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

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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 m² 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 to 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 States2-3 and Germany4 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,7 physical inactivity7 and depression,7 which are each associated with an increased risk for CKD.6,9 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;10-12 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.13 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 or older methods of estimating glomerular filtration rate (GFR) such as the change in the reciprocal serum creatinine, Cockcroft-Gault equation or Modification of Diet in Renal Disease (MDRD) Study equation, which are less accurate than the Chronic Kidney Disease-Epidemiology (CKD-EPI) equations in patients without CKD, women and the elderly. 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. Fourth, patients over 65 years of age, an important demographic for CKD, were not included in most previous analyses. Since older women with diabetes have a high prevalence of CKD risk factors and cardiovascular risk increases in women after menopause, 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 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. 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 m² 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.
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 m² by CKD-EPI equations or sex-specific microalbuminuria (urine albumin/creatinine ratio (UACR) ≥ 25 mg/g for women and ≥17 mg/g for men). EGF and UACR were obtained from GH clinical laboratory results. Secondary outcomes were the incidence of eGFR < 60 mL/min per 1.73 m² 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. 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. 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 χ² 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 years old as the majority of women reach menopause by age 60. To address survival bias, all-cause mortality was incorporated into the model as a competing event. 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 m² vs 81.9 ± 14.2 mL/min per 1.73 m²), 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% CI 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 m² 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 m² (SHR 1.35, 95% CI 1.13, 1.61). The association between female sex and incident eGFR < 60 mL/min per 1.73 m² 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
### Table 1: Baseline characteristics of study cohort by sex (n = 1464)

| Variable                        | Women (n = 762) | Men (n = 702) | P    |
|---------------------------------|----------------|--------------|------|
| Age (years)                     | 60.8 ± 13.4    | 62.1 ± 12.6  | 0.06 |
| Age ≥60 years                   | 399 (52.4)     | 407 (58.0)   | 0.03 |
| Race/ethnicity                  |                |              | 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                         |                 |              |      |
| Education beyond high school    | 584 (77.3)     | 583 (84.1)   | <0.001|
| Salary ≥$20,000/year            | 348 (57.4)     | 410 (69.1)   | <0.001|
| Smoker                          | 58 (7.6)       | 57 (8.1)     | 0.7  |
| Creatinine (mg/dL)              | 0.8 ± 0.1      | 1.0 ± 0.2    | <0.001|
| EGFR (mL/min per 1.73 m²)       | 83.6 ± 15.2    | 81.9 ± 14.2  | 0.02 |
| Type 1 diabetes                 | 32 (4.2)       | 39 (5.6)     | 0.2  |
| Duration of diabetes (years)    | 8.0 ± 8.2      | 8.9 ± 8.9    | 0.05 |
| Body mass index (kg/m²)         | 33.1 ± 8.3     | 29.9 ± 5.6   | <0.001|
| Hypertension                    | 295 (38.7)     | 264 (37.6)   | 0.7  |
| Low-density lipoprotein (mg/dL) | 115.5 ± 34.2   | 109.5 ± 31.4 | 0.004|
| Patient Health Questionnaire-9 score | 6.3 ± 5.7 | 4.6 ± 4.9 | <0.001|

**Summary of Diabetes Self-Care Activities score†**

|                       | Women (n = 762) | Men (n = 702) | P    |
|-----------------------|----------------|--------------|------|
| General diet          | 4.6 ± 2.0      | 4.8 ± 2.6    | 0.07 |
| Special diet          | 4.0 ± 1.6      | 3.8 ± 1.6    | 0.01 |
| Exercise              | 2.5 ± 2.1      | 3.1 ± 2.1    | <0.001|
| Blood glucose testing | 4.0 ± 2.8      | 4.2 ± 2.7    | 0.1  |
| Foot care             | 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.

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

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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 m²; 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, previous prospective studies in patients with type 2 diabetes generally found that men were at greater risk for incident microalbuminuria, macroalbuminuria and eGFR < 60 mL/min per 1.73 m² compared with women. 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. Since oestrogen levels may have renoprotective effects, the inclusion of elderly, presumably post-menopausal women in our study may be partially responsible

Table 2 Incidence rates of chronic kidney disease by sex†

| Total events (n) | eGFR < 60 mL/min per 1.73 m² 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 m² 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.
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.\textsuperscript{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\textsuperscript{2} by the MDRD equation adjusted for Chinese race\textsuperscript{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

### 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\textsuperscript{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\textsuperscript{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)              |
| Barlood 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.

### Figure 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.
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, and a score ≥10 has been shown to be a risk factor for macro and microvascular diabetic complications. 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. In postmenopausal women, oestrogen supplementation is associated with lower levels of proteinuria and fibroblast growth factor-23, the latter of which is associated with tubular damage, whereas oestrogen reduces albuminuria, glomerulosclerosis and tubulointerstitial fibrosis. A genome-wide association study found a sex-specific genetic variant rs4972593 that was associated with ESRD risk in patients with type 1 diabetes; although no association was found in 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.

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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REFERENCES

1. U.S. Renal Data System. USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2013.
2. Ferrara A, Mangione CM, Kim C et al. Sex disparities in control and treatment of modifiable cardiovascular disease risk factors among patients with diabetes: Translating Research Into Action for Diabetes (TRIAD) Study. Diabetes Care 2008; 31: 69–74.
3. Wexler DJ, Grant RW, Meigs JB, Nathan DM, Cagliero E. Sex disparities in treatment of cardiac risk factors in patients with type 2 diabetes. *Diabetes Care* 2005; 28: 514–20.

4. Gouni-Berthold I, Berthold HK, Mantiszos CS, Bohm M, Krone W. Sex disparities in the treatment and control of cardiovascular risk factors in type 2 diabetes. *Diabetes Care* 2008; 31: 1389–91.

5. Yu MK, Lyles CR, Bent-Shaw LA, Young BA. Sex disparities in diabetes process of care measures and self-care in high-risk patients. *J. Nephrol.* 2013; 2013: 575814.

6. Yu MK, Lyles CR, Bent-Shaw LA, Young BA: Pathways Authors. Risk factor, age and sex differences in chronic kidney disease prevalence in a diabetic cohort: The pathways study. *Am. J. Nephrol.* 2012; 36: 245–51.

7. Yu MK, Katon W, Young BA. Diabetes self-care, major depression, and chronic kidney disease in an outpatient diabetic population. *Nephron Clin. Pract.* 2013; 124: 106–12.

8. Hallan S, de Mutsert R, Carlsen S, Dekker FW, Aasarod K, Holmen J. Obesity, smoking, and physical inactivity as risk factors for CKD: Are men more vulnerable? *Am. J. Kidney Dis.* 2006; 47: 396–405.

9. Yu MK, Weiss NS, Ding X, Katon WJ, Zhou H, Young BA. Associations between depressive symptoms and incident ESRD in a diabetic cohort. *Clin. J. Am. Soc. Nephrol.* 2014; 9: 920–28.

10. Gall MA, Hougaard P, Borch-Johnsen K, Parving HJ. Risk factors for development of incipient and overt diabetic nephropathy in patients with non-insulin dependent diabetes mellitus: Prospective, observational study. *BMJ* 1997; 314: 783–8.

11. Ravid M, Brosh D, Ravid-Safran D, Levy Z, Rachmani R. Main risk factors for nephropathy in type 2 diabetes mellitus are plasma cholesterol levels, mean blood pressure, and hyperglycemia. *Arch. Intern. Med.* 1998; 158: 998–1004.

12. Retnakaran R, Cull CA, Thorne KI, Adler AI, Holman RR. Risk factors for renal dysfunction in type 2 diabetes: U.K. Prospective Diabetes Study 74. *Diabetes* 2006; 55: 1832–9.

13. Luk AO, So WY, Ma RC, et al. Metabolic syndrome predicts new onset of chronic kidney disease in 5,829 patients with type 2 diabetes: A 5-year prospective analysis of the Hong Kong Diabetes Registry. *Diabetes Care* 2008; 31: 2357–61.

14. Maric C. Sex, diabetes and the kidney. *Am. J. Physiol. Renal Physiol.* 2009; 296: F680–88.

15. Franco OH, Steyenberg EW, Hu FB, Mackenbach J, Nusselder W. Associations of diabetes mellitus with total life expectancy and life expectancy with and without cardiovascular disease. *Arch. Intern. Med.* 2007; 167: 1145–51.

16. Mattix HJ, Hsu CY, Shaykевич S, Curhan G. Use of the albumin/creatinine ratio to detect microalbuminuria: Implications of sex and race. *J. Am. Soc. Nephrol.* 2002; 13: 1034–9.

17. Levey AS, Stevens LA, Schmid CH et al. A new equation to estimate glomerular filtration rate. *Ann. Intern. Med.* 2009; 150: 604–12.

18. Michels WM, Grootendorst DC, Verduijn M, Elliott EG, Dekker FW, Krediet RT. Performance of the Cockcroft-Gault, MDRD, and new CKD-EPI formulas in relation to GFR, age, and body size. *Clin. J. Am. Soc. Nephrol.* 2010; 5: 1003–9.

19. Kilbride HS, Stevens PE, Eaglestone G et al. Accuracy of the MDRD (Modification of Diet in Renal Disease) study and CKD-EPI (CKD Epidemiology Collaboration) equations for estimation of GFR in the elderly. *Am. J. Kidney Dis.* 2013; 61: 57–66.

20. Matsuhashita K, Mahmoood BK, Woodward M et al. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. *JAMA* 2012; 307: 1941–51.

21. Kannel WB, Hjortland MC, McNamara PM, Gordon T. Menopause and risk of cardiovascular disease in Framingham study. *Ann. Intern. Med.* 1976; 85: 447–52.

22. Kato W, Lin EH, Williams LH et al. Comorbid depression is associated with an increased risk of dementia diagnosis in patients with diabetes: A prospective cohort study. *J. Gen. Intern. Med.* 2010; 25: 423–9.

23. Watnick S, Wang PL, Demadura T, Ganzini L. Validation of 2 depression screening tools in dialysis patients. *Am. J. Kidney Dis.* 2005; 46: 919–24.

24. Toobert DJ, Hampson SE, Glasgow RE. The summary of diabetes self-care activities measure: Results from 7 studies and a revised scale. *Diabetes Care* 2000; 23: 943–50.

25. Krailo M, Pike M. Estimation of the distribution of age at natural menopause from prevalence data. *Am. J. Epidemiol.* 1983; 117: 356–61.

26. Fine JP, Gray RJ. A Proportional hazards model for the subdistribution of a competing risk. *J. Am. Stat. Assoc.* 1999; 94: 496–509.

27. Holl RW, Grabert M, Thon A, Heinz E. Urinary excretion of albumin in adolescents with type 1 diabetes: Persistent versus intermittent microalbuminuria and relationship to duration of diabetes, sex, and metabolic control. *Diabetes Care* 1999; 22: 1555–60.

28. Lin EH, Rutter CM, Katon W et al. Depression and advanced complications of diabetes: A prospective cohort study. *Diabetes Care* 2010; 33: 264–9.

29. Ix JH, Chenchol M, Laughlin GA, Shlipak MG, Whooley MA. Relation of sex and estrogen therapy to serum fibroblast growth factor 23, serum phosphorus, and urine phosphorus: The Heart and Soul Study. *Am. J. Kidney Dis.* 2011; 58: 737–45.

30. Tien KJ, Hsiao JY, Hsu SC et al. Gender-dependent effect of ACE I/D and AGT M235T polymorphisms on the progression of urinary albumin excretion in Taiwanese with type 2 diabetes. *Am. J. Nephrol.* 2009; 29: 299–308.

31. Ihalmo M, Pissessman M, Kaunisto MA et al. Association analysis of podocyte slit diaphragm genes as candidates for diabetic nephropathy. *Diabetologia* 2008; 51: 86–90.

32. Sandholm N, McNicholl AJ, Salem RM et al. Chromosome 2q31.1 associates with ESRD in women with type 1 diabetes. *J. Am. Soc. Nephrol.* 2013; 24: 1537–43.