An Association between the Estimated Glomerular Filtration Rate and Carotid Atherosclerosis

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Abstract

Objective Chronic kidney disease (CKD) is a major public health problem. There is conflicting evidence concerning whether CKD is an independent risk factor for carotid intima-media thickness (IMT).

Patients and Methods The study subjects were 428 men aged 70 ± 15 (mean $\pm$ standard deviation) years and 582 women aged 75 ± 12 years enrolled consecutively from patients in the Medical Department of Seiyō Municipal Nomura Hospital. Carotid IMT was derived via B-mode ultrasonography and CKD was evaluated by the estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease Study equation.

Results In men, age ($p < 0.001$), systolic blood pressure ($p < 0.001$), antihypertensive drug use ($p < 0.001$), HDL-C ($p = 0.006$), LDL-C ($p = 0.004$), prevalence of diabetes ($p = 0.035$) and eGFR ($p < 0.001$) were significantly correlated with carotid IMT. In women, age ($p < 0.001$), systolic blood pressure ($p < 0.001$), antihypertensive drug use ($p < 0.001$), HDL-C ($p = 0.035$), LDL-C ($p = 0.017$) and eGFR ($p < 0.001$) were significantly correlated with carotid IMT. Stepwise multiple linear regression analysis using IMT as an objective variable, adjusted by various factors as explanatory variables, showed that eGFR was a significant independent contributing factor along with known risk factors in men (β , -0.096 ; $p = 0.018$) and women (β , -0.080 ; $p = 0.035$).

Conclusions Our data suggested that eGFR was associated with an increased prevalence of carotid atherosclerosis independent of common cardiovascular risk factors in both men and women.

Key words: risk factor, atherosclerosis, renal function, eGFR, carotid artery

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Introduction

Chronic kidney disease (CKD) is a devastating disease with clinical, economic and ethical dimensions, and is a recently recognized major public health problem. Current guidelines define CKD as kidney damage or glomerular filtration rate (GFR) less than $60 \text{ mL/min/1.73 m}^2$ for 3 months or more, regardless of cause (1). On the basis of clinical practice guidelines established by The Japanese Society of Nephrology, 18.7% of adults in Japan have CKD, with 4.1% of these classified with moderate or severe kidney disease (2).

Recent independent studies identified the decline of renal function in patients as an independent predictor of all-cause mortality as well as adverse cardiovascular disease (CVD)

events. In a community-based population with pre-existing CVD defined as an estimated GFR (eGFR) of less than $60 \text{ mL/min/1.73 m}^2$, the presence of CKD has been associated with an increased risk of recurrent CVD outcomes after adjustment for traditional CVD risk factors (3, 4). Other studies suggest the absence of an independent predictor between CKD and CVD after adjustment for traditional risk factors (5, 6). Some authors demonstrated that increased carotid intima-medial thickness (IMT), which is clinically considered as the surrogate endpoint of CVD, occurs early in the course of CKD (7, 8). These changes are associated with higher CVD risk factors in patients with CKD (9, 10). Limited information is available on whether or not the decline in renal function is an independent risk factor for CVD.

First, this study investigated the decline in renal function and its relation to potential risk factors such as hypertension,

hyperglycemia and lipids. Secondly, we investigated whether or not there is an independent association of GFR with a direct and early measure of carotid IMT by B-mode ultrasound. To examine these two issues, cross-sectional data from participants were used.

Materials and Methods

Subjects

Participants were consecutively enrolled from patients in the Medical Department of Seiyō Municipal Nomura Hospital between June 2000 and February 2007. Patients with a clinical history of severe cardio-renal or nutritional disorders that would affect blood pressure, lipids or glucose metabolism were excluded. Furthermore, we excluded 53 participants (22 men and 31 women) with an eGFR <30 mL/min/1.73 m² and enrolled 1,010 patients in this study. There were 428 men aged 70±15 (mean±standard deviation) years and 582 women aged 75±12 years. Informed consent for the procedure was obtained from each patient. All procedures were approved by the Ethics Committee of Seiyō Municipal Nomura Hospital.

Evaluation of risk factors

Information on demographic characteristics and risk factors was collected using the clinical files in all cases. We measured blood pressure in the right upper arm of patients in a sedentary position using a standard sphygmomanometer or an automatic oscillometric blood pressure recorder. Cigarette smoking was quantified based on daily consumption and duration of smoking. Fasting total cholesterol (T-C), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), fasting blood glucose (FBG), creatinine (enzymatic method) and uric acid levels were measured within 24 hours of admission. Low-density lipoprotein cholesterol (LDL-C) level was calculated by the Friedewald formula (11). Patients with TG levels ≥400 mg/dL were excluded (12 cases). The presence of diabetes mellitus was defined as a history of treatment for diabetes mellitus. Glomerular filtration rate was estimated by using the following equations: eGFR=0.741×175×Cr^{-1.154}×Age^{-0.203}×0.742 (for females) (12, 13).

Ultrasound image analysis

An ultrasonograph (Hitachi EUB-565 or Aloka SSD-2000) equipped with a 7.5 MHz linear type B-mode probe was used by an ultrasonograph specialist to evaluate sclerotic lesions of the common carotid arteries within two days of blood biochemistry analysis. Patients were in the supine position, and the bilateral carotid arteries were observed obliquely from the anterior and posterior directions. We measured the thickness of the intima-media complex (IMT) on the far wall of the bilateral common carotid artery at about 10 mm proximal to the bifurcation of the carotid artery. The image at this site is more clearly depicted than that

at the near wall (14, 15). Wall thickness near the 10 mm point on the B-mode monitor was also measured. The mean values were used for the analysis.

Statistical analysis

Statistical analysis was performed using SPSS 10.0J (Statistical Package for Social Science, Inc., Chicago, IL, USA). All values are expressed as means±standard deviation, unless otherwise specified. Because the distribution of smoking status, TG and FBG was skewed, it was logarithmically transformed for analysis. Differences among the groups were analyzed by 2-tailed Student's t-test or χ^2 test. To investigate the relation between eGFR and various factors, all subjects were divided into three groups based on eGFR (eGFR-1, ≥90 mL/min/1.73 m²; eGFR-2, 60-89 mL/min/1.73 m²; eGFR-3, 30-59 mL/min/1.73 m²). The correlation between the three groups based on eGFR and background parameters was determined by 1-way ANOVA or χ^2 test. Correlations between various characteristics and IMT were determined using Pearson's correlation test. Multiple linear regression analysis was used to evaluate the contribution of each risk factor including eGFR for carotid IMT. A value of $p < 0.05$ was considered significant.

Results

Characteristics of patients by gender

Table 1 shows the background characteristics by gender. Several characteristics differed between men and women; log smoking status ($p < 0.001$), diastolic blood pressure ($p = 0.036$), log FBG ($p = 0.035$), serum creatinine ($p < 0.001$), serum uric acid ($p < 0.001$) and prevalence of ischemic stroke ($p = 0.036$) were higher in men than in women, whereas age ($p < 0.001$), antihypertensive drug use ($p = 0.001$), T-C, ($p < 0.001$), HDL-C ($p < 0.001$), LDL-C ($p < 0.001$) and antilipidemic drug use ($p = 0.004$) were higher in women than in men. There were no inter-group differences in BMI, systolic blood pressure, Log TG, prevalence of diabetes and CKD, carotid IMT and the prevalence of ischemic heart disease.

Characteristics of various risk factors of subjects categorized by estimated glomerular filtration rate and gender

Table 2 shows the value of each cardiovascular risk factor categorized by eGFR in men and women. In men, age ($p < 0.001$), antihypertensive drug use ($p < 0.001$), serum creatinine ($p < 0.001$), serum uric acid ($p < 0.001$) and the prevalence of atherosclerotic disease ($p = 0.011$) were higher in the group with lower eGFR, but antilipidemic drug use ($p = 0.033$) was lower in the group with lower eGFR. In women, age ($p < 0.001$), BMI ($p = 0.009$), antihypertensive drug use ($p = 0.002$), Log TG ($p < 0.001$), serum creatinine ($p < 0.001$), serum uric acid ($p < 0.001$) and prevalence of ischemic heart disease ($p = 0.025$) were increased in the group with lower

Table 1. Characteristics of Subjects Categorized by Gender

Characteristic	Men n=428	Women n=582	p-value*
Age (years)	70 ± 15	75 ± 12	<0.001
Body mass index † (kg/m ²)	22.4 ± 3.9	22.2 ± 4.1	0.525
Smoking status ‡ (pack year)	23 (0-45)	0 (0)	-----
Log smoking status ‡ (pack year)	1.05 ± 0.73	0.05 ± 0.26	<0.001
Systolic blood pressure (mmHg)	136 ± 22	136 ± 20	0.629
Diastolic blood pressure (mmHg)	78 ± 13	76 ± 12	0.036
Antihypertensive drug use, n (%)	179 (41.8)	303 (52.1)	0.001
Total cholesterol (mg/dL)	171 ± 43	191 ± 42	<0.001
Triglycerides (mg/dL)	83 (60-115)	81 (59-109)	-----
Log triglycerides (mg/dL)	1.93 ± 0.22	1.92 ± 0.20	0.288
HDL-cholesterol (mg/dL)	50 ± 18	55 ± 17	<0.001
LDL-cholesterol (mg/dL)	101 ± 37	117 ± 35	<0.001
Antilipidemic drug use, n (%)	17 (4.0)	49 (8.4)	0.004
Fasting blood glucose (mg/dL)	116 (97-150)	110 (93-140)	-----
Log fasting blood glucose (mg/dL)	2.10 ± 0.15	2.07 ± 0.14	0.035
Diabetes, n (%)	117 (27.3)	136 (23.4)	0.163
Serum creatinine (mg/dL)	0.84 ± 0.23	0.66 ± 0.18	<0.001
Serum uric acid (mg/dl)	5.5 ± 1.8	4.7 ± 1.6	<0.001
Chronic kidney disease §, n (%)	137 (32.0)	187 (32.1)	1.000
Carotid intima-media thickness (mm)	0.98 ± 0.24	0.96 ± 0.21	0.108
Atherosclerotic disease, n (%)	174 (40.7)	218 (37.5)	0.327
Ischemic stroke, n (%)	158 (36.9)	178 (30.6)	0.036
Ischemic heart disease, n (%)	33 (7.7)	56 (9.6)	0.313

Data are means ± standard deviation or median (interquartile range). † Body mass index was calculated using weight in kilograms divided by the square of the height in meters. ‡ Smoking status: daily consumption (pack) × duration of smoking (year). HDL, high-density lipoprotein; LDL, low-density lipoprotein. § Chronic kidney disease was defined as an estimated glomerular filtration rate less than 60 mL/min/1.73 m². * 2-tailed Student's t-test or χ^2 test.

eGFR.

Figure 1 shows the correlation between eGFR and carotid IMT by gender. The correlation coefficient between the eGFR and carotid IMT was significant in both men ($r=-0.210$, $p<0.001$) and women ($r=-0.208$, $p<0.001$).

Relationship between various risk factors including estimated glomerular filtration rate and carotid intima-media thickness

Table 3 shows the relationship between the background characteristics and carotid IMT by gender. In men, age ($p<$

0.001), systolic blood pressure ($p<0.001$), antihypertensive drug use ($p<0.001$), HDL-C ($p=0.006$), LDL-C ($p=0.004$), prevalence of diabetes ($p=0.035$) and eGFR ($p<0.001$) were significantly correlated with carotid IMT. In women, age ($p<0.001$), systolic blood pressure ($p<0.001$), antihypertensive drug use ($p<0.001$), HDL-C ($p=0.035$), LDL-C ($p=0.017$) and eGFR ($p<0.001$) were significantly correlated with carotid IMT.

Multiple linear regression analysis for carotid intima-media thickness

In Model 1, stepwise multiple linear regression analysis

Table 2. Characteristics of Various Risk Factors of Subjects Categorized by Estimated Glomerular Filtration Rate

eGFR group (mL/min/1.73 m ²)	Men n=428			Women n=582		
	eGFR-1 ≥90 n=93	eGFR-2 60-89 n=198	eGFR-3 30-59 n=137	eGFR-1 ≥90 n=100	eGFR-2 60-89 n=295	eGFR-3 30-59 n=187
Characteristic						
Age (years)	65±16	68±16	76±11	69±17	74±11	79±9
Body mass index † (kg/m ²)	21.9±4.3	22.7±3.7	22.2±3.8	21.1±3.3	22.4±3.9	22.5±4.5
Log smoking status ‡ (pack year)	1.01±0.73	1.11±0.71	1.00±0.77	0.06±0.27	0.03±0.20	0.07±0.34
Systolic blood pressure (mmHg)	134±20	137±21	138±25	134±21	136±20	135±21
Diastolic blood pressure (mmHg)	78±11	79±13	77±14	76±12	77±11	76±13
Antihypertensive drug use, n (%)	29 (31.2)	71 (35.9)	79 (57.7)	41 (41.0)	147 (49.8)	115 (61.5)
Total cholesterol (mg/dL)	172±46	173±41	167±44	186±43	193±41	190±43
Log triglycerides (mg/dL)	1.94±0.25	1.93±0.22	1.92±0.19	1.83±0.20	1.92±0.20	1.95±0.19
HDL cholesterol (mg/dL)	52±20	51±18	47±17	58±17	56±17	53±15
LDL cholesterol (mg/dL)	100±38	102±35	101±38	112±34	119±34	117±38
Antilipidemic drug use, n (%)	8 (8.6)	6 (3.0)	3 (2.2)	5 (5.0)	25 (8.5)	19 (10.2)
Log fasting blood glucose (mg/dL)	2.11±0.16	2.09±0.15	2.10±0.16	2.08±0.13	2.06±0.14	2.09±0.15
Diabetes, n (%)	31 (33.3)	54 (27.3)	32 (23.4)	16 (16.0)	67 (22.7)	53 (28.3)
Serum creatinine (mg/dL)	0.57±0.08	0.78±0.08	1.11±0.17	0.44±0.06	0.60±0.06	0.87±0.14
Serum uric acid (mg/dL)	4.6±1.6	5.2±1.6	6.4±1.7	3.7±1.2	4.4±1.3	5.7±1.7
Atherosclerotic disease, n (%)	28 (30.1)	78 (39.4)	68 (49.6)	32 (32.0)	104 (35.3)	82 (43.9)
Ischemic stroke, n (%)	28 (30.1)	71 (35.9)	59 (43.1)	26 (26.0)	85 (28.8)	67 (35.8)
Ischemic heart disease, n (%)	4 (4.3)	16 (8.1)	13 (9.5)	7 (7.0)	22 (7.5)	27 (14.4)

Data are means±standard deviation. eGFR (estimated glomerular filtration rate) was estimated by using the following equations: $=0.741 \times 175 \times \text{Cr}^{-1.154} \times \text{Age}^{-0.203} \times 0.742$ (if female) † Body mass index was calculated using weight in kilograms divided by the square of the height in meters. ‡ Smoking status: daily consumption (pack) × duration of smoking (year). HDL, high-density lipoprotein; LDL, low-density lipoprotein. * 1-way ANOVA or χ^2 test.

using IMT as an objective variable, adjusted for various risk factors as explanatory variables, showed that eGFR was a significant independent contributing factor along with known risk factors in men (β , -0.096; $p=0.018$) and women (β , -0.080; $p=0.035$) (Table 4). In Model 2, antihypertensive drug use and antilipidemic drug use were added to eliminate the possible effect of medications along with the variables in Model 1, and Model 3 was adjusted for all risk factors by the forced entry method. The eGFR was a significant independent factor in men, but not in women. Moreover, in both men and women, in subjects without atherosclerotic disease, eGFR was not independently associated with carotid IMT. However, in subjects with atherosclerotic disease, eGFR was

an independent risk factor for carotid IMT only in men (β , -0.169; $p=0.019$) (data not shown).

Discussion

To examine the possible contribution of eGFR to advanced atherosclerosis, we studied the relationship between CVD risk factors, including eGFR and carotid IMT. This study showed that eGFR was independently related to carotid IMT evaluated by ultrasound. Increased carotid IMT occurred in parallel with the decline in renal function in patients with mild to moderate CKD. In addition, this study confirmed associations of early-stage CKD, which has been

Figure 1. Relationship between eGFR (estimated glomerular filtration rate) and carotid intima-media thickness by gender. $\text{eGFR (estimated glomerular filtration rate)} = 0.741 \times 175 \times \text{Cr}^{-1.154} \times \text{Age}^{-0.203} \times 0.742$ (if women).

defined as a creatinine-based estimated GFR (eGFR) of less than 60 mL/min/1.73 m² (1) and carotid IMT. The risk associated with CKD was apparent in men and women in this study.

Previous studies including subjects at high risk for CVD consistently demonstrated an independent association between decreased level of renal function and CVD events as well as the mortality. However, the role of renal function as an independent risk factor remains controversial as reported in previous community-based studies (6, 10). Because of the different methods of estimating renal function used in the previous studies, direct comparisons between those studies are very difficult. Some studies have used serum creatinine concentrations as a marker of renal function (6, 16). Other studies have used the values based on the Cockcroft-Gault equation (16). Serum creatinine is the most widely used method of assessing renal function in clinical practice, although it has been established that serum creatinine alone is not correlated with true GFR (17), especially in older individuals (18). The Cockcroft-Gault equation has been shown to underestimate true GFR in very old patients, because of the strong effect of higher age on the estimating equation (19). In accordance with some recent studies (10, 20, 21), we used the MDRD Study equation from GFR because it has been thoroughly validated in adults (22).

The relationship between carotid IMT and CKD has not

been widely tested in subjects with early-stage CKD. In the Chinese population older than 40 years, carotid IMT has been reported to be significantly higher in subjects with early-stage CKD (eGFR 30 to 89 mL/min/1.73 m²) (10). eGFR and urinary albumin-creatinine ratio significantly correlated with carotid IMT in univariate analysis, however, this was not the case after adjusting for traditional cardiovascular risk factors. The greater prevalence of CVD risk factors in patients with CKD is reported to account for the higher carotid IMT. This study showed that the significant association between eGFR and carotid IMT provided direct evidence of the contribution of the decreased eGFR to advanced carotid atherosclerosis.

Some community-based longitudinal studies investigated the effect of renal function on cardiovascular and all-cause mortality. Rahman et al (21) reported that patients ≥ 55 years with hypertension and one or more risk factors for coronary heart disease and reduced GFR are more likely to develop coronary heart disease than to develop end-stage renal disease. A low GFR of less than 53 mL/1.73 m² independently predicts increased risk of coronary heart disease (21). Muntner et al (23) investigated the association between eGFR and CVD-related and all-cause mortality rates during 16 years of follow-up monitoring from the Second National Health and Nutrition Examination Survey Mortality Study. Compared with subjects with eGFR ≥ 90 mL/min, those

Table 3. Relationship between Various Risk Factors Including Estimated Glomerular Filtration Rate and Carotid Intima-Media Thickness

Characteristic	Pearson's correlation coefficient			
	Men n=428		Women n=582	
	r	p-value	r	p-value
Age (years)	0.540	<0.001	0.463	<0.001
Body mass index † (kg/m ²)	−0.055	0.253	−0.021	0.616
Log smoking status ‡ (pack year)	0.070	0.151	−0.034	0.409
Systolic blood pressure (mmHg)	0.197	<0.001	0.188	<0.001
Diastolic blood pressure (mmHg)	−0.031	0.526	−0.024	0.567
Antihypertensive drug use (Yes=1, No=0)	0.234	<0.001	0.162	<0.001
Log triglycerides (mg/dL)	−0.046	0.338	0.063	0.129
HDL cholesterol (mg/dL)	−0.133	0.006	−0.088	0.035
LDL cholesterol (mg/dL)	0.138	0.004	0.099	0.017
Antilipidemic drug use (Yes=1, No=0)	0.047	0.327	−0.010	0.808
Log fasting blood glucose (mg/dL)	−0.022	0.655	0.081	0.050
Diabetes (Yes=1, No=0)	0.102	0.035	0.059	0.156
eGFR (mL/min/1.73m ²) §	−0.210	<0.001	−0.208	<0.001

† Body mass index was calculated using weight in kilograms divided by the square of the height in meters. ‡ Smoking status: daily consumption (pack) × duration of smoking (year). HDL, high-density lipoprotein; LDL, low-density lipoprotein. § eGFR (estimated glomerular filtration rate) = $0.741 \times 175 \times \text{Cr}^{-1.154} \times \text{Age}^{-0.203} \times 0.742$ (if woman).

with eGFR <70 mL/min exhibited higher relative risks of death from CVD and all causes [hazard ratio (HR), 1.68; 95% confidence interval (CI), 1.33 to 2.13] and 1.51 (95% CI, 1.19 to 1.91), respectively] in multivariate analyses. Weiner et al (24) demonstrated from a pooled analysis of recent community-based studies that CKD, which was defined as a GFR between 15 and 60 mL/min/1.73 m², is a risk factor for the composite outcome of CVD and all-cause mortality (HR, 1.19; 95%CI, 1.07 to 1.32) in the general population. This risk factor was more pronounced in Blacks than in Whites (24). Meisinger et al (4) confirmed the association of reduced eGFR and increased risk of CVD mortality in a large population-based study. It may be that the effect of CKD on atherosclerosis is evident.

The reasons for the high CVD risk in patients with CKD remain unknown. A possible explanation is that decreased renal function may be associated with other non-traditional risk factors that were not evaluated in this study. Such factors include uric acid, homocysteine (25), C-reactive protein (26), albuminuria (27), oxidative stress (28), endothelial dysfunction (29) and cytokines (30). Chronic kidney disease may be complicated by both duration and severity of other causes of CVD, and exacerbate atherosclerosis caused by

CVD risk factors. The duration of exposure to adverse CVD risk factors may be the largest in patients with pronounced CKD.

However, interpreting our results has several limitations that must be considered. First, based on its cross-sectional study design, the present findings are inherently limited in the ability to eliminate causal relationships between risk factors and carotid atherosclerosis. Secondly, since all subjects were hospitalized patients, we could not eliminate the possible effect of underlying diseases and medications used for hypertension and dyslipidemia on the present findings. Third, secondary prevention interventions in obesity, hypertension, dyslipidemia and diabetes mellitus may be successful in reducing risk factors, thus attenuating the observed association of risk factors with disease. Fourth, our definition of eGFR is based on a single assessment of serum creatinine and this may introduce misclassification bias. Therefore the demographics and referral source may limit ability to generalize.

In conclusion, the present study showed that eGFR is strongly associated with an increased prevalence of carotid atherosclerosis in both men and women. The underlying mechanism behind this relationship is unclear, but it seems

Table 4. Multiple Linear Regression Analysis for Carotid Intima-media Thickness

Characteristic	Men n=428 β (p-value)			Women n=582 β (p-value)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Age (years)	0.515 (<0.001)	0.505 (<0.001)	0.459 (<0.001)	0.424 (<0.001)	0.419 (<0.001)	0.405 (<0.001)
Body mass index † (kg/m ²)	-----	-----	-0.045 (0.322)	-----	-----	-0.045 (0.259)
Log smoking status ‡ (pack year)	-----	-----	0.058 (0.145)	-----	-----	0.007 (0.838)
Systolic blood pressure (mmHg)	0.094 (0.021)	0.086 (0.036)	0.162 (0.002)	0.184 (<0.001)	0.173 (<0.001)	0.191 (<0.001)
Diastolic blood pressure (mmHg)	-----	-----	-0.078 (0.126)	-0.099 (0.018)	-0.094 (0.026)	-0.096 (0.023)
Antihypertensive drug use (Yes=1, No=0)	-----	0.046 (0.276)	0.042 (0.329)	-----	0.048 (0.206)	0.049 (0.197)
Log triglycerides (mg/dL)	-----	-----	-0.027 (0.554)	-----	-----	-0.003 (0.949)
HDL cholesterol (mg/dL)	-----	-----	-0.063 (0.131)	-----	-----	-0.069 (0.080)
LDL cholesterol (mg/dL)	0.132 (0.001)	0.130 (0.001)	0.151 (<0.001)	0.116 (0.001)	0.114 (0.002)	0.117 (0.003)
Antilipidemic drug use (Yes=1, No=0)	-----	0.009 (0.814)	0.018 (0.646)	-----	-0.008 (0.822)	-0.009 (0.812)
Log fasting blood glucose (mg/dL)	-----	-----	-0.072 (0.133)	-----	-----	0.053 (0.189)
Diabetes (Yes=1, No=0)	0.100 (0.012)	0.095 (0.019)	0.137 (0.004)	-----	-----	0.017 (0.684)
eGFR (mL/min/1.73m ²) §	-0.096 (0.018)	-0.090 (0.029)	-0.096 (0.019)	-0.080 (0.035)	-0.074 (0.050)	-0.072 (0.067)
R ²	0.345 (<0.001)	0.347 (<0.001)	0.366 (<0.001)	0.262 (<0.001)	0.264 (<0.001)	0.272 (<0.001)

† Body mass index was calculated using weight in kilograms divided by the square of the height in meters. ‡ Smoking status: daily consumption (pack)×duration of smoking (year). HDL, high-density lipoprotein; LDL, low-density lipoprotein. § eGFR (estimated glomerular filtration rate) = $0.741 \times 175 \times \text{Cr}^{-1.154} \times \text{Age}^{-0.203} \times 0.742$ (if female). R², multiple coefficient of determination. β , standard regression coefficient. Model 1, stepwise method. Model 2 and Model 3, forced entry method.

to be independent from traditional cardiovascular risk factors such as age, BMI, smoking, hypertension, dyslipidemia and diabetes. Estimation of GFR in addition to the consideration of present conventional risk factors may be useful for individual risk assessment. Further prospective population-based studies are needed to investigate the mechanisms underlying this association.

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