Proteinuria and Rate of Change in Kidney Function in a Community-Based Population

Tanvir Chowdhury Turin,* Matthew James,*[†] Pietro Ravani,*[†] Marcello Tonelli,[‡]
Braden J. Manns,*[†] Robert Quinn,*[†] Min Jun,[†] Scott Klarenbach,[‡] and
Brenda R. Hemmelgarn* [‡]

*Department of Community Health Sciences and [†]Department of Medicine, University of Calgary, Calgary, Alberta,
Canada, and [‡]Department of Medicine, University of Alberta, Edmonton, Alberta, Canada

ABSTRACT

Proteinuria identifies patients at risk for adverse clinical outcomes, but it is unclear whether proteinuria correlates with the rate of renal decline. We examined the association between proteinuria and rate of change in estimated GFR (eGFR) in a cohort of 638,150 adults from a province-wide registry in Alberta, Canada, who had a measure of proteinuria and three or more outpatient serum creatinine measurements over a period of ≥1 year. An adjusted sex-specific linear mixed-effects model was used to determine the rate of change in eGFR per year for patients with normal, mild, and heavy proteinuria, stratified by baseline kidney function (eGFR ≥90, 60–89.9, 45–59.9, 30–44.9, and 15–29.9 ml/min per 1.73 m^2). In men, heavy proteinuria and a baseline eGFR of 45–59.9 ml/min per 1.73 m^2 correlated with a change in eGFR of −2.16 (95% confidence interval [CI], −2.37 to −1.95) ml/min per 1.73 m^2 per year, whereas mild proteinuria and a baseline eGFR of 30–44.9 ml/min per 1.73 m^2 correlated with a change in eGFR of −0.51 (95% CI, −0.70 to −0.32) ml/min per 1.73 m^2 per year. Similar trends were observed for female, elderly, and diabetic patients. Notably, normal protein levels and a lower baseline eGFR (15–29.9 ml/min per 1.73 m^2) correlated with stable or improved renal function. In conclusion, our results suggest that proteinuria of increasing severity is associated with a faster rate of renal decline, regardless of baseline eGFR, and the combined effect should be considered in patients with CKD.

Reduced kidney function is a marker of adverse clinical outcomes.[1,2] Emphasis has been placed on early detection and implementation of strategies to slow the diminution of kidney function, despite a limited understanding of the rate of change in kidney function and factors affecting progression. Although previous studies have examined progression of kidney function, these reports were predominantly based on selected patient populations (older adults) or involved a relatively small number of participants.[3–6]

The presence of proteinuria, a marker of kidney damage, identifies patients at increased risk of adverse clinical outcomes, including progression to ESRD.[7–12] However, whether the effects of proteinuria on earlier signs of kidney damage, namely the rate of change in estimated GFR (eGFR), vary by baseline level of kidney function is less clear. A

more detailed understanding of the relationship among proteinuria, kidney function, and progression of renal disease would permit the identification of those who are at greatest risk of a progressive decline in kidney function and aid in implementation of interventions to slow the progression or prevent the development of ESRD.

We sought to determine the association between proteinuria and rate of change in eGFR among a

Table 1. Demographic and clinical characteristics of participants, by level of kidney function or proteinuria

Characteristic	Proteinuria Measured by Dipstick (n=612,776)			Proteinuria Measured by ACR (n=86,830)		
	None (n=560,326)	Mild (n=43,729)	Heavy (n=8,711)	None (n=64,680)	Mild (n=17,536)	Heavy (n=4,614)
Mean age (yr) ± SD	51.7±15.8	54.0±18.3	55.6±18.4	56.9±13.9	60.3±14.9	60.0±15.4
Mean eGFR (ml/min per 1.73 m^2) ± SD	88.6±19.6	83.5±24.0	73.5±29.0	83.6±19.8	79.2±23.6	70.1±27.4
Female	60	51	42	47	44	40
Aboriginal	2	3	4	2	4	6
Diabetes	9	18	34	52	67	72
Hypertension	29	41	56	52	63	70
Cerebrovascular disease	2	4	7	3	5	6
PVD	1	3	5	2	4	6
CHF	2	5	9	3	7	10
Cancer	4	6	7	5	6	6
COPD	14	18	20	16	18	20
Dementia	1	2	3	1	1	1
Metastatic solid tumor	0	1	1	0	0	1
Myocardial infarction	2	4	6	4	6	8
Mild liver disease	1	1	2	1	1	2
Paralysis	0	1	1	0	1	1
PUD	2	3	3	3	3	3
Rheumatic disease	2	2	3	1	1	2
Socioeconomic status						
Pensioner	22	31	35	30	41	38
Low	15	14	14	18	16	16
Low with subsidy	3	5	6	4	4	7

Unless otherwise noted, data are expressed as percentages. Totals do not always add to 100% because of rounding. Socioeconomic status was categorized as high (annual adjusted taxable family income ≥$39,250 CAD), low (annual adjusted taxable family income < $39,250 CAD), low with subsidy (receiving social assistance), and pensioners (age ≥65 years) according to government of Alberta health care insurance records. PVD, peripheral vascular disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; PUD, peptic ulcer disease.

large cohort of individuals receiving routine care in a single Canadian province. We also evaluated whether the association between proteinuria and rate of change in eGFR varied by baseline level of kidney function, and among prespecified subgroups stratified by sex, age, and diabetic status.

RESULTS

Participant Characteristics

A total of 638,150 participants had three or more outpatient serum creatinine measurements over a period >1 year. Of these participants, 612,776 (96.0%) had a urine dipstick measurement and 86,830 (13.6%) had a measurement of the albumin-to-creatinine ratio (ACR). Most participants had a baseline eGFR (ml/min per 1.73 m^2 per year) of ≥90 (47.5%) and 89.9–60 (43.4%), whereas 6.4%, 2.0%, and 0.6% had a baseline eGFR of 45–59.9, 30–44.9, and 15–29.9, respectively. The median follow-up time was 4.4 years, during which a median of four serum creatinine measurements per patient were obtained. Among the participants, 7.7% had a follow-up of <2 years, 13.5% had a follow-up of <3 years, 18.6% had a follow-up of <4 years, and 60.1% had a follow-up of ≥4 years. As outlined in Table 1, participants without proteinuria were younger and more likely to be female. As the

participants' baseline urine protein deteriorated, the prevalence of diabetes, hypertension, and other comorbid conditions increased. Mild proteinuria was present in 7.1% of participants with proteinuria measured by urine dipstick and in 20.2% of participants with proteinuria measured by ACR. Participants who had their proteinuria measured by ACR were older, more likely to be male, and more likely to have diabetes and hypertension.

Rate of Change in eGFR

The adjusted rates of change in eGFR (ml/min per 1.73 m^2 per year) are shown in Figure 1 for men and Figure 2 for women. Within each stratum of eGFR, the rate of change in kidney function varied substantially according to presence and severity of proteinuria. After adjustment for sociodemographic characteristics and comorbidity, men with heavy proteinuria and baseline kidney function of 45–59.9 ml/min per 1.73 m^2 had an annual rate of decline in eGFR of −2.16 (95% confidence interval [CI], −2.37 to −1.95) ml/min per 1.73 m^2, whereas those with baseline kidney function of 30–44.9 ml/min per 1.73 m^2 and mild proteinuria had an annual rate of change of −0.51 (95% CI, −0.70 to −0.32) ml/min per 1.73 m^2. The trend was similar for women (Figure 2). However, the rate of decline among participants with heavy proteinuria was consistently greater for men than women, except for those in the
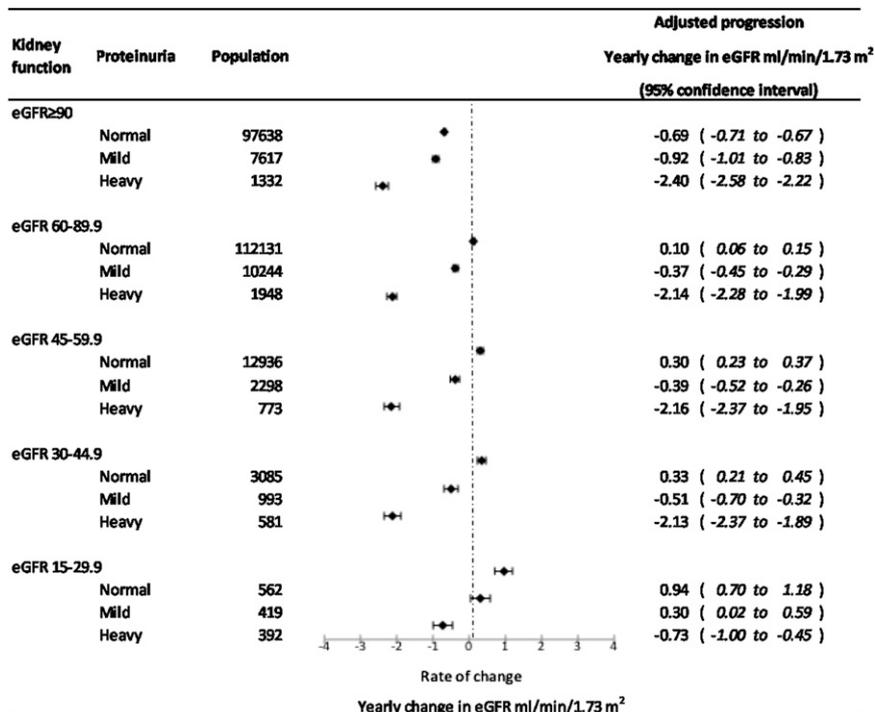
Kidney function	Proteinuria	Population	Adjusted progression
			Yearly change in eGFR ml/min/1.73 m²
			(95% confidence interval)
eGFR≥90			
	Normal	97638	-0.69 (-0.71 to -0.67)
	Mild	7617	-0.92 (-1.01 to -0.83)
	Heavy	1332	-2.40 (-2.58 to -2.22)
eGFR 60-89.9			
	Normal	112131	0.10 (0.06 to 0.15)
	Mild	10244	-0.37 (-0.45 to -0.29)
	Heavy	1948	-2.14 (-2.28 to -1.99)
eGFR 45-59.9			
	Normal	12936	0.30 (0.23 to 0.37)
	Mild	2298	-0.39 (-0.52 to -0.26)
	Heavy	773	-2.16 (-2.37 to -1.95)
eGFR 30-44.9			
	Normal	3085	0.33 (0.21 to 0.45)
	Mild	993	-0.51 (-0.70 to -0.32)
	Heavy	581	-2.13 (-2.37 to -1.89)
eGFR 15-29.9			
	Normal	562	0.94 (0.70 to 1.18)
	Mild	419	0.30 (0.02 to 0.59)
	Heavy	392	-0.73 (-1.00 to -0.45)

Rate of change
Yearly change in eGFR ml/min/1.73 m²

Figure 1. Rate of change in eGFR varied substantially across categories of proteinuria for men in every level of kidney function. Squares and horizontal bars represent the estimates and 95% CIs respectively for multivariate adusted rate of change in eGFR (ml/min per 1.73 m² per year) of participants for various levels of kidney function status and proteinuria (measured by dipstick).

lowest eGFR category (15–29.9 ml/min per 1.73 m²). Of note, among participants with a baseline eGFR of 15–29.9 ml/min per 1.73 m², the rate of decline in kidney function was less pronounced across categories of proteinuria, although the trend of a greater rate of decline with increasing proteinuria persisted, as in other eGFR categories. Men with eGFR of 15–29.9 ml/min per 1.73 m² and heavy proteinuria had an annual rate of change of −0.73 (95% CI, −1.00 to −0.45) ml/min per 1.73 m². Results for women were similar.

Subgroup Analyses
Similar gradients in the rate of change in kidney function by level of proteinuria were observed when analyses were performed among the subset of 86,830 participants who had proteinuria estimated by urinary ACR measurements (Figures 3 and 4). Men with heavy proteinuria and baseline kidney function of 45–59.9 ml/min per 1.73 m² had an adjusted annual rate of change in eGFR of −3.05 (95% CI, −3.40 to −2.71) ml/min per 1.73 m², whereas those with baseline kidney function of 30–44.9 ml/min per 1.73 m² and mild proteinuria had a rate of change of −0.63 (95% CI, −0.95 to −0.31) ml/min per 1.73 m². Similar trends were observed for women (Figure 5). The rate of change in eGFR was greater with heavy proteinuria measured by ACR compared with that measured by dipstick proteinuria, within all eGFR strata and for both men and women.

We repeated analyses that further stratified by age. Findings among participants who were 65 years and older were similar to those of participants 18–64 years of age. Analysis of the subset of participants with a follow-up of 2 years or more showed similar results. Analyses stratified by presence and absence of diabetes mellitus revealed similar results, with proteinuria of increasing severity associated with a more rapid rate of decline in kidney function, across all levels of baseline kidney function. The adjusted annual rate of change in eGFR for diabetic men and women by proteinuria measured by ACR are shown in Supplemental Figures 1 and 2, respectively.

DISCUSSION

In this population-based cohort, we observed that the rate of decline in kidney function within a given level of eGFR varied substantially according to the presence and severity of proteinuria. Persons with heavy proteinuria but without overtly abnormal eGFR had more rapid progression of kidney function than did those with moderately reduced eGFR but mild proteinuria. Within each strata of eGFR, patients with normal proteinuria experienced the lowest rate of decline in kidney function. Results were consistent for men and women, young and old, for patients with and without diabetes mellitus, and in further subgroup analyses in which proteinuria was measured by ACR and in patients with ≥2 years of follow-up.

Our study findings further emphasize the importance of considering proteinuria in classifying kidney function status.[11–13] Our findings demonstrate that change in eGFR over time is relatively insensitive to assessment of kidney function alone but are highly dependent on the degree of underlying proteinuria. Although dipstick urinalysis has less favorable diagnostic properties compared with ACR for the assessment of proteinuria,[14] dipstick urinalysis was the most common test used to measure proteinuria in our study population. Quantitative and semi-quantitative measurements of proteinuria, such as ACR, are preferable in the assessment of CKD,[15] but dipstick urinalysis is considerably less expensive and easier to administer, and thus more widely used. Further, the consistency of the results for both urine dipstick and ACR assessment of proteinuria is reassuring.

Observations from prior studies suggest sex-specific differences in progression of CKD, pointing toward a higher rate of progression of kidney disease for men.[3,16,17] On the contrary, Jafar et al.,[18] in a patient-level meta-analysis of a pooled database of 11 randomized controlled trials, reported that

Kidney function	Proteinuria	Population	Adjusted progression Yearly change in eGFR ml/min/1.73 m² (95% confidence interval)
eGFR≥90			
	Normal	175015	-0.86 (-0.88 to -0.85)
	Mild	10517	-0.87 (-0.94 to -0.79)
	Heavy	1393	-1.99 (-2.15 to -1.82)
eGFR 60-89.9			
	Normal	132058	-0.05 (-0.09 to -0.02)
	Mild	7903	-0.28 (-0.36 to -0.20)
	Heavy	1118	-1.86 (-2.04 to -1.69)
eGFR 45-59.9			
	Normal	19580	0.29 (0.24 to 0.35)
	Mild	2199	-0.36 (-0.49 to -0.23)
	Heavy	483	-2.07 (-2.31 to -1.82)
eGFR 30-44.9			
	Normal	6036	0.52 (0.44 to 0.60)
	Mild	118	-0.29 (-0.46 to -0.12)
	Heavy	409	-1.76 (-2.02 to -1.50)
eGFR 15-29.9			
	Normal	1285	0.79 (0.64 to 0.95)
	Mild	421	-0.20 (-0.47 to 0.07)
	Heavy	282	-0.95 (-1.26 to -0.64)

Rate of change
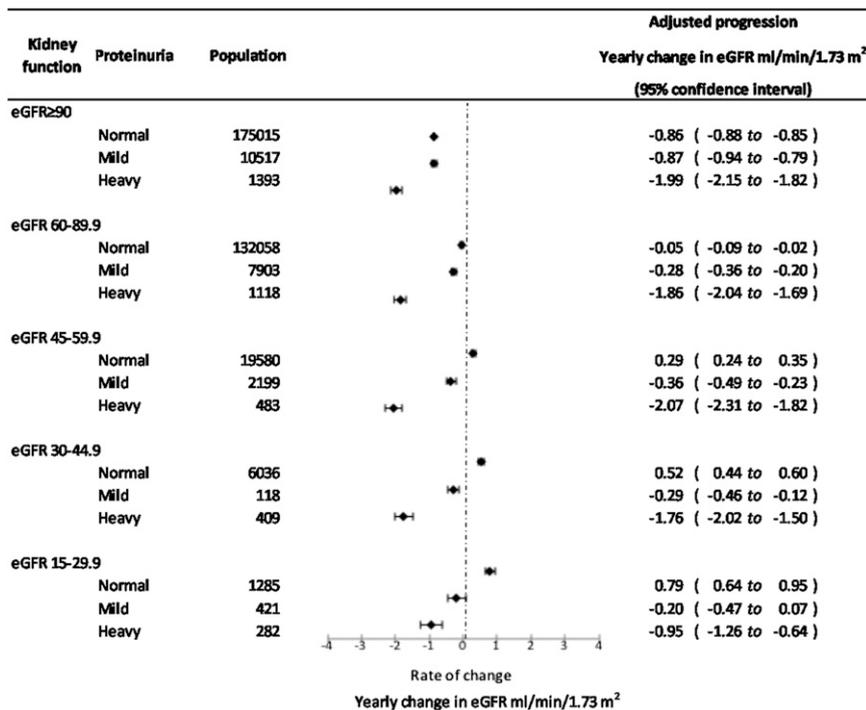Yearly change in eGFR ml/min/1.73 m²

Figure 2. Rate of change in eGFR varied substantially across categories of proteinuria for women in every level of kidney function. Squares and horizontal bars represent the estimates and 95% CIs respectively for multivariate adusted rate of change in eGFR (ml/min per 1.73 m² per year) of participants for various levels of kidney function status and proteinuria (measured by dipstick).

that these patients receive because of their more severe kidney disease. Another factor that might be associated with this observed stable/improved kidney function is the statistical phenomenon of regression to mean, which would have the greatest effect on extreme values of eGFR. The phenomenon implies that if a variable is extreme on its first measurement, it will tend to be closer to the average on subsequent measurements,[20,21] which is more likely to occur at higher levels of serum creatinine (and lower levels of eGFR). Also, the small number of participants in this group might have affected the analysis results. Importantly, however, our results add to those of prior studies by highlighting that stable kidney function, or improvements over time, occur in patients with normal proteinuria. These results identify the importance of proteinuria in predicting which patients with CKD are more likely to progress and which will have a more stable disease course.

Our study has several strengths, including the ability to study a large cohort of community-dwelling participants using multiple measurements of eGFR. We were also able to demonstrate the robustness of our results in several sensitivity analyses. However, several limitations due to the observational nature of this study also need to be considered. The cohort was limited to individuals who had at least three outpatient serum creatinine measurements over a period of at least 1 year and a measure of urinary protein. These assessments of creatinine or proteinuria were made for clinical purposes, and therefore do not include individuals who did not use medical services, which would affect the generalizability of our findings. We also did not have information on the physician who ordered the serum creatinine measurement or the indications. Because we used multiple serum creatinine measurements over time, laboratory drift over time may have influenced the study results. However, the effect of this potential laboratory drift is expected to be minimal because we calibrated measurements across time periods against a subset of healthy participants.[22] Also, although we have estimated the rate of change in eGFR stratified by baseline kidney function categories, the estimation of the change in eGFR could have been affected by the baseline eGFR as a result of the statistical phenomenon of the relation between change and initial value. Although we adjusted for comorbid conditions, we could not adjust for BP control, cause of kidney disease, smoking habit, or lipid control, variables that may be associated with change in kidney function. Finally, we also could not adjust for drug use, such as use of blockers of the renin-angiotensin system, because this information is available for only a subset of the population in Alberta aged 65 years and

progression of kidney disease in women was similar to that in men after correcting for baseline covariates. Similarly, in our study, we did not observe any definitive negative effect of male sex on the rate of change in eGFR.

We found that patients with normal proteinuria experienced relatively stable kidney function over time. Also, interestingly, patients with lower baseline levels of eGFR (15–29.9 mL/min per 1.73 m²) showed a trend toward stable or improved kidney function during the 4.4-year study period. Although CKD has traditionally been regarded as unremittingly progressive, our findings do not support those views and are similar to results from other recent studies. In a cohort of 3047 patients from a Norwegian clinical practice who had stage 3 CKD, Erikson and Ingebretsen reported that 27% of participants did not experience a decline in eGFR during a mean observation time of >4 years.[3] Al-Aly et al. also reported that after a median observation period of 2.6 years, 38% of patients with stage 3 CKD maintained stable kidney function.[19] In our study, a subset of participants with stage 3 and 4 CKD and normal proteinuria showed stable or improved kidney function.

Why would patients with lower levels of kidney function and normal or mild proteinuria experience relatively stable kidney function over time? We speculate that this may be related to several factors, including the closer follow-up and treatment

Kidney function	Proteinuria	Population	Adjusted progression Yearly change in eGFR ml/min/1.73 m2 (95% confidence interval)	
eGFR≥90				
	Normal	13467	-0.65	(-0.71 to -0.60)
	Mild	3352	-1.48	(-1.67 to -1.30)
	Heavy	726	-3.56	(-3.87 to -3.25)
eGFR 60-89.9				
	Normal	17118	0.02	(-0.11 to 0.16)
	Mild	4461	-1.19	(-1.36 to -1.02)
	Heavy	1042	-3.51	(-3.77 to -3.24)
eGFR 45-59.9				
	Normal	2605	0.32	(0.13 to 0.52)
	Mild	1182	-0.87	(-1.12 to -0.62)
	Heavy	461	-3.05	(-3.40 to -2.71)
eGFR 30-44.9				
	Normal	728	0.31	(0.01 to 0.60)
	Mild	577	-0.63	(-0.95 to -0.31)
	Heavy	348	-2.51	(-2.90 to -2.12)
eGFR 15-29.9				
	Normal	104	0.67	(0.01 to 1.33)
	Mild	191	0.06	(-0.44 to 0.57)
	Heavy	199	-1.48	(-1.96 to -0.99)

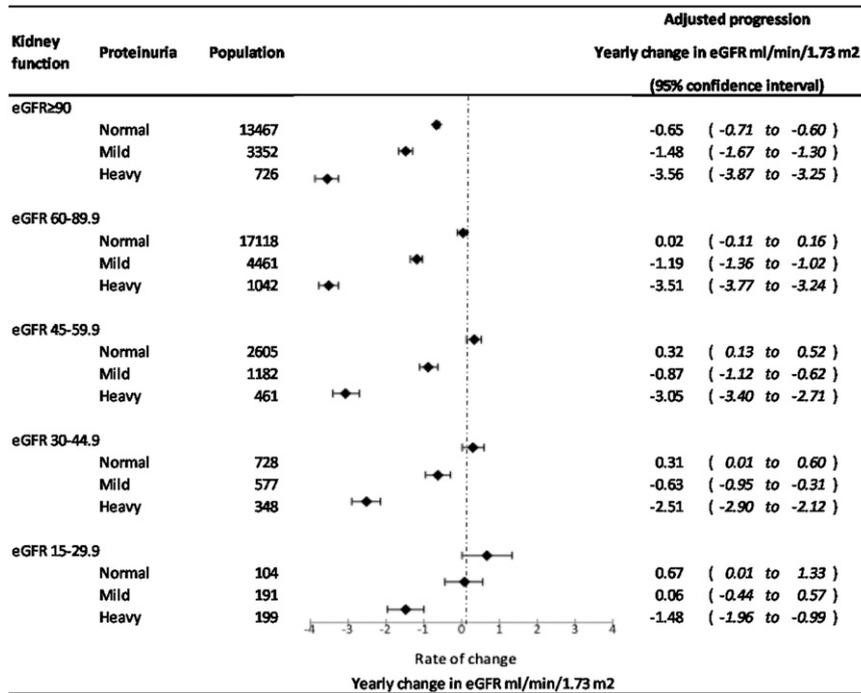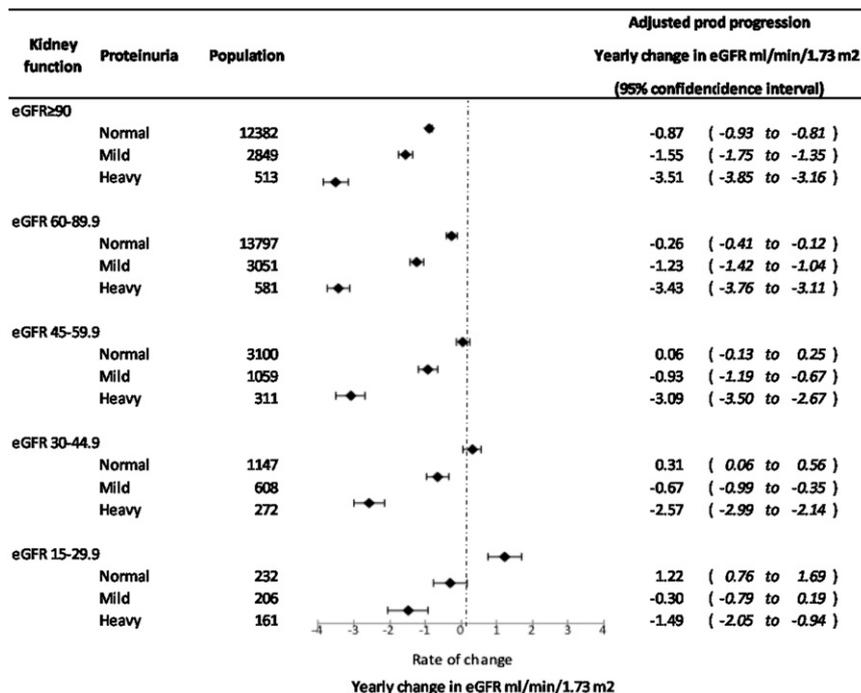Rate of change
Yearly change in eGFR ml/min/1.73 m2

Figure 3. Rate of change in eGFR varied substantially across categories of proteinuria for men in every level of kidney function. Squares and horizontal bars represent the estimates and 95% CIs respectively for multivariate adusted rate of change in eGFR (ml/min per 1.73 m^2 per year) of participants for various levels of kidney function status and proteinuria (measured by albumin to creatinine ratio).

Kidney function	Proteinuria	Population	Adjusted prod progression Yearly change in eGFR ml/min/1.73 m2 (95% confidencidence interval)	
eGFR≥90				
	Normal	12382	-0.87	(-0.93 to -0.81)
	Mild	2849	-1.55	(-1.75 to -1.35)
	Heavy	513	-3.51	(-3.85 to -3.16)
eGFR 60-89.9				
	Normal	13797	-0.26	(-0.41 to -0.12)
	Mild	3051	-1.23	(-1.42 to -1.04)
	Heavy	581	-3.43	(-3.76 to -3.11)
eGFR 45-59.9				
	Normal	3100	0.06	(-0.13 to 0.25)
	Mild	1059	-0.93	(-1.19 to -0.67)
	Heavy	311	-3.09	(-3.50 to -2.67)
eGFR 30-44.9				
	Normal	1147	0.31	(0.06 to 0.56)
	Mild	608	-0.67	(-0.99 to -0.35)
	Heavy	272	-2.57	(-2.99 to -2.14)
eGFR 15-29.9				
	Normal	232	1.22	(0.76 to 1.69)
	Mild	206	-0.30	(-0.79 to 0.19)
	Heavy	161	-1.49	(-2.05 to -0.94)

Rate of change
Yearly change in eGFR ml/min/1.73 m2

Figure 4. Rate of change in eGFR varied substantially across categories of proteinuria for men in every level of kidney function. Squares and horizontal bars represent the estimates and 95% CIs respectively for multivariate adusted rate of change in eGFR (ml/min per 1.73 m^2 per year) of participants for various levels of kidney function status and proteinuria (measured by albumin to creatinine ratio).

older. Because the aim of this study was to illustrate the progression of kidney function over time in a community-based cohort, not to identify the predictors of progression, lack of information on these variables specifically would not change the overall interpretation of our study results.

In conclusion, we found that the rate of change in the kidney function associated with a given level of eGFR varies substantially according to the presence and severity of proteinuria. These findings further support information on both proteinuria and eGFR needs be considered together when identifying patients at higher rate of kidney function decline.

CONCISE METHODS

Study Population
The Alberta Kidney Disease Network repository of laboratory data was used to create the study cohort.[22] Eligible participants included adults in the province of Alberta, Canada, age 18 years or older who had at least three outpatient creatinine measurements over a period of at least 12 months in the period of May 2002 to March 2008 (Figure 5). To avoid episodes of acute renal failure, laboratory measurements associated with a hospital admission were not considered. Patients were excluded if they were treated with dialysis or a kidney transplant at baseline,[23] or if the baseline eGFR was <15 ml/min per 1.73 m^2.

Measurement of Kidney Function and Proteinuria
The eGFR for each participant was estimated using the CKD-Epidemiology Collaboration equation.[24] Although data on race were not available from the data sources, <1% of the Alberta population is black.[25] Thus, the population-level effect of eliminating race from the estimate of GFR was expected to be minimal. The first available eGFR was used to define the index (baseline) eGFR. All outpatient eGFR measurements until study end (December 31, 2009) were considered. The index eGFR (baseline kidney function) was categorized as ≥90, 60–89.9, 45–59.9, 30–44.9, and 15–29.9 ml/min per 1.73 m^2.

Outpatient random spot urine dipstick and ACR measurements were used to estimate proteinuria. All outpatient urine dipstick and ACR measurements in the 6-month period around
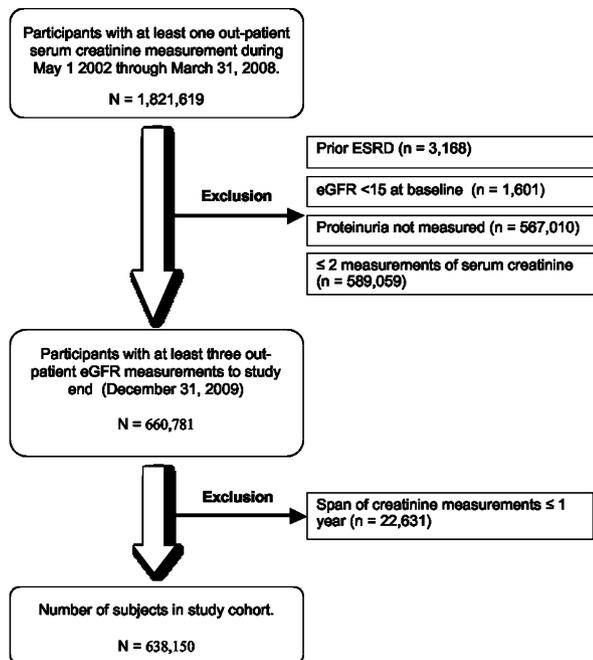
```
┌──────────────────────────────────┐
│ Participants with at least one out-patient │
│ serum creatinine measurement during │
│ May 1 2002 through March 31, 2008. │
│            N = 1,821,619          │
└──────────────────────────────────┘
```

Prior ESRD (n = 3,168)

eGFR <15 at baseline (n = 1,601)

Proteinuria not measured (n = 567,010)

≤ 2 measurements of serum creatinine
(n = 589,059)

Exclusion

```
┌──────────────────────────────────┐
│ Participants with at least three out- │
│ patient eGFR measurements to study │
│ end  (December 31, 2009)          │
│            N = 660,781            │
└──────────────────────────────────┘
```

Exclusion

Span of creatinine measurements ≤ 1
year (n = 22,631)

```
┌──────────────────────────────────┐
│ Number of subjects in study cohort. │
│            N = 638,150           │
└──────────────────────────────────┘
```

Figure 5. Overview of cohort formation.

the index eGFR were used to establish baseline proteinuria. In the primary analysis, all patients with at least one urine dipstick measurement were included and proteinuria was categorized as normal (urine dipstick negative), mild (urine dipstick trace or 1+), or heavy (urine dipstick 2+).[26] In sensitivity analyses, proteinuria based on ACR was used; the proteinuria categories were normal (ACR <30 mg/g), mild (ACR 30–300 mg/g), or heavy (ACR >300 mg/g).[26]

Covariates

Administrative data files of the provincial health ministry (Alberta Health) were used to define demographic characteristics and comorbid conditions. First Nations status was determined from the registry file; it was not possible to identify other race/ethnic groups, although >85% of the Alberta population is white.[25] Socioeconomic status was categorized according to government records as high income (annual adjusted taxable family income ≥$39,250 CAD), low income (annual adjusted taxable family income <$39,250 CAD), low income with subsidy (receiving social assistance), and pensioners (≥65 years of age).[27] Presence of diabetes mellitus and hypertension were identified from hospital discharge records and physician claims based on validated algorithms.[28,29] Other comorbid conditions were identified from physician claims and hospitalization data using validated coding algorithms for the International Classification of Diseases, Ninth Revision, Clinical Modification, and International Classification of Diseases, Tenth Revision.[30]

Statistical Analyses

For the assessment of progression of kidney function across the eGFR and proteinuria levels, we determined the rate of change in eGFR in ml/min per 1.73 m^2 per year, using a linear mixed-effects model

regression analysis to model longitudinal change in the eGFR in association with kidney function and proteinuria categories. The mixed-effect model, with random intercepts and random slopes, estimates the rate of change in eGFR over time, taking into account the varying number and spacing of measurements of eGFR, as well as the variable follow-up for each patient. The analysis incorporated random-effects terms to account for patient and patient × time differences in the eGFR values. Covariates considered were age, sex, socioeconomic status, kidney function, proteinuria category, and comorbid conditions listed in Table 1. All variables were retained in the final model, and no criterion for removal of variables was applied.[31] In addition, a term was incorporated into the model to assess interactive effects of eGFR level and proteinuria categories. Mixed-effects model assumptions, that random effects are linear and normally distributed, were examined using graphical diagnostics. Residuals were examined to ensure that they were normally distributed, and plots of residuals against predicted values and effects were examined to verify that nonlinear trends in the data were not present. We performed sex-stratified analysis because the preliminary analyses found evidence of a statistically significant interaction ($P<0.01$) between sex and progression of kidney function, as well as prior literature indicating that men show a more rapid decline in kidney function than women.[16,32] Results are presented as the rate of change in eGFR per year.

The primary analysis was based on the cohort of participants with proteinuria defined from dipstick urinalysis. We undertook many sensitivity analyses to ensure the robustness of our results. We repeated all analyses with further stratification by age (18–64 and ≥65 years) and presence of diabetes mellitus, and among the subset of participants with a follow-up of 2 years or more. Finally, we repeated estimations for the subset of participants who had data for proteinuria based on urinary ACR. Statistical analyses were performed using SAS software, version 9.2 (SAS Institute Inc., Cary, NC) and Stata software, version 11.0 (Stata Corp., College Station, TX). The institutional review board of the University of Calgary approved the study. The institutional conjoint health research ethics review board approved the study and granted waiver of patient consent.

REFERENCES

1. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 351: 1296–1305, 2004

2. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW; American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention: Kidney disease as a risk factor for development of cardiovascular disease: A statement from the american heart association councils on kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. *Circulation* 108: 2154–2169, 2003

3. Eriksen BO, Ingebretsen OC: The progression of chronic kidney disease: A 10-year population-based study of the effects of gender and age. *Kidney Int* 69: 375–382, 2006

4. Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH: Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med* 164: 659–663, 2004

5. Hemmelgarn BR, Zhang J, Manns BJ, Tonelli M, Larsen E, Ghali WA, Southern DA, McLaughlin K, Mortis G, Culleton BF: Progression of kidney dysfunction in the community-dwelling elderly. *Kidney Int* 69: 2155–2161, 2006

6. Halbesma N, Kuiken DS, Brantsma AH, Bakker SJL, Wetzels JFM, De Zeeuw D, De Jong PE, Gansevoort RT: Macroalbuminuria is a better risk marker than low estimated GFR to identify individuals at risk for accelerated GFR loss in population screening. *J Am Soc Nephrol* 17: 2582–2590, 2006

7. Culleton BF, Larson MG, Parfrey PS, Kannel WB, Levy D: Proteinuria as a risk factor for cardiovascular disease and mortality in older people: A prospective study. *Am J Med* 109: 1–8, 2000

8. Jafar TH, Stark PC, Schmid CH, Landa M, Maschio G, Marcantoni C, de Jong PE, de Zeeuw D, Shahinfar S, Ruggenenti P, Remuzzi G, Levey AS; AIPRD Study Group. Angiotensin-converting enzyme inhibition and progression of renal disease: Proteinuria as a modifiable risk factor for the progression of non-diabetic renal disease. *Kidney Int* 60: 1131–1140, 2001

9. Lea J, Greene T, Hebert L, Lipkowitz M, Massry S, Middleton J, Rostand SG, Miller E, Smith W, Bakris GL: The relationship between magnitude of proteinuria reduction and risk of end-stage renal disease: Results of the African American study of kidney disease and hypertension. *Arch Intern Med* 165: 947–953, 2005

10. van der Velde M, Halbesma N, de Charro FT, Bakker SJL, de Zeeuw D, de Jong PE, Gansevoort RT: Screening for albuminuria identifies individuals at increased renal risk. *J Am Soc Nephrol* 20: 852–862, 2009

11. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT; Chronic Kidney Disease Prognosis Consortium: Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: A collaborative meta-analysis. *Lancet* 375: 2073–2081, 2010

12. Hemmelgarn BR, Manns BJ, Lloyd A, James MT, Klarenbach S, Quinn RR, Wiebe N, Tonelli M; Alberta Kidney Disease Network: Relation between kidney function, proteinuria, and adverse outcomes. *JAMA* 303: 423–429, 2010

13. Hallan SI, Ritz E, Lydersen S, Romundstad S, Kvenild K, Orth SR: Combining GFR and albuminuria to classify CKD improves prediction of ESRD. *J Am Soc Nephrol* 20: 1069–1077, 2009

14. Ciavarella A, Silletti A, Forlani G, Morotti L, Borgnino LC, D'Apote M, Vannini P: A screening test for microalbuminuria in type 1 (insulin-dependent) diabetes. *Diabetes Res Clin Pract* 7: 307–312, 1989

15. Eknoyan G, Levin NW; National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am J Kidney Dis* 39[Suppl 1]: S1–S266, 2002

16. Neugarten J, Acharya A, Silbiger SR: Effect of gender on the progression of nondiabetic renal disease: A meta-analysis. *J Am Soc Nephrol* 11: 319–329, 2000

17. Seliger SL, Davis C, Stehman-Breen C: Gender and the progression of renal disease. *Curr Opin Nephrol Hypertens* 10: 219–225, 2001

18. Jafar TH, Schmid CH, Stark PC, Toto R, Remuzzi G, Ruggenenti P, Marcantoni C, Becker G, Shahinfar S, De Jong PE, De Zeeuw D, Kamper AL, Strangaard S, Levey AS: The rate of progression of renal disease may not be slower in women compared with men: A patient-level meta-analysis. *Nephrol Dial Transplant* 18: 2047–2053, 2003

19. Al-Aly Z, Zeringue A, Fu J, Rauchman MI, McDonald JR, El-Achkar TM, Balasubramanian S, Nurutdinova D, Xian H, Stroupe K, Abbott KC, Eisen S: Rate of kidney function decline associates with mortality. *J Am Soc Nephrol* 21: 1961–1969, 2010

20. Bland JM, Altman DG: Some examples of regression towards the mean. *BMJ* 309: 780, 1994

21. Barnett AG, van der Pols JC, Dobson AJ: Regression to the mean: What it is and how to deal with it. *Int J Epidemiol* 34: 215–220, 2005

22. Hemmelgarn BR, Clement F, Manns BJ, Klarenbach S, James MT, Ravani P, Pannu N, Ahmed SB, MacRae J, Scott-Douglas N, Jindal K, Quinn R, Culleton BF, Wiebe N, Krause R, Thorlacius L, Tonelli M: Overview of the Alberta Kidney Disease Network. *BMC Nephrol* 10: 30, 2009

23. Manns BJ, Mortis GP, Taub KJ, McLaughlin K, Donaldson C, Ghali WA: The Southern Alberta Renal Program database: A prototype for patient management and research initiatives. *Clin Invest Med* 24: 164–170, 2001

24. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration): A new equation to estimate glomerular filtration rate. *Ann Intern Med* 150: 604–612, 2009

25. Census Canada: 2006 Census of Population. Available at: http://www12.Statcan.Ca/english/census06/data/highlights/ethnic/index.Cfm?Lang=e%3E. Accessed June 15, 2009

26. Lamb EJ, MacKenzie F, Stevens PE: How should proteinuria be detected and measured? *Ann Clin Biochem* 46: 205–217, 2009

27. Sin DD, Svenson LW, Cowie RL, Man SF: Can universal access to health care eliminate health inequities between children of poor and nonpoor families? A case study of childhood asthma in Alberta. *Chest* 124: 51–56, 2003

28. Hux JE, Ivis F, Flintoft V, Bica A: Diabetes in Ontario: Determination of prevalence and incidence using a validated administrative data algorithm. *Diabetes Care* 25: 512–516, 2002

29. Quan H, Khan N, Hemmelgarn BR, Tu K, Chen G, Campbell N, Hill MD, Ghali WA, McAlister FA; Hypertension Outcome and Surveillance Team of the Canadian Hypertension Education Programs: Validation of a case definition to define hypertension using administrative data. *Hypertension* 54: 1423–1428, 2009

30. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali WA: Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 43: 1130–1139, 2005

31. Sun GW, Shook TL, Kay GL: Inappropriate use of bivariable analysis to screen risk factors for use in multivariable analysis. *J Clin Epidemiol* 49: 907–916, 1996

32. Silbiger SR, Neugarten J: The impact of gender on the progression of chronic renal disease. *Am J Kidney Dis* 25: 515–533, 1995