Association of TNF Receptor 2 and CRP with GFR Decline in the General Nondiabetic Population

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Abstract

Background and objectives Higher levels of inflammatory markers have been associated with renal outcomes in diabetic populations. We investigated whether soluble TNF receptor 2 (TNFR2) and high-sensitivity C-reactive protein (hsCRP) were associated with the age-related GFR decline in a nondiabetic population using measured GFR (mGFR).

Design, setting, participants, & measurements A representative sample of 1590 middle-aged people from the general population without prevalent kidney disease, diabetes, or cardiovascular disease were enrolled in the Renal Iohexol-Clearance Survey in Tromsø 6 (RENIS-T6) between 2007 and 2009. After a median of 5.6 years, 1296 persons were included in the Renal Iohexol-Clearance Survey Follow-Up Study. GFR was measured using iohexol clearance at baseline and follow-up.

Results The mean decline of mGFR during the period was −0.84 ml/min per 1.73 m^2 per year. There were 133 participants with rapid mGFR decline, defined as an annual mGFR loss >3.0 ml/min per 1.73 m^2, and 26 participants with incident CKD, defined as mGFR<60 ml/min per 1.73 m^2 at follow-up. In multivariable adjusted mixed models, 1 mg/L higher levels of hsCRP were associated with an accelerated decline in mGFR of −0.03 ml/min per 1.73 m^2 per year (95% confidence interval [95% CI], −0.05 to −0.01), and 1 SD higher TNFR2 was associated with a slower decline in mGFR (0.09 ml/min per 1.73 m^2 per year; 95% CI, 0.01 to 0.18). In logistic regression models adjusted for sex, age, weight, and height, 1 mg/L higher levels of hsCRP were associated with higher risk of rapid mGFR decline (odds ratio, 1.03; 95% CI, 1.01 to 1.06) and incident CKD (odds ratio, 1.04; 95% CI, 1.00 to 1.08).

Conclusions Higher baseline levels of hsCRP but not TNFR2 were associated with accelerated age-related mGFR decline and incident CKD in a general nondiabetic population.

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Introduction

The prevalence of CKD increases dramatically with age, affecting nearly half of individuals >70 years (1). Age-related loss of GFR is a major contributor to CKD in the elderly (2). However, there is considerable interindividual variation in the loss of kidney function that persists after accounting for traditional CKD risk factors (3,4). Low-grade inflammation has been proposed as a risk factor for several age-related diseases, including age-related GFR decline and CKD. In particular, TNF and its two soluble receptors, TNF receptor type 1 (TNFR1) and TNF receptor type 2 (TNFR2), have been associated with glomerular endothelial damage, increased tubular apoptosis, and renal fibrosis in animal studies (5). In humans, the serum levels of soluble TNF receptors and C-reactive protein (CRP) have been associated with a reduced GFR in several cross-sectional studies (6–12). Furthermore, higher serum levels of soluble TNF receptors have been associated with incident CKD, ESRD, and the eGFR decline noted in individuals with diabetes mellitus (13–17).

However, it is unknown whether soluble TNF receptors or CRP predict GFR decline in the nondiabetic population without CKD. A limitation of previous studies is the use of the eGFR on the basis of serum creatinine or cystatin C (11,18,19). The eGFR lacks precision in the near normal range of the GFR and is biased by non-GFR related factors, including inflammation (20–23). In the Renal Iohexol-Clearance Survey in Tromsø 6 (RENIS-T6) and Renal Iohexol-Clearance Survey Follow-Up Study (RENIS-FU), we measured GFR (mGFR) at baseline and at follow-up using the plasma clearance of iohexol in a middle-aged nondiabetic population. Our aim was to investigate the association of TNFR2 and high-sensitivity C-reactive protein (hsCRP) with the age-related mGFR decline as well as the eGFR decline assessed from three Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations. In addition, we investigated the association of TNFR2 and hsCRP with the risk of rapid GFR decline and CKD.

Materials and Methods

Study Population

The RENIS-T6 study has previously been described in detail (24). All participants in RENIS-T6 were invited

to the RENIS-FU, except 23 participants who had died and seven who had a possible delayed allergic reaction to iohexol. The RENIS-FU was accomplished between September of 2013 and January of 2015. Of the 1597 people invited, 1368 (86%) gave a positive response. Thirty-nine participants did not show up to their appointment, and five participants were excluded because the antecubital vein could not be cannulated. There were four people with missing TNFR2 values, and 33 people who were diagnosed with diabetes (fasting glucose ≥7.0 mmol/L and/or hemoglobin A_{1c} [HbA_{1c}] ≥6.5%) at baseline who were excluded, leaving a total of 1296 (81%) participants with a follow-up measurement in this study (Figure 1). A random sample of 87 (5.5%) participants in the follow-up study underwent an additional third measurement of the GFR to investigate the intraindividual variation.

The study adhered to the Declaration of Helsinki and was approved by the Regional Ethics Committee of Northern Norway. All participants gave informed written consent.

Data

All measurements in both RENIS-T6 and RENIS-FU were performed at the Clinical Research Unit at the University Hospital of North Norway. Participants fasted between 08:00 a.m. and 10:00 a.m. They were instructed to avoid large meals with meat and to avoid taking any nonsteroidal anti-inflammatory drugs during the 48 hours before examination. Participants with an acute illness were rescheduled to another appointment. All participants answered a health questionnaire regarding current alcohol, tobacco, and medication use. Alcohol use was dichotomized as the use of alcohol more than once weekly, and tobacco use was dichotomized as current smoker. RENIS-FU participant characteristics are shown in Table 1.

Measurements

Iohexol Clearance. The GFR measurements have previously been described in detail (24). The iohexol concentrations were measured by high-performance liquid chromatography, as described by Nilsson-Ehle (25). The coefficient of variation (CV) for analysis was 3.0% at baseline and 3.1% at follow-up. The GFR was calculated using the equation described by Jacobsson (26). There was a mean difference of 2.28 ml/min per 1.73 m^2 between the original baseline GFR measurements and repeated

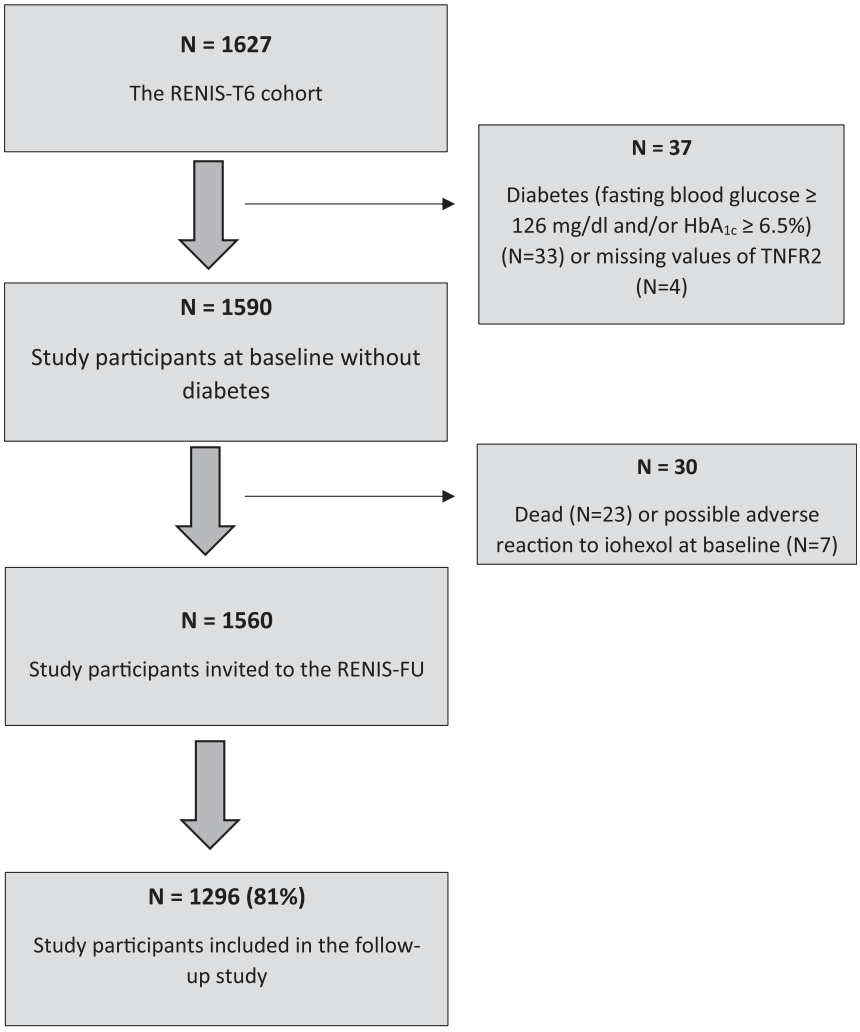

Figure 1. | Inclusion of participants in the Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6) and the Renal Iohexol Clearance Survey Follow-Up Study (RENIS-FU). HbA_{1c}, hemoglobin A_{1c}; TNFR2, soluble TNF receptor 2.

Table 1. The study population characteristics at baseline and follow-up in the Renal Iohexol-Clearance Survey Follow-Up Study

Characteristics	Baseline Measurements		Follow-Up Measurements	*P* Value[a]
	All Measurements	Included in Follow-Up		
N (%)	1590 (100)	1296 (81)	1296 (81)	
Men, *n* (%)	778 (49)	641 (49)	641 (49)	
Age, yr	58.0 (3.8)	58.0 (3.9)	63.6 (4.0)	<0.001
Height, cm	170.7 (8.7)	170.8 (8.6)	170.6 (8.6)	<0.001
Body weight, kg	79.5 (14.3)	79.4 (13.9)	79.2 (14.2)	0.25
Body mass index, kg/m^2	27.2 (4.0)	27.1 (3.8)	27.1 (4.0)	0.59
TNFR2, pg/ml	2670 (652)	2661 (624)		
hsCRP, mg/L	1.19 (0.64–2.19)	1.17 (0.64–2.13)		
Systolic BP, mmHg	129.4 (17.5)	129.1 (17.4)	130.5 (16.9)	<0.001
Diastolic BP, mmHg	83.4 (9.8)	83.3 (9.8)	81.9 (9.3)	<0.001
Fasting glucose, mg/dl	95.8 (8.7)	95.7 (8.5)	98.7 (10.1)	<0.001
Hemoglobin A_{1c}, %	5.54 (0.33)	5.5 (0.33)	5.61 (0.32)	<0.001
LDL cholesterol, mg/dl	141.5 (33.2)	141.6 (32.9)	138.2 (34.6)	<0.001
HDL cholesterol, mg/dl	59.31 (16.25)	59.46 (16.08)	63.11 (17.92)	<0.001
Fasting triglycerides, mg/dl	88.5 (70.8–132.8)	88.5 (70.8–123.9)	88.5 (70.8–115.1)	0.12
UACR, mg/g	2.04 (0.88–4.78)	1.92 (0.88–4.60)	3.00 (0.88–5.13)	<0.001
ACEi, *n* (%)	28 (1.8)	26 (2.0)	48 (3.7)	<0.001
ARB, *n* (%)	131 (8.2)	104 (8.0)	200 (15.4)	<0.001
NSAIDs, *n* (%)	37 (2.3)	30 (2.3)	77 (5.9)	<0.001
Current smoker, *n* (%)	322 (20)	241 (19)	172 (13)	<0.001
Alcohol consumption, *n* (%)	432 (27)	365 (29)	431 (33)	<0.001
Absolute mGFR, ml/min	103.8 (20.0)	103.6 (20)	98.3 (19.8)	<0.001
mGFR, ml/min per 1.73 m^2	93.8 (14.3)	93.7 (14.2)	88.9 (14.4)	<0.001
eGFR by CKD-EPI equation, ml/min per 1.73 m^2				
eGFRcre	94.8 (9.6)	94.8 (9.3)	88.1 (10.5)	<0.001
eGFRcys	105.4 (12.3)	105.7 (12.1)	98.8 (14.1)	<0.001
eGFRcrecys	103.0 (11.4)	103.1 (11.2)	95.7 (12.7)	<0.001

Estimates are given as mean (SD), median (interquartile range), or *n* (%). TNFR2, soluble TNF receptor 2; hsCRP, high-sensitivity C-reactive protein; UACR, urinary albumin-creatinine ratio; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs; mGFR, measured GFR; CKD-EPI; Chronic Kidney Disease Epidemiology Collaboration; eGFRcre, eGFR on the basis of creatinine; eGFRcys, eGFR on the basis of cystatin C; eGFRcrecys, eGFR on the basis of creatinine and cystatin C.

[a]*P* value for change between baseline and follow-up.

baseline measurements taken from the thawed sample. Accordingly, all baseline GFR measurements were corrected by adding this difference to the baseline values, as described previously (27). The mean CV for the intraindividual (day-to-day) variation in GFR was 4.2% (95% confidence interval, 3.4% to 4.9%).

Inflammatory Markers. The serum TNFR2 levels were measured using a quantitative sandwich ELISA with a QuantiKine kit from R&D Systems, Inc. (Minneapolis, MN). The baseline serum samples were collected in the RENIS-T6, stored at −80°C, and thawed at the time of analysis. The color intensity was measured on a Mikroplate Spectrophotometer (Biotek Instruments, Inc, Highland Park, VT). The inter- and intra-assay CVs were 6.0% and 3.0%, respectively.

The serum hsCRP levels were measured in the Tromsø 6 Study (28) 5.2 (3.0–6.2) months earlier than the RENIS-T6 Study. There were 18 missing values of hsCRP. The inter- and intra-CVs were 2.8% and 1.1%, respectively. RENIS-FU participant characteristics according to quartiles of TNFR2 are shown in Table 2.

Other Measurements

The measurements of creatinine and cystatin C were previously described in detail (29). The eGFR on the basis of creatinine (eGFRcre), eGFR on the basis of cystatin C (eGFRcys), and eGFR on the basis of creatinine and cystatin C (eGFRcrecys) were estimated using the CKD-EPI equations (20). The BP procedure and other laboratory measurements, including urinary albumin-to-creatinine ratio (UACR), have been described previously (30,31).

Statistical Analyses

Mean (SD), median (interquartile range) for skewed variables, and *n* (%) were estimated for the baseline characteristics. The differences between the baseline and follow-up variables were tested with paired *t* tests for continuous and normally distributed variables, Wilcoxon signed-rank sum test for skewed variables, and McNemar test for paired dichotomous variables. Differences between subjects in the follow-up study and those lost to follow-up were tested with the two independent samples *t* test,

Table 2. The baseline study population characteristics according to the quartile of TNFR2

Characteristics	Quartile of TNFR2, Range, pg/ml				*P* for Linear Trend
	Quartile 1 (*n*=399)	Quartile 2 (*n*=401)	Quartile 3 (*n*=393)	Quartile 4 (*n*=397)	
	(1186–2248)	(2249–2573)	(2574–2971)	(2972–8253)	
Men, %	42.4	45.1	52.7	55.7	<0.001
Age baseline, yr	57.3 (3.8)	57.8 (3.9)	58.4 (3.8)	58.7 (3.7)	<0.001
Height, m	169.3 (8.9)	170.0 (8.6)	171.4 (8.2)	171.9 (9.0)	<0.001
Weight, kg	75.6 (14.2)	78.1 (13.5)	80.9 (13.3)	83.6 (15.0)	<0.001
Body mass index, kg/m^2	26.3 (3.8)	26.9 (3.6)	27.5 (3.8)	28.2 (4.4)	<0.001
hsCRP, mg/L	0.91 (0.52–1.58)	0.99 (0.57–1.83)	1.37 (0.73–2.43)	1.59 (0.88–3.47)	<0.001
Systolic BP, mmHg	127.4 (17.7)	130.6 (18.0)	128.5 (17.1)	131.1 (17.1)	0.02
Diastolic BP, mmHg	82.5 (10.1)	83.9 (10.2)	83.1 (9.6)	83.9 (9.2)	0.13
Fasting glucose, mg/dl	95.79 (8.83)	95.50 (8.63)	95.86 (8.13)	96.07 (9.09)	0.49
Hemoglobin A_{1c}, %	5.52 (0.32)	5.53 (0.33)	5.51 (0.33)	5.57 (0.35)	0.09
HDL cholesterol, mg/dl	63.83 (16.28)	62.01 (15.33)	56.85 (16.01)	54.44 (15.64)	<0.001
LDL cholesterol, mg/dl	140.44 (35.44)	142.61 (30.57)	140.23 (34.01)	142.83 (32.49)	0.52
Triglycerides, mg/dl	79.7 (62.0–106.2)	88.5 (62.5–123.9)	97.4 (70.8–132.8)	97.4 (70.8–141.6)	<0.001
Albumin-to-creatinine ratio, mg/g	2.21 (0.88–4.69)	2.12 (0.88–5.22)	1.57 (0.88–4.34)	2.21 (0.88–4.78)	0.93
ACEi, %	1.5	0.7	2.3	2.5	0.12
ARB, %	7.0	6.5	9.4	10	0.05
NSAIDs, %	1.5	1.5	4.1	2.3	0.15
Current smoker, %	14	18	22	27	<0.001
Alcohol consumption, %	33	32	22	22	<0.001
Absolute mGFR, ml/min	106.2 (20.0)	104.9 (19.0)	103.2 (19.7)	100.7 (20.8)	<0.001
mGFR, ml/min per 1.73 m^2	98.6 (13.8)	95.8 (13.0)	92.3 (14.0)	88.6 (14.5)	<0.001
eGFR by CKD-EPI equation, ml/min per 1.73 m^2					
eGFRcre	97.6 (8.2)	95.3 (8.8)	94.2 (9.2)	92.2 (11.0)	<0.001
eGFRcys	112.3 (8.9)	108.7 (8.8)	104.5 (9.9)	96.2 (14.4)	<0.001
eGFRcrecys	109.1 (9.4)	105.3 (9.4)	101.8 (9.7)	95.8 (12.5)	<0.001

The Renal Iohexol-Clearance Survey Follow-Up Study. Numbers are presented as mean (SD), median (interquartile range), and percentage. TNFR2, soluble TNF receptor 2; hsCRP, high-sensitivity C-reactive protein; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs; mGFR, measured GFR; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFRcre, eGFR on the basis of creatinine; eGFRcys, eGFR on the basis of cystatin C; eGFRcrecys, eGFR on the basis of creatinine and cystatin C.

Table 3. The association of TNFR2 and hsCRP with the annual change in mGFR and eGFR in linear mixed regression models

Dependent Variable and Risk Factor	Model 1 Unadjusted			Model 2 Adjusted for Baseline Covariates[a]			Model 3 Adjusted for Time-Dependent Covariates[a]		
	Estimate (ml/min per 1.73 m^2 per yr)	95% CI	*P* Value	Estimate (ml/min per 1.73 m^2 per yr)	95% CI	*P* Value	Estimate (ml/min per 1.73 m^2 per yr)	95% CI	*P* Value
TNFR2[b]									
mGFR	0.05	−0.04 to 0.14	0.24	0.09	0.01 to 0.18	0.04	0.11	0.02 to 0.19	0.02
eGFRcre	0.03	−0.03 to 0.09	0.27	0.04	−0.02 to 0.10	0.19	0.04	−0.02 to 0.99	0.17
eGFRcys	0.04	−0.03 to 0.12	0.26	0.07	−0.01 to 0.14	0.07	0.05	−0.02 to 0.13	0.14
eGFRcrecys	0.08	0.01 to 0.14	0.02	0.09	0.02 to 0.16	0.01	0.08	0.02 to 0.15	0.01
hsCRP									
mGFR	−0.03	−0.05 to −0.02	<0.001	−0.03	−0.05 to −0.01	0.001	−0.03	−0.05 to –0.01	0.001
eGFRcre	−0.02	−0.03 to −0.01	<0.001	−0.02	−0.03 to −0.01	<0.001	−0.02	−0.03 to −0.01	0.001
eGFRcys	0.01	−0.01 to 0.02	0.46	0.01	−0.01 to 0.02	0.27	0.01	−0.01 to 0.02	0.32
eGFRcrecys	−0.01	−0.02 to 0.01	0.38	−0.01	−0.02 to 0.01	0.45	−0.01	−0.02 to 0.01	0.42

The Renal Iohexol-Clearance Survey Follow-Up Study. The estimates represent the interaction between time and 1 SD higher TNFR2 and 1 mg/L higher hsCRP on the annual change in mGFR/eGFR. A positive estimate represents a slower decline. Each row represents a separate linear mixed model with the different mGFR/eGFR as dependent variable. TNFR2, soluble TNF receptor 2; hsCRP, high-sensitivity C-reactive protein; mGFR, measured GFR; 95% CI, 95% confidence interval; eGFRcre, eGFR on the basis of creatinine; eGFRcys, eGFR on the basis of cystatin C; eGFRcrecys, eGFR on the basis of creatinine and cystatin C.

[a]Adjusted for sex; weight; height; systolic BP; LDL cholesterol; HDL cholesterol; fasting triglycerides; hemoglobin A_{1c}; urinary albumin-to-creatinine; number of cigarettes currently smoked; the use of angiotensin receptor blockers, and nonsteroidal anti-inflammatory drugs; and a dichotomous variable for the weekly use of alcohol.

[b]The SD for TNFR2 is 651.5.

Wilcoxon–Mann–Whitney test, and chi-squared or Fisher exact test, as appropriate. A linear trend across increasing quartiles of TNFR2 was tested with linear and median regression for continuous variables and logistic regression for dichotomous variables.

The association between the inflammatory marker at baseline and the mean annual mGFR and eGFR decline was analyzed in a linear mixed regression model with a random intercept and slope (32). The GFR standardized to the body surface area (milliliter per minutes per 1.73 m^2) was used as the dependent variable. The chronological age was used as the independent time variable. The association of the inflammatory marker with the GFR decline rate was modeled as interactions between the inflammatory markers and the time variable.

A linear mixed regression model provides interpretable effect estimates independent of missing observations at one or more points in time (33). Therefore, all 1590 subjects included in the baseline study were included in the model, as well as the extra follow-up measurement of the GFR for 5.5% of the subjects. The associations of TNFR2 and hsCRP with the mGFR and eGFR decline were studied in three separate models. Model 1 was unadjusted. Model 2 was adjusted for sex and baseline weight and height; the use of an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, and nonsteroidal anti-inflammatory drugs; smoking and use of alcohol; HDL and LDL cholesterol; triglyceride level; systolic BP; UACR; and HbA_{1c}. Model 3 was adjusted for the same covariates as in model 2, using time-dependent covariates measured at both baseline and follow-up.

We investigated the association of baseline TNFR2 and hsCRP levels with rapid GFR decline using logistic regression in three separate models. Model 1 was unadjusted. Model 2 was adjusted for sex, baseline age, weight, and height. Model 3 was adjusted for the same covariates as in model 2 of Table 3 as well as the baseline GFR. Rapid GFR decline was defined as an annual GFR loss >3.0 ml/min per 1.73 m^2, which is approximately three times the mean age-related GFR decline, and has been associated with increased risk of cardiovascular and all-cause mortality (27,34).

The association between baseline TNFR2 and hsCRP levels and incident CKD (GFR<60 ml/min per 1.73 m^2) was tested with a logistic regression model that was adjusted for the sex, baseline age, weight, and height, and with or without adjusting for baseline GFR.

The nonlinear association between the baseline TNFR2 and the GFR decline rate was assessed by including a second-degree fractional polynomial transformation of TNFR2 in the interaction with time in the linear mixed regression model (35).

Statistical significance was defined as $P<0.05$. Analyses were performed with STATA 14 (www.stata.com).

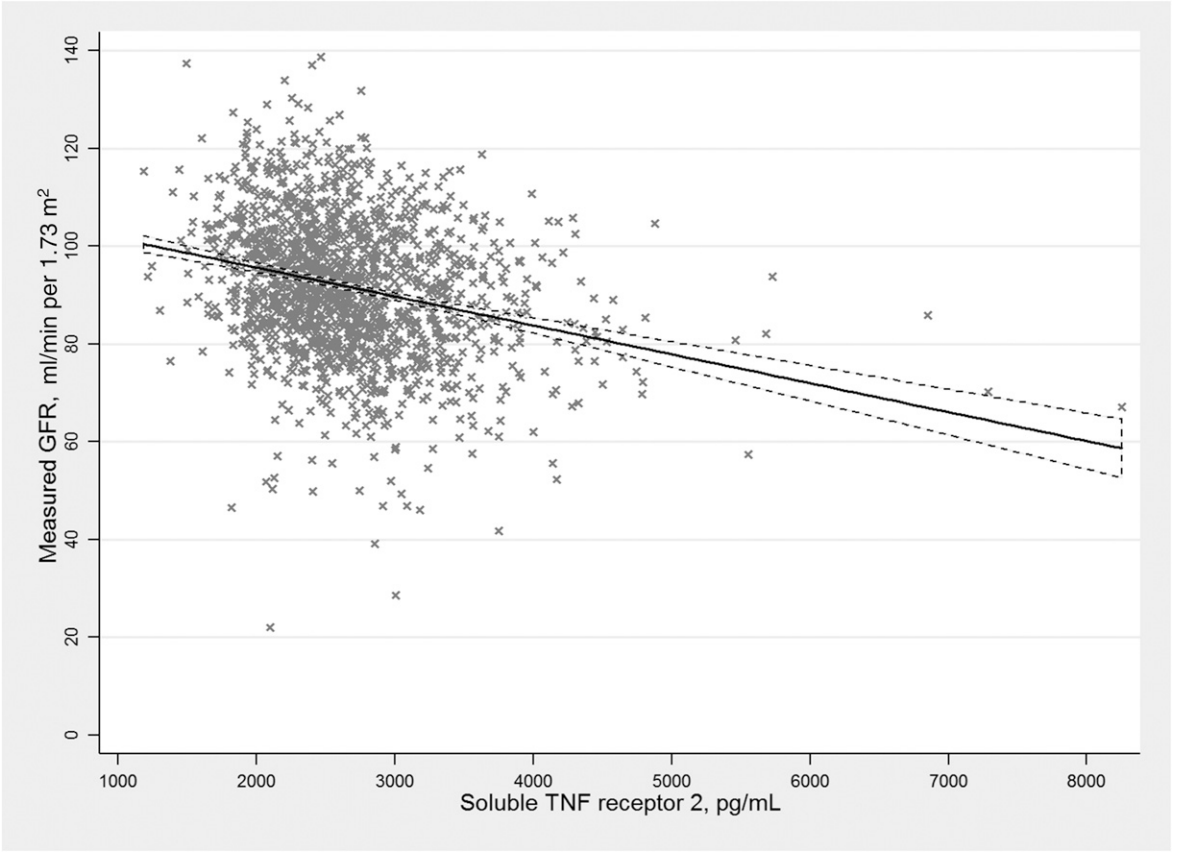

Figure 2. | **Soluble TNF receptor 2 correlates with measured GFR at baseline.** Dashed lines indicate 95% confidence intervals.

Results

The baseline and follow-up characteristics of the participants are summarized in Table 1. All variables changed significantly between baseline and follow-up ($P<0.05$), except for the body weight, body mass index, and fasting triglycerides. There were only small differences in the baseline characteristics between those included in the follow-up study and those who were lost to follow-up, except for the percentage of daily smokers (19% versus 28%; $P<0.001$) and median UACR (1.92 versus 2.65 mg/g; $P=0.02$) (Supplemental Table 1). The baseline characteristics of the study population according to the quartiles of TNFR2 are presented in Table 2. Subjects with higher TNFR2 levels had lower mGFR and eGFR. They were older, more likely to be men, had a worse metabolic profile, higher hsCRP, and were more likely to use ARB, smoke, and consume less alcohol ($P<0.05$).

The unadjusted mean (SD) mGFR decline during the observation period was −0.84 (2.00) ml/min per 1.73 m^2 per year. There was an unadjusted negative correlation between the TNFR2 level and mGFR at baseline ($r=-0.26$; $P<0.001$) (Figure 2). The baseline hsCRP and mGFR were not significantly correlated.

The baseline TNFR2 was not associated with the mGFR decline in unadjusted analyses, but it was associated with a slower mGFR decline in the fully adjusted models (Table 3). A similar association between higher TNFR2 and a slower decline in the eGFR was found for the eGFRcrecys, but not for the eGFRcre or eGFRcys. For all models, higher hsCRP level was associated with an accelerated decline in mGFR and eGFRcre, but not for eGFRcys or eGFRcrecys. The residuals were normally distributed and there were no sign of heteroscedasticity. There were no significant interactions of sex, fasting glucose, or HbA_{1c}, with either TNFR2 or hsCRP for the association with the change in mGFR or eGFR.

There was a statistically significant, nonlinear association between the TNFR2 and mGFR decline with the same covariates as in model 2 of Table 3 (Supplemental Table 2). There was an increasingly positive association between higher TNFR2 levels and the mGFR change rate, *i.e.*, a slower GFR decline, as shown in Figure 3.

In sensitivity analyses, we excluded 48 participants with a possible acute inflammatory state, defined as hsCRP>10 mg/L (36), as well as 30 participants with CKD at baseline. The associations between hsCRP and

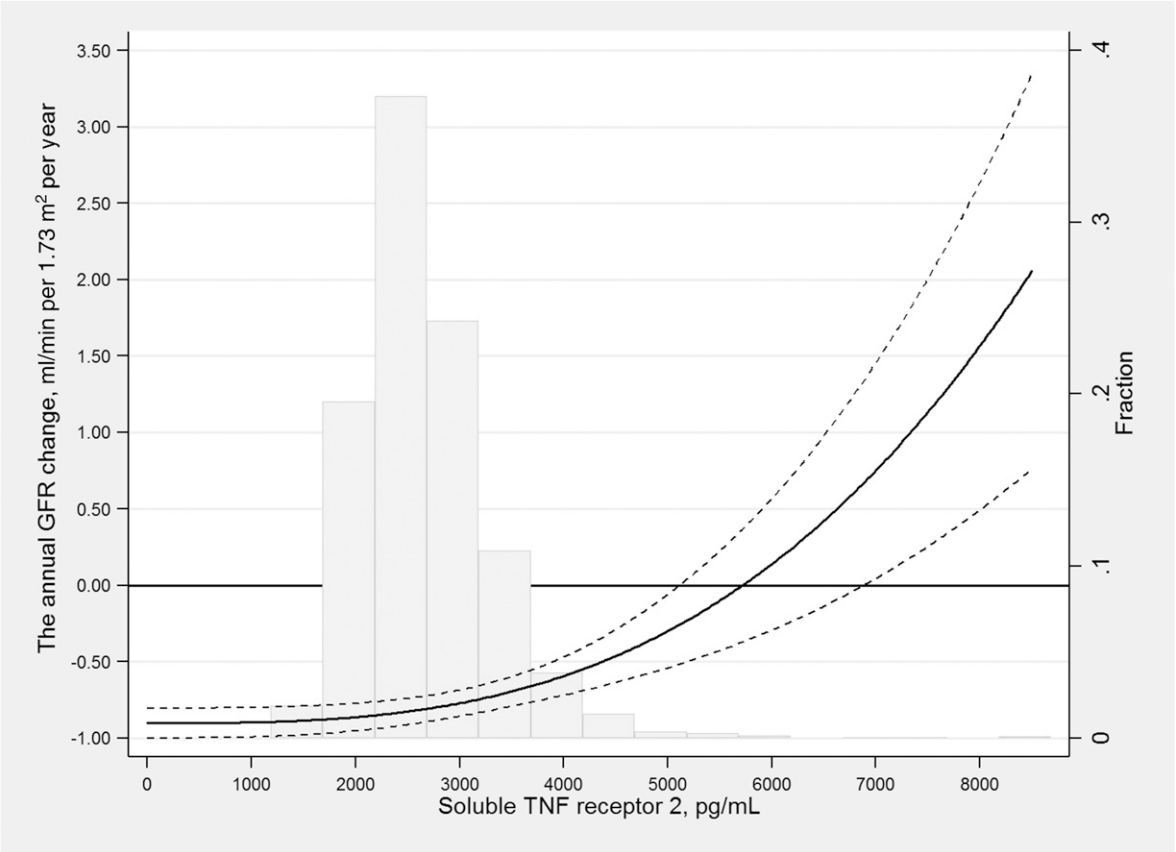

Figure 3. | Soluble TNF receptor 2 associates non-linearly with the annual GFR change as found in a linear mixed model using transformation with a second-degree fractional polynomial model. Dashed lines indicate 95% confidence intervals. The analyses were adjusted for sex; baseline weight and height; systolic BP; LDL cholesterol; HDL cholesterol; fasting triglycerides; hemoglobin A_{1c}; urinary albumin-to-creatinine ratio; number of cigarettes currently smoked; the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and non-steroidal anti-inflammatory drugs; and a dichotomous variable for the weekly use of alcohol. The distribution of soluble TNF receptor 2 in the study population is superimposed on the graph.

GFR decline for mGFR and eGFRcre disappeared (Supplemental Table 3). The estimates for the association for TNFR2 and GFR decline remained similar to those reported in Table 3 (Supplemental Table 4).

Higher hsCRP was associated with higher odds ratio for rapid mGFR decline in the unadjusted model and in the model adjusted for sex, age, weight, and height, as presented in Table 4. In addition, higher hsCRP was associated with higher odds ratio for CKD on the basis of mGFR but not eGFR, and the estimate remained unchanged after additional adjustment for baseline mGFR, as presented in Table 5. Higher TNFR2 was associated with higher odds ratio for CKD based on eGFRcys and a borderline association with eGFRcrecys. These associations disappeared after adjustment for the baseline eGFR.

Discussion

In this study, we found that the mean age-related mGFR decline was −0.84 ml/min per 1.73 m^2 per year, which is comparable with previous studies using creatinine measurements (37). Higher hsCRP level was associated with a slightly accelerated mGFR decline during the 5.6 years of follow-up, as well as higher risk of rapid mGFR decline and incident CKD. By contrast, we found that a higher TNFR2 level was associated with a slower mGFR decline, which contradicts the findings of previous longitudinal studies performed on the general population (11,18,19). Shankar *et al.* (11) reported that TNFR2 was associated with a risk for incident CKD, defined as eGFRcre<60 ml/min per 1.73 m^2, in a cohort from the general population during 15 years of follow-up. Medenwald *et al.* (18) reported an association between higher TNFR1 levels and a faster eGFR decline in men, as well as a higher risk of CKD (eGFR<60 ml/min per 1.73 m^2) in both sexes during 4 years of follow-up. Neither of the studies found an association between CRP and increased risk of CKD or GFR decline.

There are several possible explanations for the divergent results compared with our study. First, the previous studies used eGFR, which may be problematic because non-GFR–related factors, such as TNFR2 and hsCRP, influence the eGFRcre and eGFRcys independent of the mGFR (21,22,38). Indeed, we included eGFR in our analyses and found that higher hsCRP was associated with a faster decline of eGFRcre and mGFR but not with eGFRcys or eGFRcrecys. Higher TNFR2 was associated with a slower decline rate of mGFR and eGFRcrecys but not with eGFRcre or eGFRcys. The different results obtained with different GFR methods could also be explained by lower precision of eGFR in the normal range of GFR.

Second, previous studies used traditional regression analyses to assess the change in the eGFR and risk of CKD, and they did not adjust for the baseline eGFR (11,18). The inverse baseline association between soluble TNF receptors and GFR found in this study and reported by others is most likely because of renal excretion (39) and could have confounded the results of the longitudinal analyses, particularly when the outcome was defined as incident CKD (eGFR<60 ml/min per 1.73 m^2). Of note, in a recent community-based cohort, the odds ratios for the 5-year incidence of CKD associated with a higher TNFR1 were

Table 4. The association of TNFR2 and hsCRP with the risk of rapid decline in mGFR and eGFR in logistic regression models

Rapid GFR Decline	Unadjusted			Adjusted for Sex and Baseline Age, Weight, and Height			Fully Adjusted[a]		
	Odds Ratio	95% CI	*P* Value	Odds Ratio	95% CI	*P* Value	Odds Ratio	95% CI	*P* Value
TNFR2[b]									
mGFR	0.76	0.47 to 1.21	0.25	1.05	0.63 to 1.73	0.86	0.93	0.53 to 1.63	0.79
eGFRcre	1.12	0.69 to 1.93	0.59	1.13	0.67 to 1.92	0.65	1.11	0.62 to 2.00	0.72
eGFRcys	1.58	1.08 to 2.31	0.02	1.31	0.81 to 2.12	0.27	1.30	0.78 to 2.18	0.32
eGFRcrecys	1.09	0.69 to 1.71	0.72	1.06	0.63 to 1.79	0.83	1.00	0.56 to 1.78	0.99
hsCRP									
mGFR	1.04	1.01 to 1.07	0.01	1.03	1.01 to 1.06	0.02	1.03	1.00 to 1.07	0.07
eGFRcre	1.05	1.02 to 1.08	0.001	1.05	1.02 to 1.08	0.001	1.05	1.02 to 1.08	0.001
eGFRcys	1.02	0.99 to 1.04	0.29	1.01	0.98 to 1.04	0.48	1.01	0.98 to 1.04	0.67
eGFRcrecys	1.00	0.98 to 1.01	0.72	1.02	0.98 to 1.05	0.32	1.01	0.98 to 1.04	0.55

The Renal Iohexol-Clearance Survey Follow-Up Study. The odds ratios represent 1 SD higher TNFR2 and 1 mg/L higher hsCRP. Each row represents separate logistic regression models with rapid decline in mGFR or eGFR (≥3.0 ml/min per 1.73 m^2 per year) as a dependent variable. TNFR2, soluble TNF receptor 2; hsCRP, high-sensitivity C-reactive protein; mGFR, measured GFR; 95% CI, 95% confidence interval; eGFRcre, eGFR on the basis of creatinine; eGFRcys, eGFR on the basis of cystatin C; eGFRcrecys, eGFR on the basis of creatinine and cystatin C.

[a]Adjusted for sex; baseline age, weight and height; systolic BP; LDL and HDL cholesterol; fasting triglycerides; hemoglobin A_{1c}; urinary albumin-to-creatinine ratio; number of cigarettes currently smoked; angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or nonsteroidal anti-inflammatory drugs; a dichotomous variable for the weekly use of alcohol; and baseline mGFR or eGFR.

[b]The SD for TNFR2 is 651.5.

Table 5. The association of TNFR2 and hsCRP with incident CKD stage 3 in a logistic regression model with and without adjusting for baseline GFR

CKD Stage 3 (<60 ml/min per 1.73 m^2)	Adjusted for Sex and Baseline Age, Weight, and Height			Adjusted for Sex and Baseline Age Weight, Height, and mGFR/eGFR		
	Odds Ratio	95% CI	*P* Value	Odds Ratio	95% CI	*P* Value
TNFR2						
mGFR	1.32	0.59 to 2.93	0.50	0.58	0.19 to 1.74	0.33
eGFRcre	1.98	0.88 to 4.46	0.10	1.45	0.41 to 5.09	0.56
eGFRcys	5.43	2.18 to 13.5	<0.001	0.85	0.19 to 3.77	0.83
eGFRcrecys	2.65	0.91 to 7.71	0.07	0.46	0.06 to 3.43	0.45
hsCRP						
mGFR	1.04	1.00 to 1.08	0.03	1.05	1.01 to 1.09	0.02
eGFRcre	1.02	0.96 to 1.08	0.57	1.03	0.96 to 1.11	0.36
eGFRcys	1.03	0.96 to 1.10	0.47	1.01	0.94 to 1.10	0.74
eGFRcrecys	1.02	0.91 to 1.13	0.83	1.02	0.91 to 1.15	0.72

The Renal Iohexol-Clearance Survey Follow-Up Study. The odds ratios represent 1 SD higher TNFR2 and 1 mg/L higher hsCRP. Each row represents separate logistic regression models with CKD stage 3 (yes/no) as a dependent variable. TNFR2, soluble TNF receptor 2; hsCRP, high-sensitivity C-reactive protein; mGFR, measured GFR; 95% CI, 95% confidence interval; eGFRcre, estimated GFR on the basis of creatinine; eGFRcys, eGFR on the basis of cystatin C; eGFRcrecys, eGFR on the basis of creatinine and cystatin C.

attenuated and not statistically significant after additional adjustment for the baseline eGFRcys (19). There were only 14 subjects in our population who had eGFRcys<60 ml/min per 1.73 m^2 at follow-up. Still, we obtained a significantly higher odds ratio of CKD associated with higher TNFR2 when using eGFRcys in a logistic regression model without adjusting for the baseline GFR. This relationship disappeared after adjusting for the baseline eGFRcys, which indicates an impact of the cross-sectional association between TNFR2 and GFR on the longitudinal analysis. In contrast, hsCRP did not correlate with baseline mGFR or eGFR. Thus, the odds ratio for CKD (on the basis of mGFR) associated with higher hsCRP was not influenced by additional adjustment for baseline mGFR.

Third, our study participants were relatively healthy, without diabetes, kidney disease, or cardiovascular disease at baseline. None of the previous studies excluded participants with diabetes or cardiovascular disease at baseline, which may have influenced the association between TNFR2 and CKD (11,18,19). However, it should be noted that there is not necessarily any contradiction between the potential effect of TNFR2 on the mean GFR decline in our study and a possibility of soluble TNF receptors as risk factors for CKD in populations with different risk. It is also possible that the underlying pathophysiology that causes GFR decline will be different in early stages than more severe stages of CKD.

There are various reports about the longitudinal relationship between CRP and GFR decline in the general population (7,11,18,40). In accordance to our results, Hiramoto *et al.* (7) found that higher CRP levels were associated with kidney function decline using eGFRcre in a cohort performed on the general population without CVD or CKD at baseline. However, after excluding 48 subjects with an acute inflammatory state, defined as CRP>10 mg/L (36), our finding of an accelerated GFR decline disappeared. It is possible that these subjects had a chronic disease (*e.g.*, cancer or rheumatic disease) that results in steeper GFR decline.

Unexpectedly, we found that higher TNFR2 was associated with a slower mGFR decline in the multivariable adjusted models and in the nonlinear model. This association remained statistically significant even after excluding subjects with baseline hsCRP>10 mg/L and mGFR<60 ml/min per 1.73 m^2. However, these results should be interpreted with caution. We speculate that the findings could represent an association between inflammation and renal hyperfiltration, which is similar to what has been found in animal studies and patients with diabetes (41–43). In a recent study of the general Japanese and American populations, higher levels of IL-6 and CRP were associated with an increased eGFR in younger adults but with gradually lower eGFR at higher ages, indicating a possible phase of hyperfiltration (43). The mechanisms for the regulation of soluble TNF receptors and their interactions with TNFα remain unclear. Unlike CRP, which is an acute-phase protein and a nonspecific marker of inflammation, the serum concentration of soluble TNF receptors is stable over time within individuals, and it has been suggested that this may reflect long-term exposure to TNFα (13,45). However, it has also been suggested that higher concentrations of soluble TNF receptors may abrogate the effects of TNFα (45). Thus, it is possible that inflammation *via* the TNFα pathway may be a beneficial physiologic response in healthy conditions and harmful with increasing severity of disease. Longer follow-up and additional GFR measurements are needed to assess the risk of CKD and possible nonlinear trajectories of GFR that are related to soluble TNF receptors in the general population.

This study has several strengths. First, the GFR was measured in a large cohort from the general population. Single-sample iohexol clearance has been shown to be accurate compared with gold standard methods (46,47),

and the intraindividual variation in the GFR measurement in our study was lower than in most previous studies (47). To the best of our knowledge, this is the only longitudinal study examining the association between low-grade inflammation and GFR decline using actual measurements of the GFR. Furthermore, we used a state-of-the-art statistical method to investigate risk factors associated with the annual age-related GFR decline (33). On the other hand, using a slope analysis in a relatively healthy population may also have limitations, where the progression of kidney function decline is quite small during 5.6 years of follow-up. The observed associations between inflammation and the age-related GFR decline in our study are small in magnitude and may not be clinically relevant. Despite these limitations, we still found an association of hsCRP with the age-related mGFR decline, which is the most important predisposing cause of CKD in old age. The variability of inflammatory biomarkers measured at baseline may have introduced bias to our results, although most likely attenuated a possible association with the GFR decline. However, study participants were rescheduled to another appointment if they had an acute illness, which reduced but did not eliminate this possible bias. There were only middle-aged white participants included in the RENIS-FU cohort. Therefore, generalizing our results to other groups of different races or age distributions should be made with caution. The measurements of hsCRP were taken a few months earlier than the RENIS-T6 study. Therefore, comparison between hsCRP and TNFR2 is inappropriate. We only examined the baseline TNFR2 level as a marker of the TNFα pathway. However, both soluble TNF receptors are highly correlated, and the same results would be expected for TNFR1 (6,14). Finally, we acknowledge that the observed associations do not necessarily imply causality because this is an observational study.

In conclusion, a higher level of hsCRP but not TNFR2 was associated with an accelerated age-related mGFR decline and incident CKD in a nondiabetic general population during almost 6 years of follow-up.

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Disclosures

None.

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