.67)*†	3.13 (2.45 to 4.01)*	4.05 (3.07 to 5.33)*†	—	—
75–89	0.87 (0.79 to 0.96)	0.96 (0.88 to 1.05)*†	1.33 (1.22 to 1.46)*	1.43 (1.26 to 1.63)*	1.58 (1.40 to 1.79)*	1.92 (1.68 to 2.20)*†	2.39 (1.98 to 2.89)*	3.04 (2.38 to 3.88)*†	0.89 (0.81 to 0.98)*	0.95 (0.88 to 1.03)*†
60–74	0.98 (0.86 to 1.13)	1.02 (0.89 to 1.18)*†	1.30 (1.15 to 1.47)*	1.56 (1.41 to 1.72)*†	1.77 (1.52 to 2.07)*	2.15 (1.93 to 2.40)*†	2.46 (2.02 to 2.99)*	3.41 (2.74 to 4.23)*†	1.00 (0.87 to 1.14)	1.02 (0.89 to 1.17)*†
45–59	1.17 (0.97 to 1.41)	1.13 (0.94 to 1.36)	1.57 (1.32 to 1.87)*	1.83 (1.52 to 2.20)*	1.93 (1.62 to 2.31)*	2.33 (1.97 to 2.75)*†	2.83 (2.28 to 3.51)*	3.55 (2.80 to 4.51)*†	1.16 (0.98 to 1.38)	1.12 (0.94 to 1.33)
30–44	1.51 (1.23 to 1.86)*	1.86 (1.42 to 2.44)*†	2.22 (1.75 to 2.83)*	2.41 (1.90 to 3.05)*	2.58 (2.14 to 3.12)*	3.25 (2.59 to 4.07)*†	3.74 (2.89 to 4.83)*	4.62 (3.51 to 6.07)*†	1.46 (1.21 to 1.77)*	1.59 (1.27 to 2.00)*†
15–29	2.84 (1.90 to 4.23)*	3.30 (2.29 to 4.74)*	3.52 (2.34 to 5.29)*	3.85 (2.64 to 5.60)*	3.98 (2.87 to 5.53)*	4.60 (3.47 to 6.11)*	5.35 (4.07 to 7.03)*	7.19 (5.38 to 9.60)*†	2.14 (1.70 to 2.71)*	2.54 (1.95 to 3.31)*†
<15	4.55 (2.38 to 8.67)*	7.41 (3.71 to 14.80)*	11.54 (7.05 to 18.90)*	7.15 (4.36 to 11.74)*	7.29 (3.52 to 15.08)*	9.75 (7.14 to 13.32)*†	11.64 (8.58 to 15.79)*	16.07 (10.44 to 24.72)*†	3.92 (3.09 to 4.97)*	4.93 (3.97 to 6.13)*†
Marginal association for albuminuria	—	—	1.31 (1.21 to 1.46)*	1.41 (1.27 to 1.57)*†	1.66 (1.51 to 1.82)*	1.85 (1.64 to 2.09)*†	2.41 (2.16 to 2.70)*	2.86 (2.45 to 3.34)*†	—	—
Cardiovascular mortality										
>105	1.31 (1.02 to 1.70)*	1.09 (0.78 to 1.53)	1.81 (1.07 to 3.06)*	2.55 (1.25 to 5.17)*	4.45 (2.70 to 7.33)*	3.00 (1.78 to 5.06)*	5.73 (2.07 to 15.89)*	9.76 (3.07 to 30.97)*	1.30 (1.04 to 1.63)*	1.00 (0.77 to 1.29)
90–104	Reference		1.65 (1.29 to 2.12)*	1.72 (1.34 to 2.21)*	1.72 (1.37 to 2.17)*	2.21 (1.65 to 2.94)*	3.57 (2.36 to 5.38)*	4.14 (2.67 to 6.43)*	—	—
75–89	1.01 (0.93 to 1.10)	1.13 (1.02 to 1.24)*	1.59 (1.37 to 1.86)*	1.61 (1.31 to 1.97)*	1.83 (1.48 to 2.26)*	2.12 (1.71 to 2.63)*	3.13 (2.29 to 4.28)*	3.14 (2.31 to 4.26)*	1.02 (0.95 to 1.10)	1.11 (1.02 to 1.21)*
60–74	1.16 (1.06 to 1.27)*	1.27 (1.15 to 1.40)*	1.55 (1.32 to 1.82)*	1.89 (1.55 to 2.30)*	2.27 (1.92 to 2.68)*	2.53 (2.07 to 3.08)*	2.85 (2.12 to 3.84)*	3.67 (2.43 to 5.54)*	1.15 (1.06 to 1.24)*	1.27 (1.16 to 1.38)*
45–59	1.55 (1.39 to 1.73)*	1.47 (1.18 to 1.83)*	2.05 (1.71 to 2.47)*	2.32 (1.87 to 2.87)*	2.41 (1.84 to 3.16)*	3.20 (2.61 to 3.92)*†	3.48 (2.66 to 4.55)*	4.34 (3.27 to 5.76)*	1.45 (1.32 to 1.59)*	1.60 (1.36 to 1.87)*†
30–44	2.04 (1.71 to 2.45)*	2.92 (2.39 to 3.55)*†	3.52 (2.54 to 4.88)*	2.77 (1.62 to 4.73)*	3.20 (2.54 to 4.03)*	4.44 (3.25 to 6.05)*†	4.74 (3.71 to 6.04)*	5.83 (4.35 to 7.80)*	1.90 (1.68 to 2.16)*	2.37 (1.94 to 2.90)*†
15–29	9.82 (4.17 to 23.13)*	4.81 (2.92 to 7.93)*	6.20 (2.90 to 13.23)*	5.56 (2.58 to 11.99)*	4.43 (2.60 to 7.53)*	5.57 (3.34 to 9.29)*	6.66 (4.02 to 11.03)*	9.59 (6.79 to 13.54)*	2.43 (1.84 to 3.22)*	3.58 (2.64 to 4.86)*†
<15	9.75 (2.79 to 34.07)*	4.55 (0.83 to 24.92)	20.90 (9.24 to 47.25)*	6.46 (1.57 to 26.62)*	5.91 (2.94 to 11.86)*	14.23 (6.88 to 29.45)*	12.15 (6.22 to 23.73)*	8.76 (5.13 to 14.99)*	4.54 (2.42 to 8.50)*	4.09 (2.74 to 6.11)*
Marginal association for albuminuria	—	—	1.43 (1.33 to 1.53)*	1.44 (1.33 to 1.57)*	1.68 (1.46 to 1.93)*	2.02 (1.73 to 2.36)*†	2.21 (1.87 to 2.61)*	2.94 (2.25 to 3.85)*†	—	—

ACR= urinary albumin-creatinine ratio. Dipstick= dipstick proteinuria.

*Associations that reach P<0.05 compared with the reference category.

†Interactions with sex that reach P<0.05.

Figures

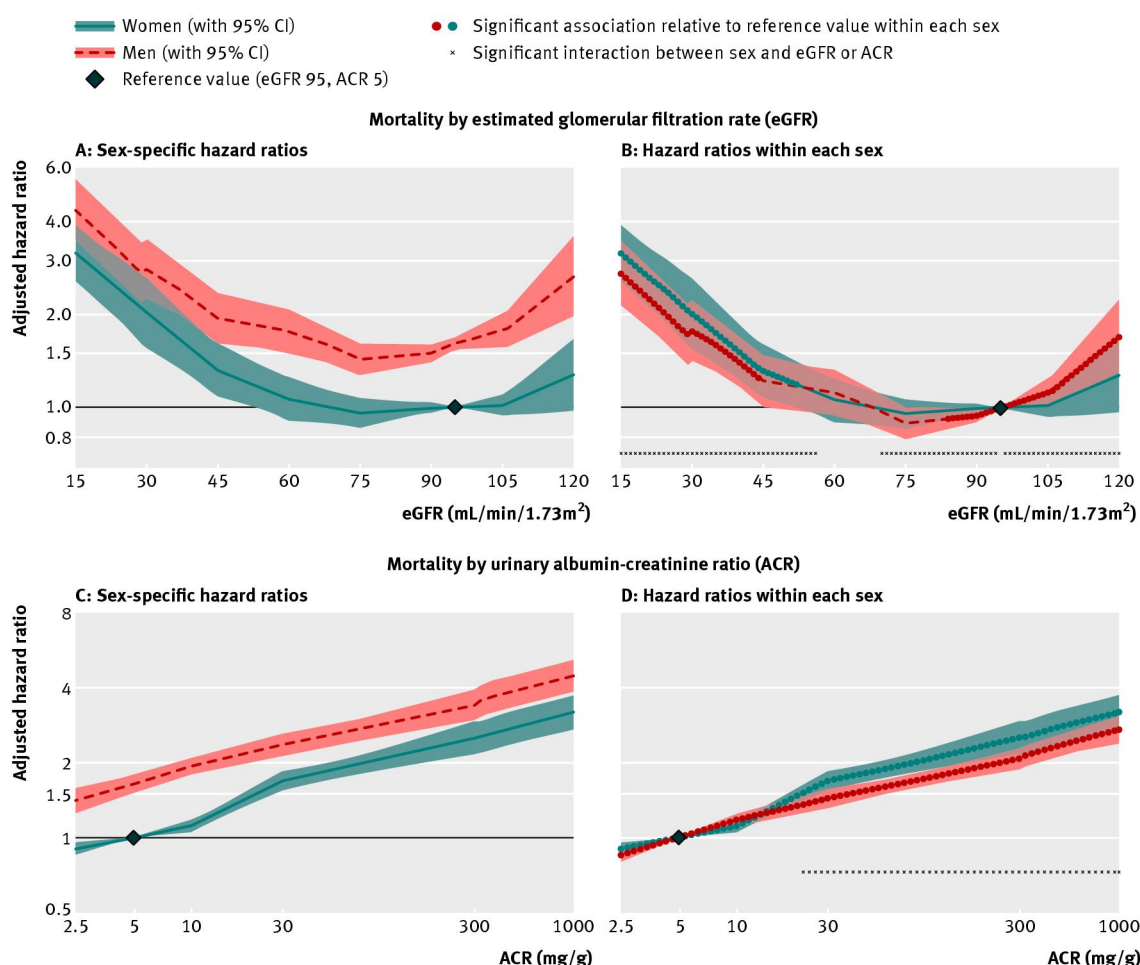


Fig 1 Hazard ratios of all-cause mortality according to estimated glomerular filtration rate (A and B) and urinary albumin-creatinine ratio (C and D) in men versus women in general population cohorts and high cardiovascular risk cohorts. Panels A and C show sex-specific hazard ratios including a main effect for male sex at the reference point. Panels B and D show hazard ratios within each sex, thus visually removing the baseline difference between men and women. Hazard ratios were adjusted for age, sex, race, smoking status, systolic blood pressure, history of cardiovascular disease, diabetes, serum total cholesterol concentration, body mass index, and estimated glomerular filtration rate splines or albuminuria

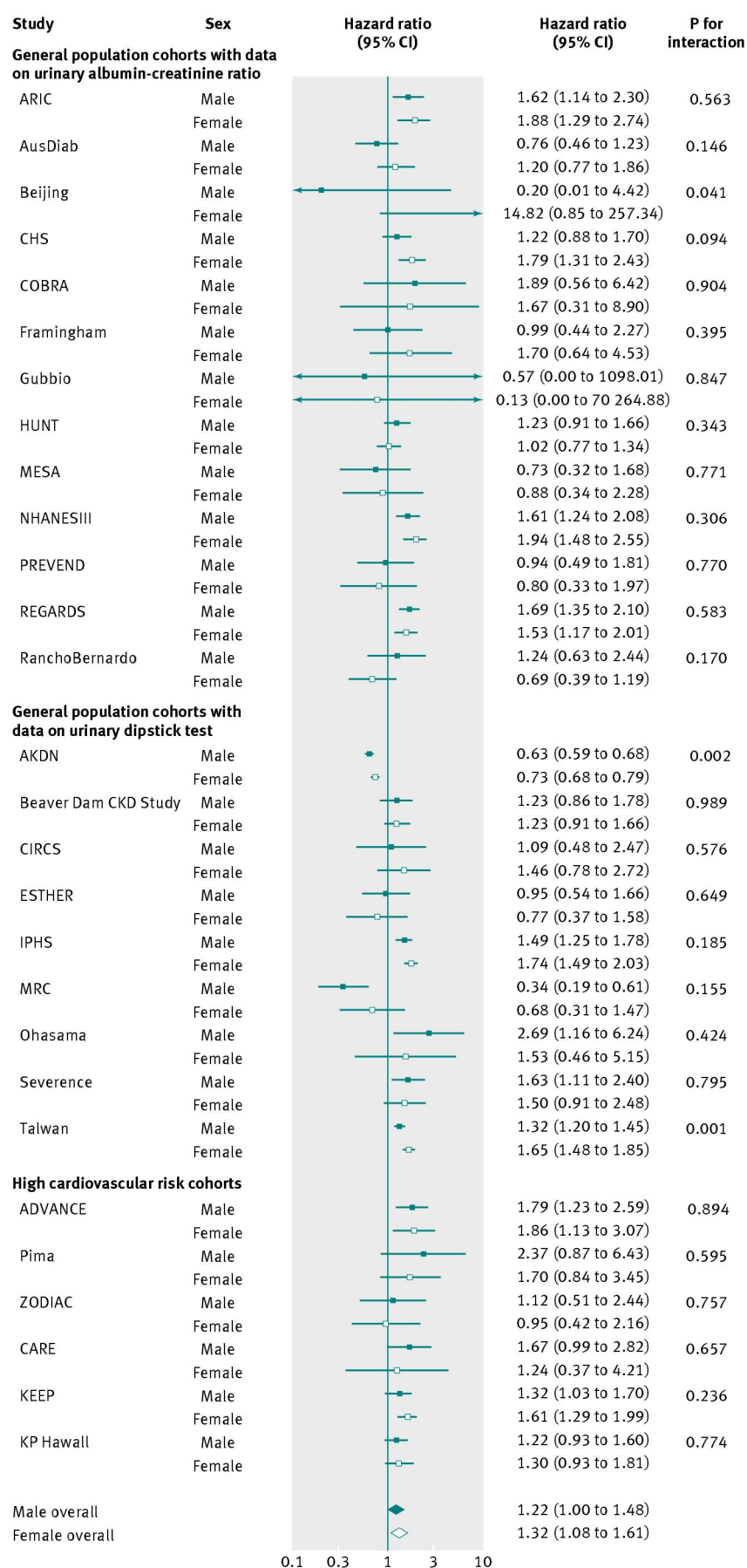


Fig 2 Hazard ratios of all-cause mortality at estimated glomerular filtration rate of 45 (v rate of 95) in women and men per study. Hazard ratios were adjusted for age, sex, race, smoking status, systolic blood pressure, history of cardiovascular disease, diabetes, serum total cholesterol concentration, body mass index, and albuminuria

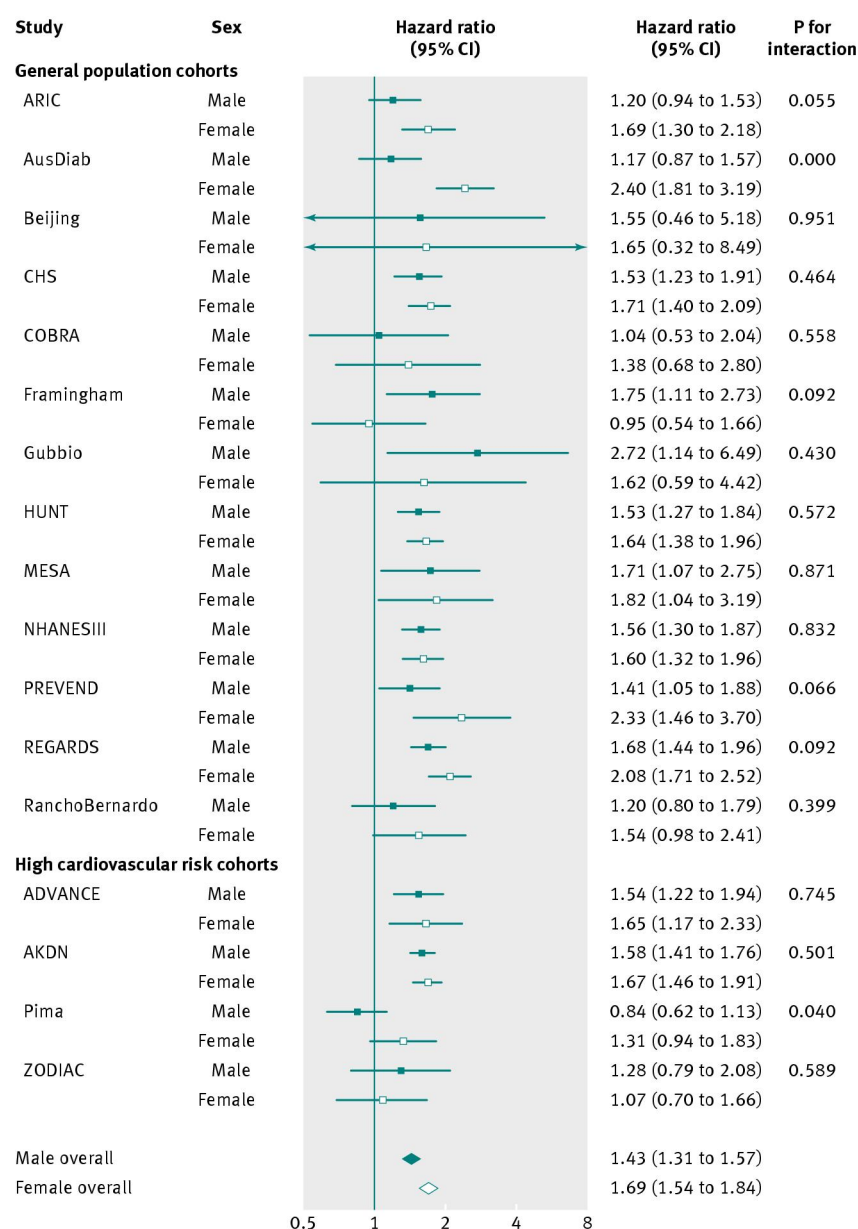


Fig 3 Hazard ratios of all-cause mortality at urinary albumin-creatinine ratio of 30 (v ratio of 5) in women and men per study. Hazard ratios were adjusted for age, sex, race, smoking status, systolic blood pressure, history of cardiovascular disease, diabetes, serum total cholesterol concentration, body mass index, and estimated glomerular filtration rate splines.

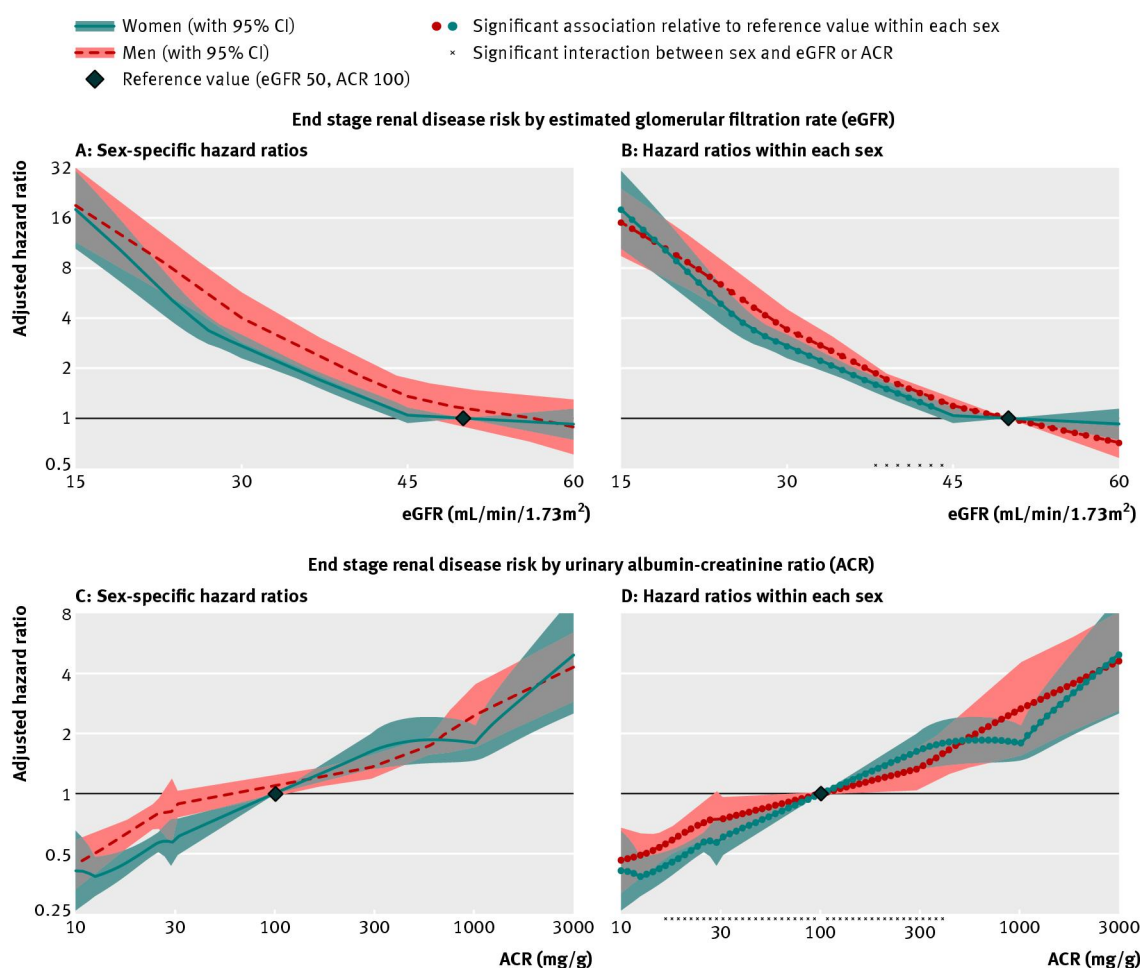


Fig 4 Hazard ratios of end stage renal disease according to estimated glomerular filtration rate (A and B) and urinary albumin-creatinine ratio (C and D) in men versus women in chronic kidney disease cohorts. Panels A and C show sex-specific hazard ratios including a main effect for male sex at the reference point. Panels B and D show hazard ratios within each sex, thus visually removing the baseline difference between men and women. Hazard ratios were adjusted for age, sex, race, smoking status, systolic blood pressure, history of cardiovascular disease, diabetes, serum total cholesterol concentration, body mass index, and estimated glomerular filtration rate splines or albuminuria