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Original Article

Associations between sex and incident chronic kidney disease in a prospective diabetic cohort

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SUMMARY AT A GLANCE

The authors have evaluated associations between sex and chronic kidney disease (CKD) incidence in a primary care population with diabetes using Chronic Kidney Disease-Epidemiology equations for estimating glomerular filtration rate (GFR) and sex-specific definitions of microalbuminuria. They found that women had an increased risk of incident CKD compared with men. They also found that this difference in incident CKD was primarily driven by differences in incident eGFR < 60 mL/min per 1.73 m^2.

ABSTRACT:

Aim: **Women with diabetes have a higher prevalence of chronic kidney disease (CKD) risk factors compared with men, but whether they are at higher risk for incident CKD remains uncertain.**

Methods: **This was a prospective, observational cohort study of 1464 patients with diabetes and normal renal function, recruited from primary care clinics at a vertically integrated healthcare system in Seattle, WA, USA. The primary predictor was sex. Incident CKD was defined by an estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m^2 by Chronic Kidney Disease-Epidemiology equations or sex-specific microalbuminuria (urine albumin/creatinine ratio ≥25 mg/g for women or ≥17 mg/g for men).**

Results: **Of the 1464 patients (52.0% women), CKD incidence rates were 154.0 and 144.3 cases per 1000 patient-years for women and men, respectively. In the competing risks regression, women had an increased risk of incident CKD (sub-hazard ratio 1.37, 95% confidence interval (CI) 1.17, 1.60) compared with men after adjustment for demographics, baseline eGFR and duration of diabetes, which persisted after additional adjustment for CKD risk factors, depressive symptoms and diabetes self-care (sub-hazard ratio 1.35, 95% CI 1.15, 1.59). Sex differences in incident CKD were consistent across age groups and appeared to be driven by differences in the development of low eGFR rather than microalbuminuria.**

Conclusion: **Women with diabetes had a higher risk of incident CKD compared with men, which could not be entirely explained by differences in biologic CKD risk factors, depression or diabetes self-care. Additional work is needed determine if these sex differences contribute to worse outcomes in women with diabetes.**

Diabetes mellitus is a leading cause of kidney failure,[1] and strategies to prevent chronic kidney disease (CKD) in these patients include optimizing glycaemic control, blood pressure and the use of medications to block the renin-angiotensin-aldosterone system. Ideally, these strategies would be applied universally to all patients with diabetes; however, studies from the United States[2,3] and Germany[4] have demonstrated that women with diabetes are less likely than men to attain these clinical targets or receive recommended medications. Women with diabetes also have a high prevalence of dyslipidaemia,[2,3,5,6] obesity,[6] physical inactivity[5] and depression,[7] which are each associated with an increased risk for CKD.[8,9] However, whether women with diabetes have a greater risk than men for incident CKD remains unclear.

Prospective cohort studies in patients with diabetes have generally found that men had a greater risk of incident CKD than women;[10–14] however, these studies were not designed to examine sex differences and are limited in several ways. First, mortality was not accounted for as a competing event, which is relevant because diabetic men have a shorter life expectancy than women.[15] Second, most studies did not use sex-specific microalbuminuria cut-offs,[10–12] which account for sex differences in urine creatinine concentrations.[16]

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Third, CKD incidence was determined by incident albuminuria alone[10] or older methods of estimating glomerular filtration rate (GFR) such as the change in the reciprocal serum creatinine,[11] Cockcroft-Gault equation[12] or Modification of Diet in Renal Disease (MDRD) Study equation,[13] which are less accurate than the Chronic Kidney Disease-Epidemiology (CKD-EPI) equations in patients without CKD,[17] women[18] and the elderly.[19] Furthermore, eGFR calculated by CKD-EPI equations is superior to the MDRD equation for predicting the risk of end-stage renal disease (ESRD) and mortality.[20] Fourth, patients over 65 years of age, an important demographic for CKD, were not included in most previous analyses.[10–12] Since older women with diabetes have a high prevalence of CKD risk factors[6] and cardiovascular risk increases in women after menopause,[21] associations between sex and incident CKD may be modified by age. Finally, no prior study assessed depressive symptoms or diabetes self-care activities, which differ by sex[5,7,9] and are associated with increased CKD risk.

The purpose of this study is to evaluate associations between sex and CKD incidence in a primary care population with diabetes using CKD-EPI equations for estimating GFR and sex-specific definitions of microalbuminuria. We hypothesized that after taking into account death as a competing event, women would have a greater risk than men for incident CKD due to their higher prevalence of CKD risk factors, including depressive symptoms and poorer diabetes self-care.

METHODS

Study design and participants

The Pathways Study is a prospective, observational cohort study of associations between depression and diabetes outcomes.[22] Participants were recruited from Group Health (GH), a large vertically integrated managed care organization in Washington and Idaho, USA. Between 2001 and 2002, surveys regarding diabetes history and depression were mailed to 9063 potential subjects identified from the GH diabetes registry of selected primary care clinics near Seattle, Washington, USA (Fig. 1). Patients were eligible for this study if they had diabetes mellitus type 1 or 2 and received medical care at GH. Ineligibility criteria included inability to provide study consent or complete the study questionnaire and plans to move away from Seattle or disenroll from GH. Of the 7841 eligible patients for the study, 4839 (61.7%) returned the survey, of which 4128 (85.3%) gave permission to access GH automated data regarding clinical encounters and laboratory results. Study data linkage was deterministic. Baseline eGFR and albuminuria were defined by the average laboratory values in the 18 months prior to study enrolment. Subjects were excluded from the current analysis if they died ($n = 2$) or disenrolled ($n = 19$) before study entry, had missing baseline serum creatinine ($n = 464$), or were known to have baseline CKD (eGFR < 60 mL/min per 1.73 m^2 or sex-specific microalbuminuria) or ESRD ($n = 2323$). The final analytic cohort ($n = 1464$) was followed until the onset of incident CKD, death, GH disenrollment or the end of the 10-year study period (August 15, 2012). GH and University of Washington institutional review boards approved the study protocol.

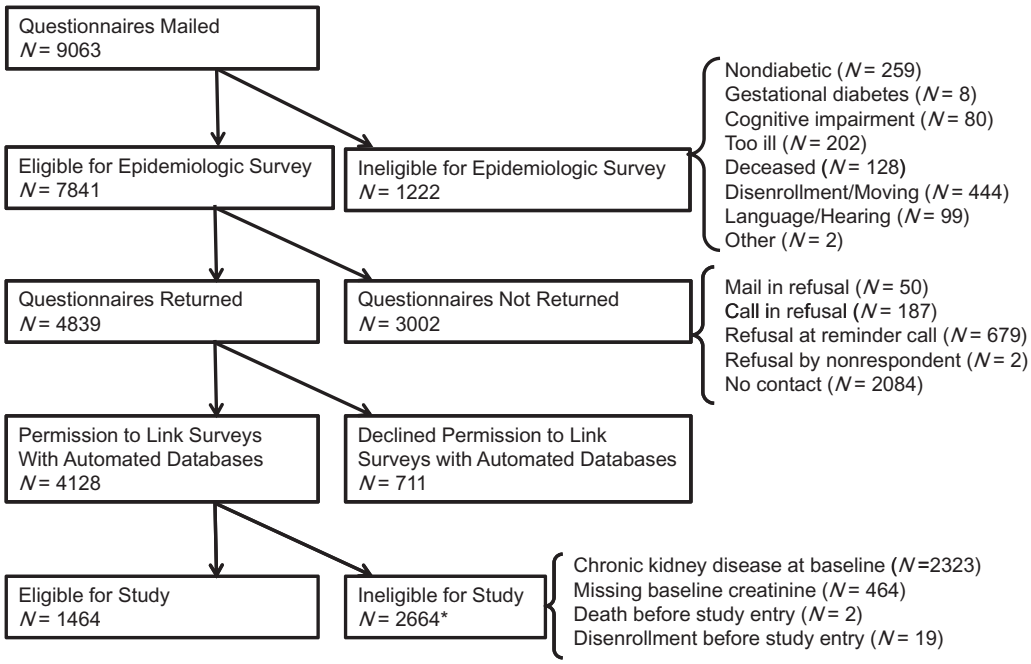

Fig. 1 Pathways Study subject recruitment. *Components add up to more than the total *N* due to overlap.

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Primary predictor and outcome

The primary predictor was self-reported sex. The primary outcome was incident CKD, as defined by the first measurement of an eGFR < 60 mL/min per 1.73 m^2 by CKD-EPI equations[17] or sex-specific microalbuminuria (urine albumin/creatinine ratio (UACR) ≥ 25 mg/g for women and ≥17 mg/g for men).[16] EGFR and UACR were obtained from GH clinical laboratory results. Secondary outcomes were the incidence of eGFR < 60 mL/min per 1.73 m^2 or microalbuminuria as separate outcomes.

Covariates

The Pathways survey provided self-reported information regarding demographics, diabetes characteristics, depression and diabetes self-care. Depressive symptoms were ascertained by the Patient Health Questionnaire-9 (PHQ-9), which has been validated in patients with CKD.[23] Diabetes self-care was assessed using the modified Summary of Diabetes Self-Care Activities (SDSCA), which asked how many days per week a self-care activity was performed.[24] The SDSCA generates a score ranging from 0 to 7 for each self-care domain (general diet, special diet, exercise, blood glucose testing and foot care), with higher scores indicating better adherence to that domain. Hypertension was identified by *International Classification of Diseases, Ninth Revision* diagnosis code 401.x. GH automated data provided laboratory results and pharmacy prescriptions of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB).

Statistical analyses

Statistical analyses were performed using STATA version 12 (StataCorp, College Station, TX, USA). Sex differences in baseline characteristics were determined using independent *t* tests and χ^2 tests. Cox proportional hazards regression was used to analyse associations between sex and incident CKD after adjustment for demographics (age, race/ethnicity, marital status, education, smoking), baseline eGFR and duration of diabetes (Model 1). To examine the effect of potential mediators of CKD, a second model (Model 2) additionally adjusted for biologic CKD risk factors (haemoglobin A1c, body mass index (BMI), hypertension, ACE inhibitor or ARB use, and low-density lipoprotein (LDL)), depressive symptoms and diabetes self-care adherence (diet, exercise, blood glucose monitoring and self-foot examination). Multiple imputation by chained equations was used for covariates with missing values. Interactions between sex and age or race/ethnicity were examined. Analyses were also stratified by age ≥60 and <60 years old as the majority of women reach menopause by age 60.[25] To address survival bias, all-cause mortality was incorporated into the model as a competing event.[26] Participants were censored at GH disenrollment or at the end of the study. Sensitivity analyses were conducted in the subgroup of participants with type 2 diabetes and in those without missing baseline UACR results.

RESULTS

Of the 4128 potentially eligible individuals, 1464 (35.5%) met criteria for the current study, of which 762 (52.0%) were women (Table 1). A smaller proportion of women were ≥60 years old (52.4%) compared with men (58.0%). Women were less likely to be married, had lower levels of education and income, and higher baseline mean eGFR (83.6 ± 15.2 mL/min per 1.73 m^2 *vs* 81.9 ± 14.2 mL/min per 1.73 m^2), BMI, LDL and PHQ-9 scores compared with men. Women reported better adherence to a special diet (high consumption of fruits/vegetables and low consumption of high fat foods) but less exercise than men. There were 132 deaths in women and 170 deaths in men. Men had a higher mortality rate (57.5 deaths per 1000 patient-years, 95% confidence interval (CI) 49.4, 66.8) compared with women (40.9 deaths per 1000 patient-years, 95% CI 34.5, 48.5; Fig. 2).

Primary outcome

There were 924 cases of incident CKD over 6187 patient-years, yielding a total incidence rate of 149.3 cases per 1000 patient-years (95% CI 140.0, 159.3; Table 2). The incidence rate of CKD was 154.0 cases per 1000 patient-years in women (95% CI 141.0, 168.1) and 144.3 cases per 1000 patient-years in men (95% CI 131.2, 158.7). The cumulative incidence of CKD by sex is shown in Figure 3.

Taking into account death as a competing risk, women had a 30% greater risk of incident CKD (subhazard ratio (SHR) 1.30, 95% CI 1.12, 1.50) in unadjusted analyses (Table 3). In the adjusted competing risks regression, female sex was associated with a 37% increased risk of CKD (SHR 1.37, 95% CI 1.17, 1.60) in Model 1, which is persistent after additional adjustment for CKD mediators in Model 2 (SHR 1.35, 95% 1.15, 1.59). These results were robust in sensitivity analyses in those with type 2 diabetes or without missing baseline UACR results. Other variables associated with an increased risk of incident CKD were younger age, Asian race, lower baseline eGFR, hypertension and a higher SDSCA score for exercise. There were no interactions between sex and age ($P = 0.3$) or sex and race ($P = 0.6$). Patterns of sex differences were similar in patients ≥60 and <60 years of age (Fig. 4).

Secondary outcomes

The incidence of eGFR < 60 mL/min per 1.73 m^2 was 116.2 events per 1000 patient-years (95% CI 105.0, 128.5) in women and 106.5 events per 1000 patient-years (95% CI 95.3, 118.9) in men. In the unadjusted competing risks regression, women had a 35% increased risk of incident eGFR < 60 mL/min per 1.73 m^2 (SHR 1.35, 95% CI 1.13, 1.61). The association between female sex and incident eGFR < 60 mL/min per 1.73 m^2 persisted in both Model 1 (SHR 1.53, 95% CI 1.26, 1.85) and Model 2 (SHR 1.51, 95% CI 1.24, 1.84).

The incidence of sex-specific microalbuminuria per 1000 patient-years was 96.3 (95% CI 86.2, 107.7) in women and 95.6 (95% CI 85.1, 107.5) in men. There was a trend toward an increased risk of microalbuminuria in women that was

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Table 1 Baseline characteristics of study cohort by sex (*n* = 1464)

Variable	*n* Missing	Women (*n* = 762)	Men (*n* = 702)	*P*
Age (years)	0	60.8 ± 13.4	62.1 ± 12.6	0.06
Age ≥60 years	0	399 (52.4)	407 (58.0)	0.03
Race/ethnicity	4			0.5
Non-Hispanic White		605 (79.5)	576 (82.4)	
Non-Hispanic Black		66 (8.7)	47 (6.7)	
Asian		57 (7.5)	46 (6.6)	
Other		33 (4.3)	30 (4.3)	
Married	14	391 (51.9)	523 (75.0)	<0.001
Education beyond high school	15	584 (77.3)	583 (84.1)	0.001
Salary ≥$20 000/year	265	348 (57.4)	410 (69.1)	<0.001
Smoker	0	58 (7.6)	57 (8.1)	0.7
Creatinine (mg/dL)	0	0.8 ± 0.1	1.0 ± 0.2	<0.001
EGFR (mL/min per 1.73 m^2)	0	83.6 ± 15.2	81.9 ± 14.2	0.02
Type 1 diabetes	0	32 (4.2)	39 (5.6)	0.2
Duration of diabetes (years)	1	8.0 ± 8.2	8.9 ± 8.9	0.05
Haemoglobin A1c (%)	17	7.6 ± 1.4	7.7 ± 1.5	0.3
Body mass index (kg/m^2)	9	33.1 ± 8.3	29.9 ± 5.6	<0.001
Hypertension	0	295 (38.7)	264 (37.6)	0.7
ACE inhibitor or ARB use	76	395 (55.0)	378 (56.4)	0.6
Low-density lipoprotein (mg/dL)	452	115.5 ± 34.2	109.5 ± 31.4	0.004
Patient Health Questionnaire-9 score	2	6.3 ± 5.7	4.6 ± 4.9	<0.001
Summary of Diabetes Self-Care Activities score†				
General diet	24	4.6 ± 2.0	4.8 ± 2.6	0.07
Special diet	12	4.0 ± 1.6	3.8 ± 1.6	0.01
Exercise	9	2.5 ± 2.1	3.1 ± 2.1	<0.001
Blood glucose testing	10	4.0 ± 2.8	4.2 ± 2.7	0.1
Foot care	13	3.3 ± 2.4	3.1 ± 2.4	0.09

Data are mean ± standard deviation or *n* (%). †Self-care scores correspond with how many days per week that the self-care activity was performed. SI conversion factors: To convert low-density lipoprotein to mmol/L, multiply by 0.0259; creatinine to μmol/L, multiply by 88.4. ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate.

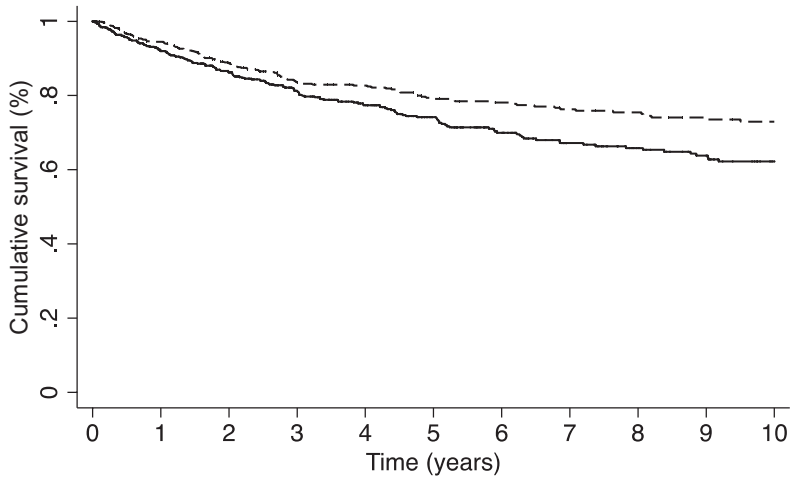

Fig. 2 Kaplan–Meier survival curve by sex. —, Men; - - -, Women.

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Table 2 Incidence rates of chronic kidney disease by sex†

	Total events (*n*)	eGFR < 60 mL/min per 1.73 m^2 events (*n*)	Microalbuminuria events (*n*)	Total patient-years	Median years of follow-up (IQR)	Total incidence rate/1000 patient-years (95% CI)
Total	924	690	594	6187	3.13 (1.36, 6.84)	149.3 (140.0, 159.3)
Women	497	375	311	3228	3.03 (1.37, 7.21)	154.0 (141.0, 168.1)
Men	427	315	283	2959	3.37 (1.33, 6.36)	144.3 (131.2, 158.7)
<60 Years	315	170	238	3266	4.49 (1.71, 8.81)	96.4 (86.4, 107.7)
Women	184	96	135	1830	4.53 (1.73, 9.04)	100.5 (87.0, 116.1)
Men	131	74	103	1436	4.34 (1.66, 7.94)	91.2 (76.9, 108.3)
≥60 Years	609	520	356	2921	2.66 (1.15, 5.25)	208.5 (192.6, 225.7)
Women	313	279	176	1398	2.50 (1.24, 5.04)	224.0 (200.5, 250.2)
Men	296	241	180	1523	2.83 (1.11, 5.39)	194.3 (173.3, 217.7)

†Number of eGFR < 60 mL/min per 1.73 m^2 and microalbuminuria events adds up to more than the total number of events due to overlap. CI, confidence interval; eGFR, estimated glomerular filtration rate; IQR, interquartile range.

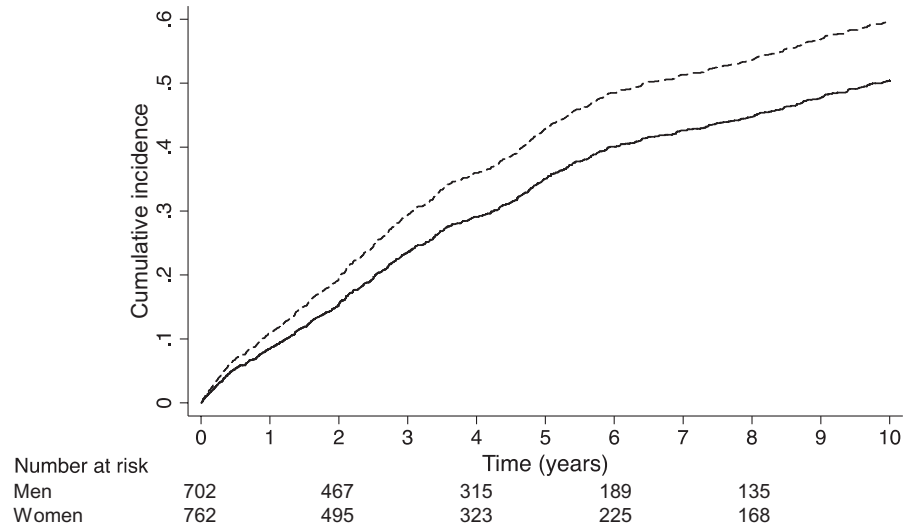

Fig. 3 Nelson–Aalen cumulative incidence of incident chronic kidney disease by sex. —, Men; - - -, Women.

not statistically significant in the unadjusted competing risks regression (SHR 1.18, 95% CI 0.99, 1.41), reached borderline significance in Model 1 (SHR 1.21, 95% CI 1.00, 1.46) and was not significant in Model 2 (SHR 1.20, 95% CI 0.99, 1.46).

DISCUSSION

We found that in a primary care population of patients with diabetes and normal baseline kidney function, women had an increased risk of incident CKD compared with men after a median follow up of 3.1 years after taking into account mortality as a competing event. This sex difference in incident CKD did not substantially differ after adjustment for CKD risk factors including depressive symptoms and diabetes self-care. The sex difference in incident CKD was primarily driven by differences in incident eGFR < 60 mL/min per 1.73 m^2; although there was a trend toward an increased risk for microalbuminuria in women, this did not reach statistical significance. Patterns of sex differences were consistent across age groups.

To our knowledge, this is the first study to find that women with diabetes had a greater risk of developing CKD compared with men, after taking into account mortality as a competing risk factor. Although female sex was found to be a risk factor for the development of microalbuminuria in children and young adults with type 1 diabetes,[27] previous prospective studies in patients with type 2 diabetes generally found that men were at greater risk for incident microalbuminuria,[10–12] macroalbuminuria[10,12] and eGFR < 60 mL/min per 1.73 m^2 compared with women.[13] The reasons for the discrepancy between our study and past results are not obvious. Previous studies did not take into account mortality as a competing event; however, this should have biased those studies toward a lower risk of CKD in men than women. None of the other studies used sex-specific definitions of microalbuminuria, but this again should have biased those studies toward a lower risk of CKD in men than women. One consideration is that most of the previous studies excluded patients over the age of 65 years.[10–12] Since oestrogen levels may have renoprotective effects,[14] the inclusion of elderly, presumably post-menopausal women in our study may be partially responsible

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Table 3 Cox proportional hazards models for incident chronic kidney disease

Variable	Unadjusted HR (95% CI)	Model 1 Adjusted HR (95% CI)†	Model 2 Adjusted HR (95% CI)‡
Female	1.30 (1.12, 1.50)	1.37 (1.17, 1.60)	1.35 (1.15, 1.59)
Age (year)	1.00 (0.99, 1.00)	0.98 (0.98, 0.99)	0.98 (0.97, 0.99)
Race/ethnicity			
Non-Hispanic White	Reference	Reference	Reference
Non-Hispanic Black	1.11 (0.84, 1.45)	1.21 (0.91, 1.62)	1.13 (0.84, 1.53)
Asian	1.32 (1.00, 1.75)	1.39 (1.04, 1.87)	1.39 (1.02, 1.89)
Other	1.28 (0.86, 1.89)	1.34 (0.90, 2.01)	1.40 (0.93, 2.09)
Married	1.04 (0.89, 1.21)	1.09 (0.92, 1.28)	1.11 (0.94, 1.30)
Education beyond high school	1.10 (0.91, 1.33)	1.08 (0.88, 1.33)	1.07 (0.87, 1.32)
Smoker	0.97 (0.73, 1.29)	0.97 (0.71, 1.32)	0.98 (0.71, 1.35)
eGFR (10 mL/min per 1.73 m^2)	0.87 (0.82, 0.92)	0.77 (0.71, 0.82)	0.77 (0.72, 0.83)
Duration of diabetes (10 years)	0.93 (0.84, 1.02)	0.94 (0.86, 1.03)	0.94 (0.85, 1.04)
Haemoglobin A1c (%)	1.03 (0.98, 1.08)	–	1.04 (0.99, 1.10)
Body mass index (5 kg/m^2)	1.06 (1.01, 1.11)	–	1.05 (0.99, 1.11)
Hypertension	1.21 (1.04, 1.41)	–	1.20 (1.01, 1.41)
ACE inhibitor or ARB use	1.11 (0.95, 1.29)	–	1.08 (0.91, 1.27)
Low-density lipoprotein (10 mg/dL)	1.01 (0.99, 1.04)	–	1.00 (0.97, 1.03)
Patient Health Questionnaire-9 score	1.01 (0.99, 1.02)	–	1.00 (0.99, 1.02)
General diet (day/week)	0.97 (0.94, 1.01)	–	0.96 (0.92, 1.00)
Special diet (day/week)	1.02 (0.97, 1.06)	–	1.03 (0.98, 1.08)
Exercise (day/week)	1.03 (1.00, 1.06)	–	1.06 (1.02, 1.10)
Blood glucose testing (day/week)	0.99 (0.96, 1.02)	–	0.99 (0.96, 1.02)
Foot care (day/week)	1.01 (0.98, 1.04)	–	1.01 (0.98, 1.04)

†Adjusted for age, race/ethnicity, marital status, education level, smoking status, eGFR and duration of diabetes. ‡Additionally adjusted for haemoglobin A1c, body mass index, hypertension, ACE inhibitor or ARB use, low-density lipoprotein, Patient Health Questionnaire-9 score and Summary of Diabetes Self-Care Activities scores for general diet, special diet, exercise, blood glucose testing and foot care. ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CI, confidence interval; eGFR, estimated glomerular filtration rate.

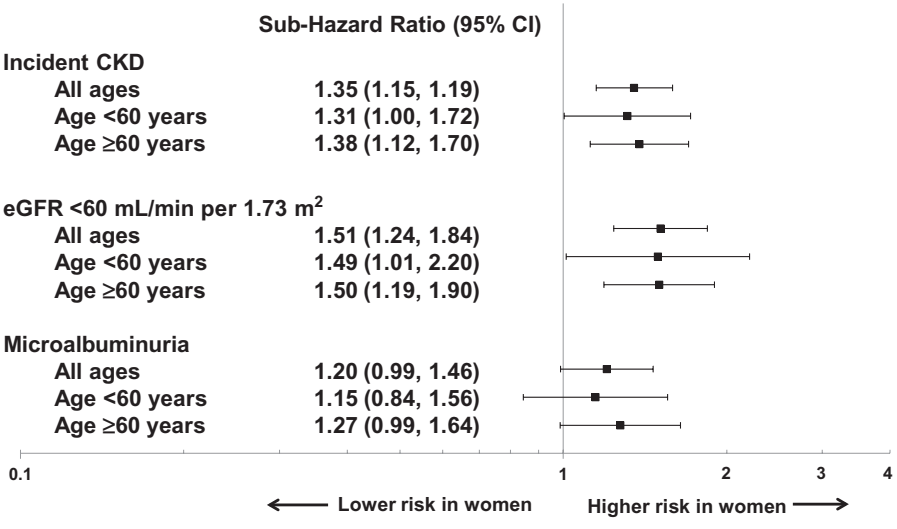

Fig. 4 Age-stratified risk of chronic kidney disease in women compared with men. Adjusted for age, race/ethnicity, marital status, education level, smoking status, estimated glomerular filtration rate, duration of diabetes, haemoglobin A1c, body mass index, hypertension, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use, low-density lipoprotein, Patient Health Questionnaire-9 score and Summary of Diabetes Self-Care Activities scores for general diet, special diet, exercise, blood glucose testing and foot care.

for the difference in our results; however, we did not find any interaction between sex and age. Similar to our study, Retnakaran *et al*. found that women had a greater risk of renal impairment as measured by the Cockcroft-Gault equation compared with men.[12] In contrast, Luk *et al*. found that Chinese men with type 2 diabetes had a greater risk than women of incident eGFR < 60 mL/min per 1.73 m^2 by the MDRD equation adjusted for Chinese race[13] however, the differences in the study populations and eGFR equations make it difficult to compare those results with the current study. Our results may also differ from previous studies because we had access to a larger number of covariates and

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mediators, including variables for depression and diabetes self-care, than other studies.

This is also the first study to evaluate depression and diabetes self-care as potential mediators for sex differences in CKD incidence. Adjustment for these variables did not substantially attenuate the association between female sex and incident CKD, which may be due to several factors. Our analysis used self-rated scales, which may be imprecise. Although the PHQ-9 may overestimate the presence of depression compared with the gold standard clinical interview, it has been validated in patients with CKD,[23] and a score ≥10 has been shown to be a risk factor for macro and microvascular diabetic complications.[28] Diabetes self-care was not objectively measured and is therefore subject to recall bias. Additionally, our study only assessed depression and self-care at study enrolment, yet these factors may change throughout the study period. Finally, depression and diabetes self-care may be weaker predictors of CKD incidence than sex, and thereby may not have a considerable impact on the risk estimates.

Female sex may be associated with a higher risk of CKD incidence through several pathways. Although sex disparities exist in the prevalence of CKD risk factors, since sex differences in CKD incidence persisted after adjustment for these variables, other mechanisms for sex differences may be involved such as sex hormones or sex-specific genetic variants. In animal models, testosterone administration is associated with tubular damage, whereas oestrogen reduces albuminuria, glomerulosclerosis and tubulointerstitial fibrosis.[14] In postmenopausal women, oestrogen supplementation is associated with lower levels of proteinuria[14] and fibroblast growth factor-23,[29] the latter of which is associated with adverse renal outcomes in patients with diabetic CKD. Sex-specific polymorphisms have been identified in genes associated with angiotensin converting enzyme[30] and the podocyte slit diaphragm.[31] A genome-wide association study found a sex-specific genetic variant rs4972593 that was associated with ESRD risk in patients with type 1 diabetes;[32] although no association was found in type 2 diabetes, other sex-specific genetic risk factors for CKD are possible.

There are several important limitations of this study to consider. Residual and unmeasured confounding remains an issue. Another limitation is differential misclassification by sex due to the use of GFR estimating equations. However, the CKD-EPI equations were designed to improve the accuracy of estimating GFR in broader populations including women[17] and were found to reduce the prevalence of CKD in women compared with the MDRD study equation[17,18] and have comparable accuracy in women as in men.[18] Our study did not account for changes in eGFR or CKD risk factors over time. It is possible that our findings may reflect an increased risk of acute kidney injury in women compared with men, which should be evaluated in future studies. Since we used clinical laboratory data, not everybody in the study had UACR measures at baseline and therefore may have been misclassified as having normal renal function; however, a sensitivity analysis in the subset with baseline UACR results showed similar findings to our primary analysis. Although we did not find sex differences in the mean number of creatinine tests during the study period, women did have a higher mean number of UACR tests compared with men (data not shown), which may provide a greater opportunity to detect CKD in women than men, although the sex differences in incident microalbuminuria were not statistically significant. There may be selection bias if healthier men were more likely to enrol in the study than women. Finally, generalizability may be limited to patient populations with comparable demographics and health insurance status. Despite these limitations, there are several strengths of this study including the prospective design; large sample size; use of a competing risks analysis, sex-specific definitions of microalbuminuria, and CKD-EPI equations for estimating GFR; and ability to adjust for multiple CKD risk factors including depression and diabetes self-care.

In summary, in a diabetic population with predominantly type 2 diabetes, women had a higher risk of incident CKD compared with men which could not be entirely explained by differences in biologic CKD risk factors, depression or diabetes self-care. These sex differences appeared to be driven by differences in the risk of developing a low eGFR and were consistent across age groups. Additional studies are needed to determine the pathophysiology behind these sex differences and whether they translate into worse clinical outcomes for women with diabetes.

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