

Mild Albuminuria Is a Risk Factor for Faster GFR Decline in the Nondiabetic Population



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Introduction: A minimal increase in the albumin-to-creatinine ratio (ACR) predicts cardiovascular disease and mortality, but whether it predicts kidney function loss in nondiabetic persons is unclear. We investigated the association between ACR in the optimal or high-normal range and the rate of glomerular filtration rate (GFR) decline in a cohort from the general population without diabetes, cardiovascular, or chronic kidney disease.

Methods: In the Renal Iohexol Clearance Survey, we measured GFR using iohexol clearance in 1567 middle-aged nondiabetic individuals with an ACR <3.40 mg/mmol (30.0 mg/g) at baseline. The ACR was measured in unfrozen morning urine samples collected on 3 days before the GFR measurements. A total of 1278 (81%) participants had follow-up with GFR measurements after a median of 5.6 years.

Results: The median ACR at baseline was 0.22 mg/mmol (interquartile range: 0.10–0.51 mg/mmol), the mean \pm SD GFR was 104.0 \pm 20.1 ml/min, and the mean \pm SD GFR decline rate was -0.95 ± 2.23 ml/min per year. Higher baseline ACR levels were associated with a steeper GFR decline in adjusted linear mixed models. Study participants with ACR levels of 0.11 to 0.45 and 0.46 \pm 3.40 mg/mmol had a 0.25 ml/min per year (95% confidence interval [95% CI]: -0.03 to 0.53) and 0.31 ml/min per year (95% CI: 0.02–0.60) steeper rate of decline than those with ACR ≤ 0.10 mg/mmol in multivariable-adjusted analyses. Among study participants with an ACR of <1.13 mg/mmol (defined as the optimal range), those with an ACR of 0.11 to 1.12 mg/mmol ($n = 812$) had a 0.28 ml/min per year (95% CI: 0.04–0.52) steeper rate of GFR decline than those with an ACR of ≤ 0.10 mg/mmol ($n = 655$).

Conclusion: A mildly increased ACR is an independent risk factor for faster GFR decline in nondiabetic individuals.

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KEYWORDS: ACR; albumin-creatinine-ratio; GFR; iohexol clearance

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Chronic kidney disease (CKD), defined as a glomerular filtration rate (GFR) <60 ml/min per 1.73 m², is highly prevalent and is attributed to 4% of deaths worldwide.¹ Therefore, it is important to identify persons at high risk of an accelerated GFR decline at an early stage. However, plasma creatinine is an insensitive marker of early GFR decline and may not increase before 30% to 40% of kidney function is lost. Moreover, clinical risk factors, such as hypertension and prediabetes, do not predict accelerated decline in measured GFR during approximately 6 years of

follow-up in nondiabetic persons.^{2,3} Therefore, noninvasive biomarkers for the prediction of GFR decline in the general population are needed.

A urinary albumin-to-creatinine ratio (ACR) ≥ 3.40 mg/mmol (30.0 mg/g) is a marker of glomerular damage, is included in the definition of CKD if it persists for ≥ 3 months, and is a risk factor for GFR decline.^{4,5} However, only a small proportion of individuals develop albuminuria; therefore, it is not a useful biomarker for GFR decline in most individuals in the general population. A low-grade increase in ACR (0.6–0.9 mg/mmol) is much more common and is a risk factor for cardiovascular disease (CVD) and all-cause mortality in the general population.⁶ Previous studies of CKD risk in the general population defined optimal ACR levels as <1.13 mg/mmol and high-normal ACR as 1.13 to 3.40 mg/mmol.⁷ Whether an ACR in this range is an

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independent risk factor for accelerated GFR decline in nondiabetic persons is unknown.

We studied the hypothesis that higher ACR within the normal range is associated with a faster decline in measured GFR in a Caucasian population without pre-existing diabetes, CVD, or CKD.

METHODS

Study Population

The Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6) was conducted from 2007 to 2009 as a substudy of the population-based sixth Tromsø Study in the municipality of Tromsø, Northern Norway.⁸ The RENIS-T6 included a representative sample of 1627 individuals, aged 50 to 62 years, from the general population who did not have self-reported kidney disease, CVD, or diabetes (Figure 1). Twenty-four subjects had albuminuria, defined as an ACR ≥ 3.40 mg/mmol, 5 subjects had missing ACR values, and 31 subjects had diabetes (defined as fasting glucose ≥ 7.0 mmol/l, hemoglobin A1c $\geq 6.5\%$, or the use of antidiabetic medication). These 60 subjects were excluded from the present study. Of the remaining 1567 subjects, 1278 (82%) had a follow-up measurement of GFR in the RENIS Follow-Up study (RENIS-FU) after a median

(interquartile range [IQR]) of 5.6 years (IQR: 5.2–6.0 years) (Figure 1). A random sample of 86 subjects had a third GFR measurement within 2 months after the second GFR measurement, which was necessary for the linear mixed regression analyses, with a random intercept and slope, and an unstructured covariance matrix.²

There were small differences in the characteristics of the included participants in RENIS-FU compared with the 18% who were lost to follow-up, except for the percentage of current smokers, which was 18% versus 28% ($P < 0.01$) (other significant differences were body mass index [BMI]: 27.1 kg/m² vs. 27.6 kg/m², $P = 0.04$; hemoglobin A1c: 5.5% vs. 5.6%, $P = 0.01$; and ACR: 0.22 mg/mmol vs. 0.30 mg/mmol, $P = 0.02$).²

The Regional Ethics Committee of Northern Norway approved the study, and all subjects provided written informed consent. The study adhered to the Declaration of Helsinki.

Data

The RENIS-T6 and RENIS-FU studies were conducted at the Clinical Research Unit at the University Hospital of Northern Norway with a standardized procedure. The participants met between 8:00 and 10:00 AM after an overnight fast, including abstinence from tobacco. Both visits included a health questionnaire with questions on tobacco use, leisure time physical exercise, and all current medications. Current smoking was categorized as daily tobacco use (yes/no).

GFR was measured using single-sample plasma clearance of iohexol, as described in detail elsewhere.⁸ All participants were instructed to avoid large meals with meat and nonsteroid anti-inflammatory drugs 2 days before the investigation. Study participants with signs of acute illness, such as respiratory or urinary infection, were rescheduled to a later appointment. The concentration of serum iohexol was measured by high-performance liquid chromatography, as described by Nilsson-Ehle.⁹ GFR was calculated as described by Jacobsson.¹⁰ The mean coefficient of variation (95% CI) for the intraindividual variation in GFR was 4.2% (3.4%–4.9%).³

Three samples of first-void morning spot urine were collected on consecutive days before the GFR measurements. Urinary albumin and creatinine concentrations were measured in fresh urine using an ABX PENTRA autoanalyzer (Horiba ABX) and kits from ABX Diagnostics (Montpellier, France).¹¹ The ACR in milligrams per millimoles was calculated for each urine specimen, and the median ACR value was used in the analyses. In samples with no detectable urinary albumin concentration, ACR was set to 0.10 mg/mmol (0.88 mg/g), which corresponded to the lowest ACR

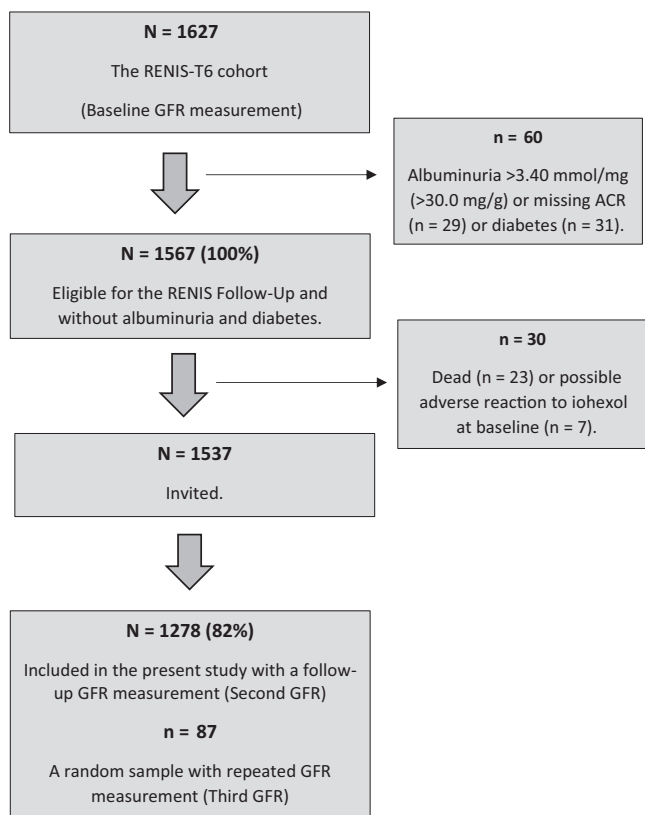


Figure 1. Inclusion of subjects. The Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6) and Follow-Up (RENIS-FU). ACR, albumin-to-creatinine ratio; GFR, glomerular filtration rate.

values in samples with detectable albumin. High-normal albuminuria was defined as an ACR of 1.13 to 3.40 mg/mmol (10.0–30.0 mg/g).¹²

Values for fasting serum glucose, triglycerides, and cholesterol were measured on the Modular model P800 (Roche Diagnostics, Mannheim, Germany). We measured fasting insulin levels using an enzyme-linked immunosorbent kit (DRG Instruments, Marburg, Germany)¹³ and high-sensitivity C-reactive protein as previously reported.¹⁴

Office blood pressure (BP) and resting heart rate were measured 3 times in a seated position after a 2-minute rest.¹⁵ Ambulatory BP was measured using the Space-lab 90207 (Spacelab Inc., Redmond, WA) from after the GFR measurement until the next day. BP and heart rate were measured at 20-minute intervals from 08:00 AM to 10:00 PM and at 45-minute intervals from 10:00 PM to 08:00 AM. Persons with invalid measurements had their measurements repeated as soon as possible. The mean daytime and nighttime systolic BP and diastolic BPs were calculated as the weighted mean of measurements from 10:00 AM to 10:00 PM and from midnight until 06:00 AM, respectively, as previously reported.¹⁵ Subjects with office systolic BP ≥ 140 mm Hg, diastolic BP ≥ 90 mm Hg, or who were using antihypertensive medication were categorized as having hypertension.

Statistical Analyses

Study population characteristics are presented as the means \pm SD, medians (IQR) for skewed data, or numbers (percentages). ACR was categorized into 3 groups (no albuminuria; ACR ≤ 0.1 mg/mmol, which corresponded to the detection limit for urinary albumin, and 2 equally sized groups based on low or high ACR). A linear trend across ACR groups was tested with analysis of variance and median regression for continuous variables and with logistic regression for dichotomous variables.

Fourteen missing values for ambulatory daytime BP and heart rate were replaced by the office BP and resting heart rate values, respectively.

The association of ACR at baseline with the GFR change rate was analyzed in a linear mixed regression model with a random intercept and slope, and by including 2-way interaction terms between the ACR variable and the time variable.^{16–18} All 1567 participants with 1 to 3 GFR measurements were included in the analyses because linear mixed models allow for missing observations at ≥ 1 timepoints.^{16,17} Although 3 measurements were only available for a random subsample ($n = 87$) in RENIS-FU, this sufficed for estimating the 3 variance components in the unstructured covariance matrix of the model.¹⁸ Absolute GFR in milliliters per minute was used as the dependent

variable. Observation time from baseline was used as the independent time variable. The association of ACR at baseline with rapid GFR decline (yes/no) was analyzed using logistic regression. Rapid GFR decline was defined as >3 ml/min per 1.73 m^2 per year.¹⁹

We adjusted for the following baseline variables in 3 models: model 1 (age, sex, body weight, and height), model 2 (model 1 plus fasting glucose, smoking status [yes/no], ambulatory systolic BP, use of antihypertensive medications, and high-sensitivity C-reactive protein), and model 3 (model 2 plus ambulatory heart rate, fasting triglycerides, low-density lipoprotein cholesterol, and fasting insulin). An interaction term between these variables and the time variable was included to adjust for each variable's effect on the slope. We tested for effect modification by age, sex, fasting glucose, and BP by including an interaction term among each of these variables, ACR, and the time variable.

Stata software version 14.1 (Stata Corp., College Station, TX) was used for statistical analysis. Statistical significance was set at $P < 0.05$.

RESULTS

Population Characteristics

The mean \pm SD age at baseline was 58.1 ± 3.8 years; mean body mass index (BMI), $27.2 \pm 4.0 \text{ kg/m}^2$; mean GFR, $103.8 \pm 19.9 \text{ ml/min}$; and the median (IQR) ACR, 0.23 mg/mmol (IQR: $0.10\text{--}0.52 \text{ mg/mmol}$). A total of 655 persons (42%) had an ACR $\leq 0.10 \text{ mg/mmol}$, which corresponded to the detection limit for urinary albumin concentration. This group was defined as the reference group. The remaining participants were divided into 2 equally sized groups based on their ACRs. The population characteristics at baseline for these 3 groups are shown in Table 1. Higher levels of ACR was associated with current smoking, higher BMI, higher triglycerides, and higher daytime and nighttime ambulatory BPs. There was also a quadratic trend between levels of ACR and GFR (Table 1).

Association Between Baseline ACR and GFR Change Rate

The unadjusted mean \pm SD absolute and body surface area adjusted GFR decline rate was $-0.95 \pm 2.23 \text{ ml/min}$ per year and $-0.84 \pm 2.00 \text{ ml/min}$ per 1.73 m^2 per year. The annual GFR decline rate in milliliters per minute was -0.79 (95% confidence interval [CI]: -0.97 to -0.62), -1.03 (-1.23 to -0.82), and -1.15 (-1.38 to -0.92) for the 3 ACR groups, respectively. A higher ACR was associated with a steeper GFR decline in 3 different multivariable-adjusted linear mixed models (Table 2). We obtained similar results when urinary albumin levels were not corrected for urinary creatinine (Table 2), when we used the mean ACR instead of the

Table 1. Characteristics at baseline by levels of albumin-to-creatinine ratio^a (The RENIS-FU Study)

Characteristics	ACR ≤0.10 mg/mmol (n = 655)	ACR 0.11–0.45 mg/mmol (n = 456)	ACR 0.46–3.40 mg/mmol (n = 456)	P value for linear trend
Urinary ACR, mg/mmol	< 0.1	0.29 (0.2–0.36)	0.76 (0.57–1.07)	
Male sex, n (%)	291 (44)	273 (60)	202 (44)	0.97 ^b
Age, yr	58.0 ± 3.8	57.8 ± 3.9	58.3 ± 3.7	0.37
Body mass index, kg/m ²	27.0 ± 3.9	27.2 ± 3.6	27.6 ± 4.3	0.02
Current smoker,	118 (18)	89 (20)	108 (24)	0.02
Office SBP, mm Hg	126.9 ± 16.6	129.7 ± 16.8	132.4 ± 19.1	<0.001
Office DBP, mm Hg	82.1 ± 9.3	84.0 ± 9.6	84.2 ± 10.2	<0.001
Resting heart rate, beats/min	66.6 ± 9.8	65.5 ± 10.1	67.4 ± 9.5	0.18 ^b
Hypertension	220 (34)	193 (42)	214 (47)	<0.001
Antihypertensive med., n (%)	105 (16)	82 (18)	91 (20)	0.09
Ambulatory BP measurements, mm Hg				
Daytime SBP	127.8 ± 11.9	130.3 ± 2.9	132.7 ± 14.2	<0.001
Daytime DBP	80.7 ± 7.9	82.8 ± 8.6	83.2 ± 9.4	<0.001
Nighttime SBP	108.9 ± 11.0	110.8 ± 12.4	113.4 ± 13.1	<0.001
Nighttime DBP	65.1 ± 7.6	66.9 ± 8.3	67.5 ± 9.2	<0.001
LDL cholesterol, mmol/l	3.66 ± 0.84	3.69 ± 0.86	3.65 ± 0.88	0.83
HDL cholesterol, mmol/l	1.57 ± 0.40	1.48 ± 0.42	1.54 ± 0.44	0.18 ^b
Fasting triglycerides, mmol/l	1.0 (0.7–1.3)	1.0 (0.8–1.5)	1.1 (0.8–1.5)	0.002
Fasting glucose, mmol/l	5.3 (5.0–5.6)	5.3 (5.0–5.6)	5.30 (5.0–5.6)	1.00
Fasting insulin	8.3 (6.1–12.0)	8.4 (6.0–12.0)	8.73 (6.1–12.9)	0.12
High-sensitivity CRP	2.36 ± 4.73	2.14 ± 3.52	3.11 ± 10.86	0.08
Absolute GFR, ml/min	102.0 ± 19.7	106.0 ± 19.2	104.2 ± 20.7	0.07 ^b
GFR, ml/min per 1.73 m ²	93.1 ± 14.3	94.8 ± 13.9	94.0 ± 14.7	0.29

ACR, albumin-to-creatinine ratio; BP, blood pressure; CRP, C-reactive protein; DBP, diastolic BP; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RENIS-FU Study, the Renal Iohexol-clearance Survey Follow-up Study; SBP, systolic BP. Estimates are given as mean ± SD, median (interquartile range), or no. (%).

^aParticipants without albuminuria (ACR <3.4 mg/mmol (30 mg/g)) and diabetes at baseline.

^bP < 0.05 for quadratic trend.

median ACR (calculated from the 3 urinary samples from each person collected on separate days at baseline), after adjusting for ambulatory diastolic BP instead of systolic BP, and after additional adjustment for change in anti-hypertensive medications from baseline to follow-up (not shown). We also repeated the analyses using body surface area adjusted GFR (milliliters per minute per 1.73 m²) instead of absolute GFR as the dependent variable. The results were essentially the same as shown in [Supplementary Table S1](#).

In the subgroup of study participants with an ACR <1.13 (n = 1467), those with an ACR of 0.11 to 1.12 (n = 812) had a 0.28 ml/min per year (95% CI: 0.04–0.52) steeper rate of GFR decline than those with an ACR ≤0.10 mg/mmol (n = 655) in the fully adjusted model.

No interaction was found for age, sex, fasting glucose, BP, or hypertension (P ≥ 0.05). However, there was a tendency toward a slightly stronger effect of the ACR on the GFR decline rate in the 940 persons without hypertension at baseline ([Table 2](#) and [Figure 2](#)). In the subgroup of study participants with no hypertension, those with an ACR >0.10 mg/mmol had a 1.89 ml/min (95% CI: 0.10–3.68) higher baseline GFR and a 0.45 ml/min per year (95% CI: 0.18–0.73) steeper GFR decline rate compared with persons with no albuminuria, in the fully adjusted model ([Figure 2](#)).

One hundred twenty-eight participants had rapid GFR decline defined as an annual decline rate >3.0 ml/min per 1.73 m². The odds ratio of rapid decline was 1.17 (95% CI: 0.97–1.42) per SD increase baseline ACR in the model adjusted for age, sex, height, and weight, and 1.10 (95% CI: 0.90–1.35) in the fully adjusted model (as model 3, [Table 2](#)).

DISCUSSION

In a cohort representative of the general population without diabetes, CKD or CVD, we found that mildly increased ACR within the optimal or high-normal⁷ range at baseline was independently associated with a steeper decline in measured GFR. Individuals with ACR between 0.11 and 0.45 mg/mmol and 0.46 and 3.40 mg/mmol had on average 0.25 ml/min per year (95% CI: –0.03 to 0.53) and 0.31 (95% CI: 0.02–0.60) steeper decline rates compared with those with no albuminuria, which was a moderate difference considering the average decline rate of 0.95 ml/min per year in this nondiabetic population.

Several large population studies have confirmed that an ACR ≥3.40 mg/mmol (30.0 mg/g) predicts GFR decline and progression of CKD.^{5,20} This has motivated the inclusion of ACR ≥3.40 mg/mmol in CKD staging.⁴

Table 2. The associations between baseline ACR and GFR change rates in separate linear mixed regression analyses

Baseline ACR levels	Model 1			Model 2			Model 3		
	ml/min per year ^a	(95% CI)	P value	ml/min per year ^a	(95% CI)	P value	ml/min per year ^a	(95% CI)	P value
All study participants ^b									
Urinary log albumin, per SD (n = 1567)	-0.18	(-0.30 to -0.06)	0.00	-0.16	(-0.28 to -0.03)	0.01	-0.14	(-0.26 to -0.02)	0.02
Urinary 1/creatinine, per SD (n = 1567)	0.10	(-0.03 to 0.24)	0.14	0.08	(-0.06 to 0.21)	0.27	0.07	(-0.07 to 0.20)	0.34
Urinary log ACR, per SD (n = 1567)	-0.14	(-0.25 to -0.02)	0.02	-0.13	(-0.24 to -0.01)	0.04	-0.11	(-0.23 to 0.01)	0.06
ACR ≤0.10 mg/mmol (n = 655)	Ref			Ref			Ref		
ACR 0.11–0.45 mg/mmol (n = 456)	-0.24	(-0.53 to 0.04)	0.09	-0.24	(-0.52 to 0.05)	0.10	-0.25	(-0.53 to 0.03)	0.08
ACR 0.46–3.40 mg/mmol (n = 456)	-0.35	(-0.63 to -0.06)	0.02	-0.33	(-0.62 to -0.04)	0.02	-0.31	(-0.60 to -0.02)	0.03
Persons without hypertension ^c									
Log ACR, per SD increase (n = 940)	-0.21	(-0.37 to -0.05)	0.01	-0.20	(-0.36 to -0.04)	0.02	-0.19	(-0.35 to -0.03)	0.02
ACR ≤0.10 mg/mmol (n = 435)	Ref			Ref			Ref		
ACR 0.11–0.45 mg/mmol (n = 263)	-0.39	(-0.72 to -0.06)	0.02	-0.42	(-0.75 to -0.09)	0.01	-0.42	(-0.74 to -0.09)	0.01
ACR 0.46–3.40 mg/mmol (n = 242)	-0.49	(-0.83 to -0.15)	<0.01	-0.47	(-0.81 to -0.13)	<0.01	-0.46	(-0.80 to -0.11)	<0.01

ACR, albumin-to-creatinine ratio; GFR, glomerular filtration rate.

Model 1: Adjusted for sex and age, height, and weight at baseline.

Model 2: As in Model 1 and adjusted for ambulatory systolic blood pressure (BP), fasting glucose, current smoking, high-sensitivity C-reactive protein, and the use of antihypertensive medications.

Model 3: As in Model 2 and adjusted for ambulatory heart rate, low-density lipoprotein cholesterol, triglycerides, and fasting insulin.

^aA negative coefficient means a steeper decline.

^bIncludes persons without diabetes, and ACR <3.40 mmol/mg (30.0 mg/g) in the Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6).

^cA total of 627 persons with hypertension were defined as having office systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg, or the use of antihypertensive medications were excluded.

Whether a lower ACR is a marker of early kidney disease and not only a more general marker of endothelial dysfunction has been debated. No previous study has assessed the independent association between ACR within the normal range and measured GFR decline in the general nondiabetic population.

Three previous publications from the population-based Prevention of Renal and Vascular End-Stage Disease (PREVEND) study reported that urinary albumin excretion (UAE) levels ≥15 mg/24 h (approximately corresponding to an ACR ≥1.13 mmol/l [≥ 10.0 mg/g]) predicted a decline in eGFR and incident CKD.^{21–23} However, these studies did not exclude participants with albuminuria defined as ACR ≥3.40 mmol/l (≥ 30.0 mg/g) from their analyses, and 2 of them did not adjust for common clinical risk factors. In the third study, Halbesma *et al.* found that UAE levels in this range predicted eGFR decline in men, but not in women, after multivariable adjustment.²³ In contrast, we did not observe any effect modification by sex in our study using measured GFR, although the ACR levels were lower than those in the PREVEND study. A few other studies of the general population found an association between ACR and accelerated decline in eGFR, but these studies did not exclude individuals with diabetes and/or albuminuria at baseline.^{24,25}

Age-related decline in GFR is an important cause of the high prevalence of CKD. Individuals who develop a moderately reduced eGFR (<45 ml/min per 1.73 m²) at the age of 55 to 74 years have an approximately 60% to 200% and 400% to 600% increased risk of death and end-stage renal disease (ESRD) versus those with estimated GFR of 80 ml/min per 1.73 m², respectively.²⁶

Different screening strategies to detect CKD have therefore been proposed, either of high-risk groups such as individuals with diabetes or of the general population aged older than 55 years.^{22,27–30} However, existing risk models may have better discriminating abilities in high-risk compared with low-risk populations and for outcomes such as ESRD compared with early GFR decline or incident CKD.^{31–34} Our study indicated that even slightly higher ACR levels than normal might be an important risk factor for GFR decline in middle-aged nondiabetic individuals independent of common risk factors for CKD. It should be noted that most participants in this study had a GFR within the normal range at follow-up, and thus we could not determine whether those with accelerated GFR decline progressed to CKD. However, in another population-based study, Hallan *et al.* found an increased risk of ESRD with a higher ACR that continued into the normo-albuminuria range, although that study included persons with diabetes, CKD, and CVD at baseline.²⁰

Larger population-based studies with longer follow-up periods should evaluate the effect of screening for albuminuria below the currently accepted thresholds. Treatment that reduces the ACR, such as the use of angiotensin-converting enzyme inhibitors, has been shown to reduce the long-term GFR decline and risk of ESRD in patients with diabetes and hypertension.^{35–37} To our knowledge, no randomized intervention trials have investigated the effects of reducing low-grade albuminuria in people without diabetes, CKD, or hypertension.

We observed a quadratic trend between baseline GFR and ACR levels in the total cohort and a higher

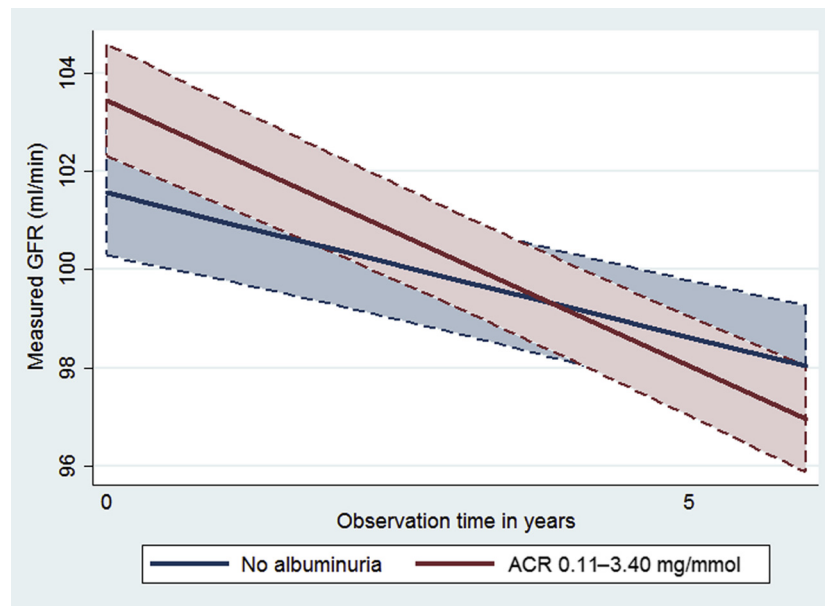


Figure 2. Adjusted glomerular filtration rate (GFR) slopes for nonhypertensive persons according to albumin-to-creatinine ratio (ACR) levels. Marginal effects on GFR levels analyzed in mixed linear regression with random intercept and slope, after adjusting for sex and baseline age, height, weight, fasting glucose, smoking status (yes/no), ambulatory systolic blood pressure and heart rate, use of antihypertensive medications, high-sensitivity C-reactive protein, fasting triglycerides, low-density lipoprotein cholesterol, and fasting insulin levels. Persons with hypertension excluded. $N_{\text{total}} = 940$; 435 with no albuminuria and 505 with an ACR of 0.11 to 3.40 mg/mmol (0.89–30.0 mg/dl). The latter group had a 0.45 ml/min per year (95% confidence interval: 0.18–0.73) steeper GFR decline rate.

baseline GFR in persons with albuminuria in the subgroup with no hypertension (Table 1 and Figure 2). This was consistent with several previous reports. Higher urinary albumin levels were associated with both lower and higher GFR in cross-sectional studies, not only in patients with diabetes,³⁸ but also in studies of the general population.^{39,40} Moreover, Halbesma *et al.* found a nonlinear association between UAE levels and change in GFR in a longitudinal study of the general population.²³ Similarly, we reported that ACR might increase in parallel with increasing GFR in persons with prediabetes during 5.6 years of follow-up, possibly indicating an association with hyperfiltration.³ In this study, we demonstrated that even lower levels of ACR at baseline are associated with a steeper GFR decline.

The major strength of this study was the use of measured instead of estimated GFR. The estimated GFR lacks precision in the near-normal range and is biased by non-GFR-related factors such as muscle wasting, particularly in older adults. RENIS-FU is the only longitudinal study with repeated measurements of GFR in a representative sample of the general population. Urine was collected from morning samples on 3 separate days, and albumin and creatinine were assessed in unfrozen specimens. Our results were not dependent on adjustment for urinary creatinine, which is important because the inclusion

of urinary creatinine in the ACR might cause bias due to the association with muscle mass (creatinine production).

In contrast to most previous studies, we adjusted for several potential confounders, such as high-sensitivity C-reactive protein, fasting insulin levels, 24-hour ambulatory BP measurement, and use of antihypertensive medication, including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Notably, a recent study from the CKD biomarker consortium found strong associations of several tubular biomarkers with GFR decline in unadjusted analyses, but these associations were not significant in multivariable adjusted models.³²

This study also had limitations. Only middle-aged Caucasian individuals participated, which limited the generalizability to other groups. Due to the observational design, we could not draw conclusions about a causal connection between an ACR in this lower range and the rate of GFR decline.

We concluded that a higher ACR within the normal range is associated with a steeper GFR decline in nondiabetic, middle-aged individuals from the general population.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Table S1. The associations between baseline albumin-to-creatinine ratio (ACR) and glomerular filtration rates (GFR) change rates (ml/min per 1.73 m² per year) in separate linear mixed regression analyses.

Supplementary material is linked to the online version of the paper at www.kireports.org.

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