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Renal function decline in older men and women with advanced CKD – Results from the EQUAL study

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Abstract

Introduction

Understanding the mechanisms underlying the differences in renal decline between men and women may improve sex-specific clinical monitoring and management. To this end, we aimed to compare the slope of renal function decline in older men and women in CKD stage 4-5, taking into account informative censoring related to the sex-specific risks of mortality and dialysis initiation.

Methods

The EQUAL study is an observational prospective cohort study in stage 4-5 CKD patients ≥65 years not on dialysis. Data on clinical and demographic patient characteristics were collected between April 2012 to December 2018. eGFR was calculated using the CKD-EPI equation. eGFR trajectory by sex was modelled using linear mixed models, and joint models were applied to deal with informative censoring.

Results

We included 7801 eGFR measurements in 1682 patients over a total of 2911 years of follow-up. Renal function declined by 14.0% (95% CI 12.9%-15.1%) on average each year. Renal function declined faster in men (16.2% per year, 95% CI 15.9%-17.1%) compared with women (9.6% per year, 95% CI 6.3%-12.1%), which remained largely unchanged after accounting for various mediators, and for informative censoring due to mortality and dialysis initiation. Diabetes was identified as an important determinant of renal decline specifically in women.

Conclusion

In conclusion, renal function declines faster in men compared with women, which remained similar after adjustment for mediators, and despite a higher risk of informative censoring in men. We demonstrate a disproportional negative impact of diabetes specifically in women.

What is already known about this subject:

- It is known that the epidemiology of chronic kidney disease (CKD) differs by sex, however, the current evidence on sex-specific slopes of renal decline in advanced CKD remains inconclusive.
- Studying renal function decline by sex is complicated by informative censoring caused by sex-specific risks of mortality and dialysis initiation.

What this study adds:

- Men progress faster than women, even after adjustment for important mediators, and despite having a higher risk of censoring.
- Diabetes is an important determinant of renal decline, with a disproportional negative impact specifically in women.

What impact this may have on practice or policy:

- Our results help understand the mechanisms underlying the differences in renal function decline between the sexes, and help achieve individualized and sex-specific management and treatment in advanced CKD.

Keywords

Renal function decline, sex disparities, EQUAL

Introduction

The epidemiology of chronic kidney disease (CKD) differs by sex. Population-based studies across the globe consistently show a higher prevalence of CKD in women compared with men [1–7], yet approximately 60% of those starting renal replacement therapy (RRT) for end-stage kidney disease (ESKD) are men [8,9]. This paradox has several potential explanations [10]. First, the longer life expectancy in women along with the natural decline of glomerular filtration rate with age may partly explain the higher prevalence of CKD in women. Second, several (population-based) studies [11–14], as well as a large meta-analysis of studies in non-diabetic CKD patients [15], point towards a faster decline of renal function in men. In contrast, others have demonstrated a more rapid progression in women in various (sub) populations [16–18], whereas some found no difference between the sexes at all [19,20]. A meta-analysis of randomized controlled trials found that women progress at an equal speed as men, with adjusted analyses even suggesting a faster progression in women [21]. Given these inconclusive results, it is clear that the estimated sex-specific decline in renal function depends on the population studied; CKD stage, the presence of diabetes mellitus, (post-menopausal) age, population-based cohorts versus referred patients, are all factors that likely contribute to the variation in current evidence.

Studying renal function decline by sex is complicated by a sex-specific selection processes caused by a higher mortality risk in men across all ranges of pre-ESKD eGFR [22,23]. The effect of eGFR decline and albuminuria on mortality risk seems stronger in women, adding complexity to the selection process [22]. Furthermore, as men and women start dialysis at different levels of eGFR [24], censoring at dialysis initiation may be deemed informative when studying CKD progression. Consequently, it is important when investigating this topic to take into account informative censoring caused by mortality and dialysis initiation, as the estimated slopes of renal function decline by sex may otherwise be biased.

Understanding the mechanisms underlying the differences in renal function decline between the sexes may aid sex-specific clinical monitoring and management. To date, very few studies have investigated renal function decline by sex specifically during pre-dialysis stages 4-5 in referred CKD patients of older age, and none have taken into account the potential bias caused by the sex-specific risk of mortality and dialysis initiation [25]. Consequently, here we aim to compare the slope of renal function decline in older men and women with advanced CKD, taking into account informative censoring due to mortality and dialysis. As a secondary aim, we will explore sex-specific determinants of renal function decline in this population.

Methods

Study design and population

The EQUAL study is an ongoing observational cohort study including stage 4-5 CKD patients not on dialysis receiving routine medical care in Germany, Italy, the Netherlands, Poland, Sweden, and the United Kingdom. Patients of 65 years of age and older were included with an incident estimated glomerular filtration rate (eGFR) < 20 ml/min/1.73m² calculated by the Modification of Diet in Renal Disease equation. Patients were excluded if the drop in eGFR resulted from an acute event or if they had previously received dialysis or a kidney transplant. Approval was obtained from the medical ethical committees in each country. Informed consent was obtained from all patients. A full description of the study has been published elsewhere [26].

Data collection

Clinical data were collected between April 2012 to December 2018 on patient demographics, primary renal disease, laboratory data, and cardiovascular risk factors (smoking status, body mass index, haemoglobin, blood pressure, cholesterol, and diabetes mellitus). Data on the following pre-existing cardiovascular comorbid conditions were also collected (definitions provided in supplement); cerebrovascular disease, peripheral vascular disease, myocardial infarction, angina pectoris, congestive heart failure, left ventricular hypertrophy, hypertension, and cardiac arrhythmias. Study visits were scheduled at 6-month intervals, and patients were followed until dialysis initiation, kidney transplantation, death, refusal for further participation, loss to follow-up, or end of follow-up. The eGFR was calculated from serum creatinine level standardized to isotope dilution mass spectrometry using the CKD-EPI equation [27]. In addition, GFR was estimated during follow-up from routine 24-hour urine collection by taking the average of creatinine clearance and urea clearance, normalized to body surface area following the Dubois & Dubois formula. Albumin-creatinine ratio was also determined following routine 24-hour urine collection or a single sample if 24h urinary collection was unavailable. Primary kidney disease was classified using the codes of the European Renal Association-European Dialysis and Transplantation Association (ERA-EDTA) and grouped as glomerulonephritis, diabetes mellitus, tubulo-interstitial disease, hypertension, and miscellaneous kidney diseases.

Statistical analysis

Patient characteristics were reported by sex as mean values with standard deviations for normally distributed continuous variables, as medians with interquartile ranges for skewed continuous variables, and as proportions for categorical variables. Linear mixed models were used to model the

eGFR trajectory. A random intercept was included to capture the variation in eGFR baseline value between patients, and a random slope for time to capture variability in the patient's eGFR trajectory. Due to non-linear patient trajectories of eGFR, the latter was included as a cubic B-spline with two equally spaced knots positioned between the minimum and maximum of follow-up. The unadjusted model includes time, sex, and their interaction, and describes the sex-specific trajectory of eGFR over time. In subsequent models, we investigate to which extent the effect of sex on the eGFR trajectory is mediated by various groups of *a priori* defined covariates (i.e. mediators). All models were adjusted for baseline eGFR and age at inclusion.

We followed patients until death or dialysis initiation. Missing eGFR values may be introduced when patients drop-out of the study due to mortality or are censored due to dialysis initiation. As the level of renal function is related to these events, drop-out is deemed informative [28–30]. We applied joint models for longitudinal and time-to-event data to avoid biased estimates of eGFR decline [31]. The joint model links the linear mixed model described above to a Cox survival model, which captures the risk of either mortality or dialysis. In this manner, the joint model informs the longitudinal eGFR trajectory on missingness caused by either of these events. To determine whether the difference in eGFR slope between men and women had changed after taking into account informative censoring due to mortality or dialysis, we tested for equality between the time-sex interaction coefficients in the linear mixed model and joint model using a Z-score test [32].

Sex-specific determinants of eGFR decline were studied through effect modification using interaction analyses, specifically through 3-way interactions between sex, time, and the characteristics of interest. Q-Q plots were used to check whether the residuals were normally distributed, and eGFR was log-transformed to fulfil this assumption. Consequently, regression coefficients were exponentiated and interpreted as the mean percent change in eGFR per year. Only complete cases were analysed, and missing values are reported in the supplement. All analyses were performed with SAS version 9.4 and R version 3.4.1.

Sensitivity analyses

We performed a number of sensitivity analyses. First, in addition to the CKDEPI equation, we also repeated the analyses using the Full Age Spectrum equation and the revised Lund-Malmö equation to estimate GFR [33,34]. Second, we studied the association between sex and GFR decline estimated from 24-hour urine collection. Third, as age is an important variable in all estimating GFRs, we also considered the relationship between sex and 1/creatinine over time. Last, due the wide range in individual follow-up time, we also repeated the analyses in patients with at least 1 year of follow-up.

Results

Patient characteristics

Table 1 describes the baseline characteristics of 1682 patients by sex. On average, patients were 76 years old at inclusion (IQR 71-81), two-thirds were men, and the eGFR at baseline was 17.0 ml/min/1.73m^2 (IQR 14.5-20.4). Women were older, had a slightly higher BMI, higher values of serum calcium, cholesterol, and potassium, but lower levels of haemoglobin. Diabetes and glomerular disease accounted for a lower proportion of primary renal disease in women compared with men, whereas tubulo-interstitial disease and hypertension were more common in women. Women had higher baseline renal function, and lower albumin creatinine ratio (ACR). Regarding comorbidity, more men had diabetes, peripheral vascular disease, myocardial infarction, and angina pectoris.

The effect of sex on the eGFR trajectory

We included 7801 eGFR measurements over a total of 2911 years of follow-up, with a median of 4 (IQR 2-7) measurements per patient, and a median follow-up time of 18.6 months (IQR 6.7 – 32.6). Renal function declined 14.0% (95% CI 12.9%-15.1%) on average each year. Figure 1A shows a faster unadjusted annual decline in renal function in men (16.2% per year, 95% CI 15.9%-17.1%) compared with women (9.6% per year, 95% CI 6.3%-12.1%), with a difference of 6.6% (95% CI 4,3%-9,1%). These estimates remained largely unchanged after accounting for various groups of mediators (table 2). For the purpose of comparison with existing literature, we determined the linear sex-specific slopes of renal function decline, without log-transformation, as -1.82 (95% CI -1.63--2.01) ml/min/1.73m2 per year for men and -0.91 (95% CI -0.40--1.43) ml/min/1.73m2 per year for women. Sensitivity analyses using GFR estimated following routine 24-hour urine collection, 1/creatinine, and eGFR calculated using the Full Age Spectrum and the revised Lund-Malmö equations provided similar results . Estimated renal function decline in a sub-group of patients with at least 1 year of follow-up was also similar to the main results (supplement).

The effect of sex on the eGFR trajectory adjusted for informative censoring

Figure 1B shows the eGFR trajectory in men and women after accounting for informative censoring due to death or dialysis initiation. The adjusted trajectories represent the average eGFR trajectory in the hypothetical situation that all patients had remained alive / had not started dialysis. After

accounting for death (5-year cumulative incidence of 21.4% in men and 19.6% in women, p-value = 0.32), the difference in renal decline between men (16.1% per year, 95% CI 15.0%-17.1%) and women (9.5% per year, 95% CI 6.3%-12.6%) remained 6.6% (p-value for change in coefficient = 0.97). Accounting for drop-out due to dialysis initiation (5-year cumulative incidence of 31.9% in men and 21.4% in women, p-value for difference <.0001) also had little effect on the difference in renal function decline between men (17.2% per year, 95%CI 16.1%-18.5%) and women (10.4% per year, 95% CI 6.9%-14.2%), increasing the difference in slope between men and women marginally from 6.6% to 6.8% (p-value for change in coefficient = 0.81).

The sex-specific determinants of the eGFR trajectory

We identified effect modification by age, diabetes, and myocardial infarction at inclusion on the slope of renal function decline by sex. We found that women of older age had slower declines in renal function compared with younger women (figure 2A), whereas age had little effect on renal decline in men (p-value for interaction= 0.03). In addition, women with diabetes had significantly faster declines in renal function compared with non-diabetics, whereas this was not the case in men (figure 2B, p-value for interaction = 0.05). The differential effect of diabetes seemed more pronounced in women under the age of 82 (p-value for interaction = 0.02, supplementary figure 1). Other baseline characteristics did not differentially affect the slope of renal decline in men and women.

Discussion

In our population of elderly CKD stage 4 and 5 patients not on dialysis, we demonstrate a faster decline of renal function in men compared with women, which persisted after taking into account important mediators. By applying joint models to account for the sex-specific risks of informative censoring due to death and dialysis, we demonstrate that men progress faster than women despite having a higher risk of drop-out. Furthermore, we identified diabetes as an important determinant of renal decline specifically in women, demonstrating that renal function in female diabetics deteriorated at a similar pace as in men. Interestingly, older women had slower declines of renal function, indicative of a certain degree of selection bias in our cohort.

To our knowledge, this is the first study to explore renal decline by sex in a referred cohort of incident CKD patients with an eGFR of <20 ml/min/1.73m2. We found that renal function in men declined approximately twice as fast as in women (-1,82 ml/min/1.73m2 per year and -0,89

ml/min/1.73m2 per year, respectively), which remained similar after adjustment for various mediators and informative censoring. Comparable studies on sex-specific renal decline during the transition period from stage 4-5 CKD to dialysis are scarce[11,25]. Nonetheless, our results are in line with studies published in cohorts consisting of patients in earlier stages of CKD[15]; a Swedish population-based study of CKD stage 3 patients estimated similar differences in renal declines between men (-1.26 ml/min/1.73m2 per year for a 70-year old) and women (-0.76 ml/min/1.73m2 per year) [13]. More recently, in a referred cohort of CKD stage 2 and 3 patients, the CRIC study also found faster declines in men (-1.43 ml/min/1.73m2 per year) compared with women (-1.09 ml/min/1.73m2 per year), although this difference was somewhat smaller compared to our estimates [12]. Even in the 'healthy' general population (cohort baseline eGFR of 80.7 ml/min/1.73m2), the PREVEND study found an eGFR slope of -0.55 ml/min/year/1.73m2 in men and -0.33 ml/min/year/1.73m2 in women [14]. Altogether, most available evidence points towards a faster decline of renal function in men, seemingly regardless of CKD stage. Nonetheless, a handful of studies exist that have found either a faster progression in women [16] or no difference at all between the sexes [19,20]. One of these studies, a large meta-analysis of randomized controlled trials, found that women progress at an equal speed as men, with adjusted analyses (baseline creatinine, blood pressure, urinary protein, age, and treatment assignment) suggesting a faster progression in women [21], although this discrepancy may be attributed to stringent patient selection common to RCTs and erroneous adjustment within the causal pathway.

This sex difference in renal decline has several potential explanations related to biological and/or sociocultural aspects [10]. Risk factors related to lifestyle, such as a poor diet and smoking, may partly be responsible for faster decline as seen in men [18,35]. Although more men had a history of smoking and a higher burden of cardiovascular co-morbidities in our cohort, adjustment for these factors had little effect on the sex difference in renal decline. Others have demonstrated differential effects of albuminuria, cholesterol, blood pressure, and glycaemic control, on renal function decline in men and women [14,16,35], although most of these studies applied methodology corresponding to prognostic research, thus not contributing to mechanistic evidence. Lastly, sex hormones also likely play a role, as animal studies have demonstrated renoprotective effects of oestrogens and damaging effects of testosterone [25,36–38].

We demonstrate that diabetes has a stronger effect on renal decline in women compared with men, to the extent that renal decline was similar between the sexes in those with diabetes. The literature surrounding this topic is inconsistent, with some reporting faster declines in diabetic men[39,40], and others finding no differences between the sexes [41]. In line with our findings, a Japanese cohort of

type 2 diabetics described faster declines in women (-3.5 per year) compared with men (-2.0 per year), attributing this finding to a poorer metabolic control in women [42]. Similarly, a UK randomised control trial in type 2 diabetics found that women had an 88% increased risk over men of declining to <60 ml/min [43]. Moreover, excess mortality risk in diabetic women has been described in the dialysis population [44], as well as in non-renal cohorts [45,46], confirming a disproportional negative impact of diabetes in women. Diminished protection of oestrogens in the hyperglycemic state may explain this disparate effect, even though the women in our population were likely post-menopausal [47].

Missing eGFR values are introduced over time as patients are censored due to dialysis initiation or death. As the level of renal function is related to these events, censoring is deemed informative [28]. More importantly, as the risks of dialysis initiation or death are specific to men and women, informative censoring may affect the estimated slopes for men and women differentially, potentially introducing bias. We are unaware of any previous studies that have taken into account the sex-specific risks of dropout when studying renal decline by sex. Here, we were able to account for this issue by modelling both eGFR decline and the risk of drop-out simultaneously, providing eGFR slopes corrected for both censoring due to death and dialysis. As the risk of death did not differ substantially between men and women in our cohort, adjustment had little effect on the difference in slopes between men and women. However, as Nitsch et al demonstrated in their meta-analysis, the mortality risk difference between men and women is far larger in earlier stages of CKD [22]. In such populations, accounting for mortality would have likely had a larger effect on the difference in renal slopes between men and women, accounting for more of the difference in renal decline compared to our cohort. Conversely, accounting for censoring caused by dialysis initiation led to marginally steeper adjusted slopes, reflecting the faster renal decline in patients that were censored due to dialysis initiation. As the risk of dialysis was higher in men, the unbiased difference in renal function decline between the sexes was amplified slightly after accounting for this event, although this change in effect was not statistically significant.

Studying renal decline by sex is complicated by a sex-specific selection process throughout the pre-dialysis period. Contrary to our expectations, we found slower renal declines in older women. The literature on the effect of age on renal decline is inconsistent, with some reporting faster renal declines with increasing age [17,48], and others reporting the opposite[49,50]. Potential explanations for our findings may be a differential mortality rate in men and women (prior to inclusion) which may be inclined to select the healthier surviving women with slowly progressing CKD. One may also

hypothesize that this finding may be caused by a sex-dependent decrease in muscle mass with age, biasing our estimated glomerular filtration rates. Lastly, considering all patients in the EQUAL cohort are referred, there may be selection mechanisms at play in the referral patterns.

The main strength of our study is that we apply joint models to deal with informative censoring caused by mortality and dialysis initiation, providing unbiased estimates of renal decline. Furthermore, patients in our cohort were prospectively included when their eGFR dropped below the pre-defined level of 20 ml/min, thus minimizing the risk of survivor bias. Our study is also subject to several limitations. Preferably, we would have used measured GFR by a reference method to estimate the slope of renal decline, however, measuring GFR with a tracer technology was unfortunately not feasible in a cohort study of the size of EQUAL.. The use of eGFR in the main analysis may partly reflect muscle mass, which may disproportionately bias eGFR estimates in women [51]. Nonetheless, others have shown mGFR to perform similarly to eGFR. Lastly, due to the observational nature of our study, residual confounding may play a role, and therefore the results should be interpreted accordingly.

In older patients with advanced CKD, we demonstrate faster declines in renal function in men compared with women, even after adjustment for multiple groups of mediators. Importantly, informative events such as death and dialysis initiation explained little of the difference in renal decline between the sexes in our advanced CKD cohort. In diabetics, however, both men and women declined at a similar rate, demonstrating a disproportional negative impact of diabetes in women. Our results help understand the mechanisms underlying the differences in renal function decline between the sexes and warrant further research to develop the sex-specific interventions needed to achieve individualized management and treatment.

Disclosures

Evans received payment for lectures and participated in advisory board meetings for Astellas, received lecture honoraria from Vifor, participated in the advisory board and received study grants for AstraZeneca.

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Table 1. Baseline patient characteristics by sex.

	Overall (n=1682)	Men (n=1099)	Women (n=583)	p-value
Demographics				
Age (mean (SD))	76.30 (6.76)	75.97 (6.45)	76.94 (7.28)	0.006
Primary renal disease n (%)				
Diabetes	341 (20.5)	238 (21.9)	103 (17.9)	0.006
Glomerular disease	152 (9.1)	111 (10.2)	41 (7.1)	
Tubulo-interstitial disease	138 (8.3)	76 (7.0)	62 (10.8)	
Hypertension	596 (35.8)	378 (34.7)	218 (37.9)	
Miscellaneous renal disorders	436 (26.2)	285 (26.2)	151 (26.3)	
Weight (kg) (mean (SD))	79.70 (17.16)	83.44 (16.10)	72.51 (16.88)	<0.001
Height (cm) (mean (SD))	167.57 (9.94)	172.17 (7.86)	158.81 (7.25)	<0.001
BMI (kg/m2) (mean (SD))	28.42 (5.34)	28.20 (4.81)	28.86 (6.23)	0.023
Blood chemistry				
Albumin (g/dL) (mean (SD))	37.70 (5.91)	37.66 (5.89)	37.78 (5.97)	0.708
Calcium (mmol/L) (mean (SD))	2.24 (0.32)	2.23 (0.32)	2.27 (0.33)	0.013
Cholesterol (mmol/L) (mean (SD))	4.53 (1.28)	4.34 (1.17)	4.89 (1.41)	<0.001
PO4 (mmol/L) (mean (SD))	1.30 (0.32)	1.30 (0.33)	1.31 (0.30)	0.303
Potassium (mmol/L) (mean (SD))	4.64 (0.61)	4.67 (0.62)	4.60 (0.60)	0.037
Cardiovascular				
Systolic blood pressure (mmHg) (mean (SD))	142.85 (21.96)	143.31 (21.61)	141.99 (22.61)	0.245
Diastolic blood pressure (mean (SD))	73.83 (11.26)	74.00 (11.35)	73.49 (11.10)	0.379
Hb (g/dL) (mean (SD))	0.72 (0.09)	0.73 (0.10)	0.71 (0.09)	<0.001
Current smoker n(%)	119 (9.3)	82 (9.7)	37 (8.4)	0.538
Ex-smoker n(%)	752 (63.1)	587 (74.5)	165 (40.8)	<0.001
Renal function				
CKDEPI (ml/min/1.73m2) (median [IQR])	17.01 [13.79, 20.11]	16.69 [13.67, 19.63]	17.63 [14.40, 21.08]	<0.001
MDRD (ml/min/1.73m2) (median [IQR])	18.57 [15.27, 21.92]	18.45 [15.05, 21.62]	18.99 [15.54, 22.62]	0.036
ACR (median [IQR])	33.67 [4.90, 154.67]	41.36 [7.47, 161.10]	19.66 [2.99, 119.00]	0.002
Comorbidities				
Diabetes n(%)	693 (42)	480 (44.5)	213 (37.4)	0.006
Chronic heart failure n(%)	290 (18.1)	195 (18.7)	95 (17.0)	0.443
Cerebrovascular disease n(%)	257 (15.7)	171 (15.9)	86 (15.3)	0.781
Peripheral vascular disease n(%)	279 (17.2)	203 (19.2)	76 (13.5)	0.005
Myocardial infarction n(%)	287 (17.4)	222 (20.6)	65 (11.4)	<0.001
Angina pectoris n(%)	239 (14.7)	178 (16.8)	61 (10.9)	0.002
Left ventricular hypertrophy n(%)	349 (23.7)	244 (25.3)	105 (20.8)	0.062
Atrial fibrillation n(%)	297 (18.2)	190 (17.9)	107 (18.9)	0.644
Hypertension n(%)	1432 (89.1)	935 (89.0)	497 (89.4)	0.860

Table 2. The average annual percent decline in eGFR by sex, adjusted for various groups of mediators.

[see Excel document]

Figure 1A. The average eGFR trajectory by sex with 95% confidence intervals.

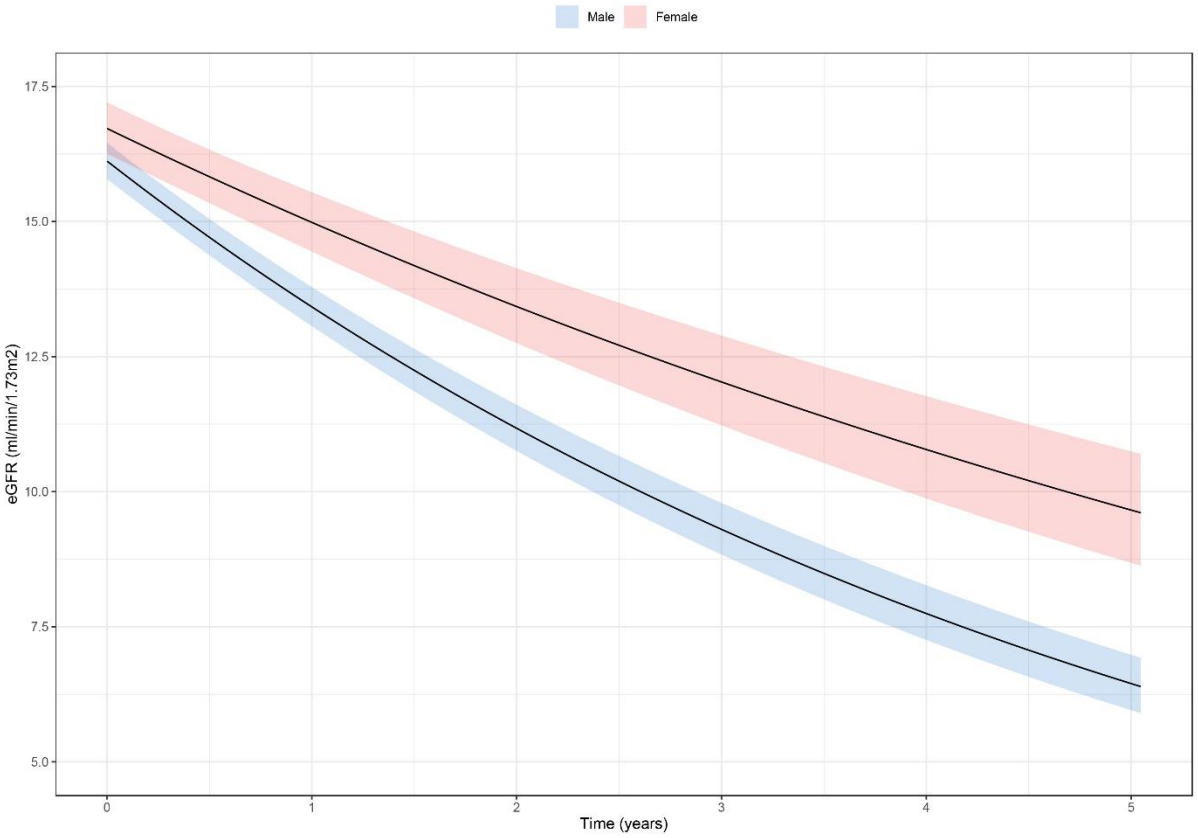


Figure 1B. The average eGFR trajectory by sex (LMM) adjusted for censoring due to death (JM: Death) and dialysis (JM: Dialysis). The adjusted trajectories represent the average eGFR trajectory in the hypothetical situation that all patients had remained alive / had not started dialysis. JM: Joint Model, LMM: linear mixed model. The top group of lines correspond to the eGFR trajectory in women and the bottom lines to that in men.

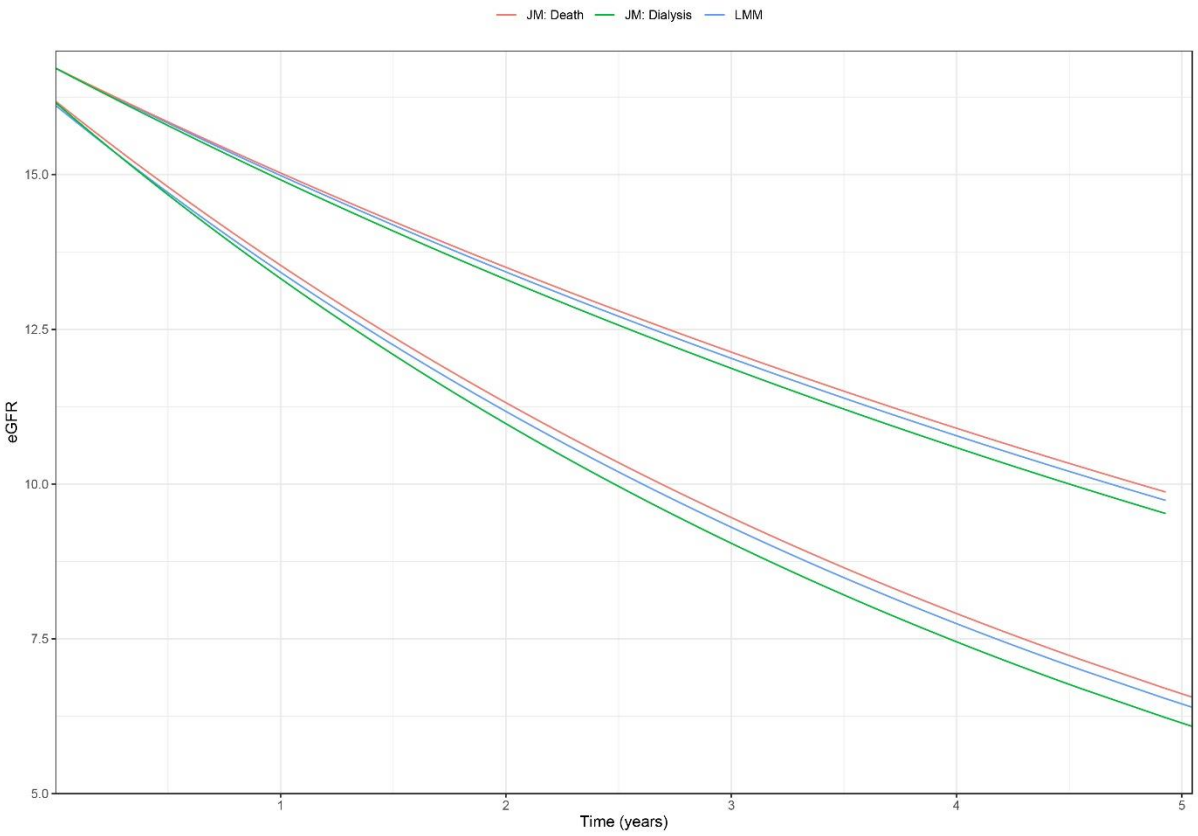


Figure 2A. Effect modification by age on renal function decline by sex.

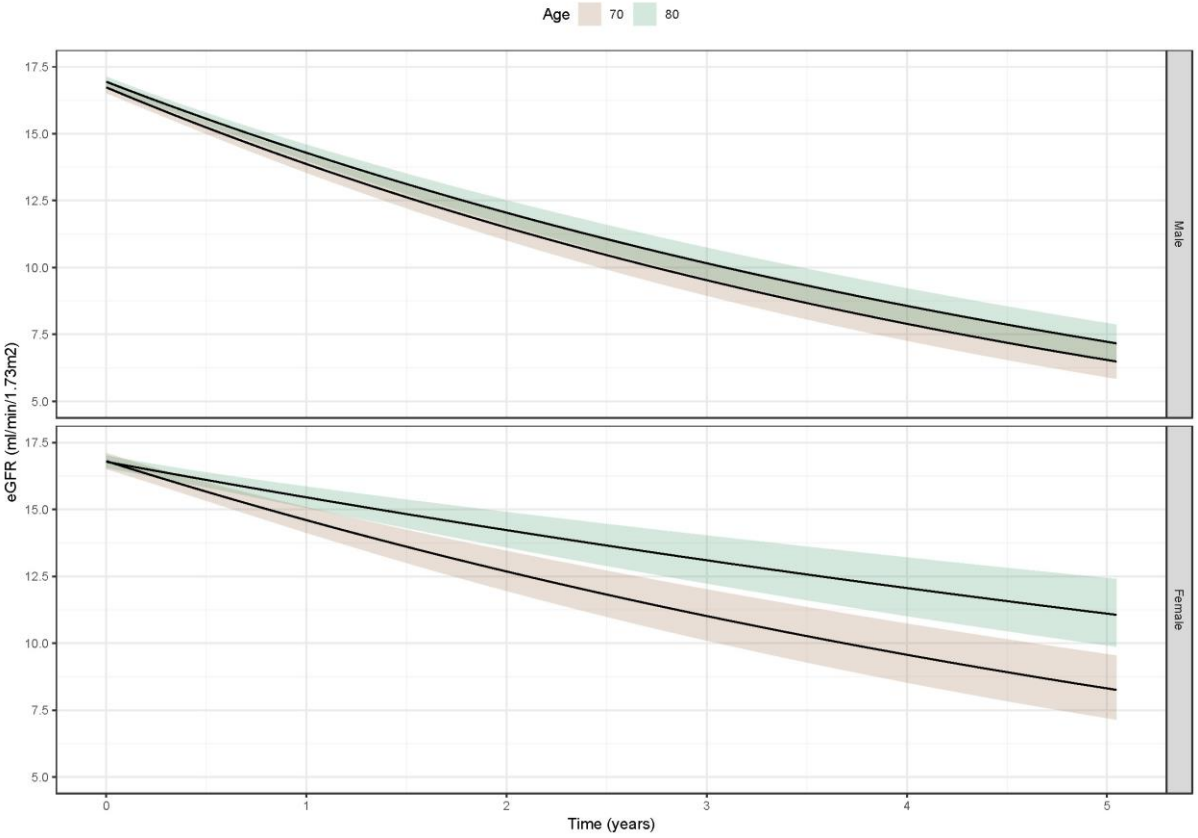
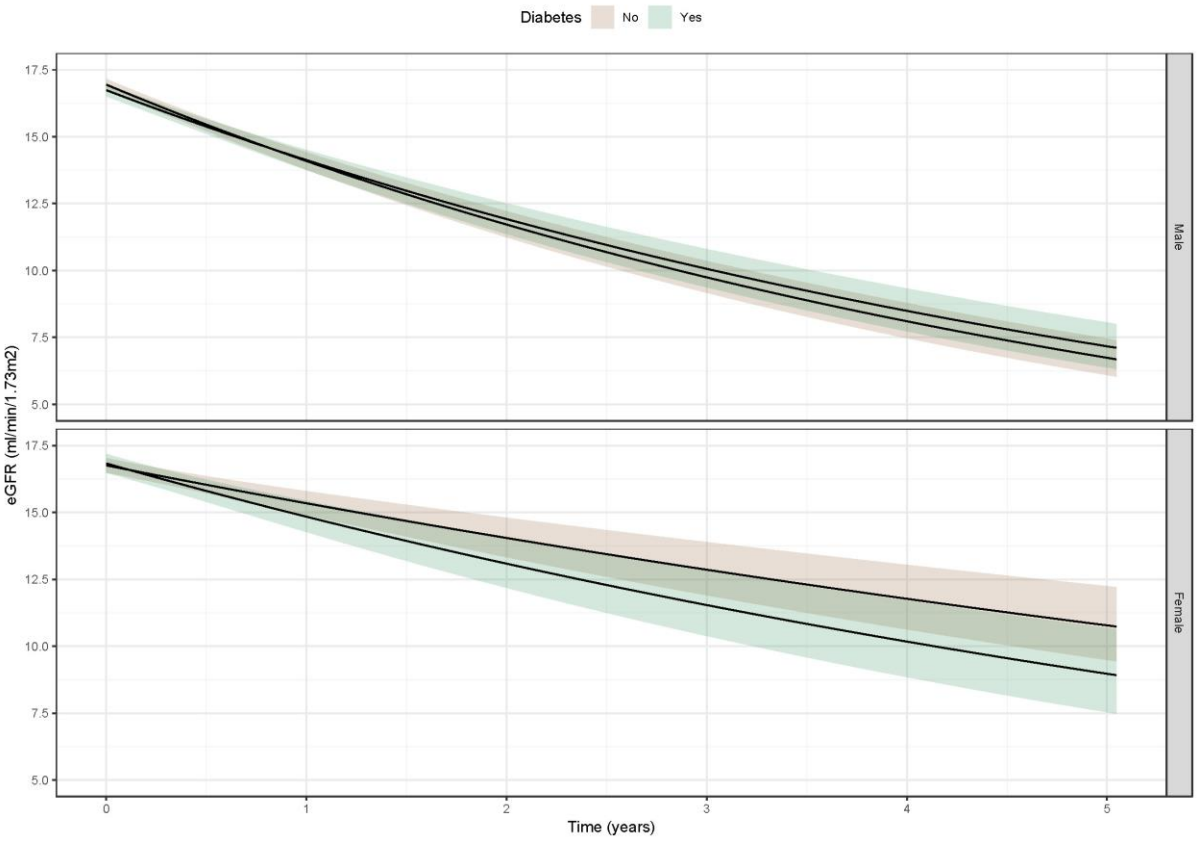


Figure 2B. Effect modification by diabetes on renal function decline by sex.



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