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Carboxymethyl-lysine, an advanced glycation end product, and decline of renal function in older community-dwelling adults

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Abstract

Background—Advanced glycation end products (AGEs) are bioactive molecules found in greater concentrations in foods that have been processed at high temperatures. AGEs have been associated with impaired renal function in diabetes and in uremia. The relationship between AGEs and renal function in community-dwelling adults has not been well characterized.

Aim of the Study—The objective was to determine whether plasma AGEs are independently associated with chronic kidney disease (CKD) and predictive of renal function in older adults.

Methods—The relationship between plasma carboxymethyl-lysine (CML), an AGE, and CKD (≥stage 3 of National Kidney Foundation classification; estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2) and eGFR at 3- and 6-years follow-up was examined in a population-based study of aging, the InCHIANTI study, in Tuscany, Italy.

Results—Of 1,008 adults, aged ≥65 years, 153 (15.2%) had CKD at enrollment. Mean (Standard Deviation [S.D.]) plasma CML was 365 (110) ng/mL. Plasma CML was associated with CKD (Odds Ratio [O.R.] expressed per 1 S.D., 1.53, 95% Confidence Interval [C.I.] 1.27-1.84, P <0.0001) in a multivariate logistic regression model, adjusting for potential confounders. Plasma CML was associated with eGFR (beta = -2.77, standard error [S.E.] = 0.51, P <0.0001) at baseline, 3-year (beta = -2.54, S.E. = 0.61, P <0.0001) and 6-year follow-up visits (beta = -1.21, S.E. = 0.70, P = 0.08) in multivariate linear regression models, adjusting for potential confounders. The associations between plasma CML and prevalent CKD, eGFR, and eGFR at 3- and 6-year follow-up were significant and nearly unchanged after exclusion of adults with diabetes.

Conclusion—Plasma CML is independently associated with CKD and is an independent predictor of decline in renal function in older community-dwelling adults.

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Conflict of Interest
The authors have no conflict of interest.

Keywords

advanced glycation end products; aging; carboxymethyl-lysine; chronic kidney disease; renal function

Introduction

Chronic kidney disease affects a large proportion of older adults, and the prevalence of chronic kidney disease has been increasing over the last two decades [5]. Established risk factors for chronic kidney disease include age, gender, blood pressure, smoking, and diabetes [12]. An increase in obesity, diabetes, and hypertension accounts for some of the increased prevalence of chronic kidney disease, but the epidemiological risk factors for chronic kidney disease are incompletely explained [5].

Advanced glycation end products (AGEs) are bioactive molecules that are found in high amounts in many common foods that are prepared at elevated temperatures, such as by deep frying, grilling, and broiling [9,13]. AGEs are formed by the non-enzymatic glycation of proteins and other molecules. AGEs in food can be absorbed in the gastrointestinal tract [13, 17,24]. AGEs have been implicated in the pathogenesis of chronic renal insufficiency [3], diabetes [26], and cardiovascular disease [1]. AGEs may also arise endogenously in the body, especially in persons with hyperglycemia or diabetes [26].

The relationship between AGEs and renal function has mainly been studied in patients with diabetic nephropathy, uremia, or end-stage renal disease [3], and the relationship in older men and women living in the community has not been well characterized. Such an examination is important because factors associated with reductions in glomerular filtration rate in older adults are not well understood. We hypothesized that older men and women with elevated plasma carboxymethyl-lysine (CML), a circulating AGE, were at greater risk of chronic kidney disease and decline in renal function over time. To examine this hypothesis, we examined the relationship between CML and renal function in a population-based cohort study of aging.

Subjects and methods

The participants consisted of men and women, aged 65 and older, who participated in the Invecchiare in Chianti, “Aging in the Chianti Area” (InCHIANTI) study, a population-based study conducted in two small towns, Greve in Chianti and Bagno a Ripoli, in Tuscany, Italy. The rationale, design, and data collection have been described elsewhere, and the main outcome of this longitudinal study is mobility disability [7]. Participants were enrolled after written, informed consent. The study protocol complied with the Declaration of Helsinki and was approved by the Italian National Institute of Research and Care on Aging Ethical Committee. The plan for secondary data analysis was approved by the Institutional Review Board of the Johns Hopkins University School of Medicine.

Demographic information and information on smoking and medication use were collected using standardized questionnaires. Smoking history was determined from self-report and dichotomized in the analysis as “current smoking” versus “ever smoked” and “never smoked.” Education was recorded as years of school. All participants were examined by a trained geriatrician, and diseases were ascertained according to standard, pre-established criteria and algorithms based upon those used in the Women’s Health and Aging Study for coronary heart disease, chronic heart failure, stroke, and cancer [11]. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Mini-Mental Status Examination (MMSE) was administered at enrollment [8]. Chronic kidney disease was defined as estimated glomerular filtration rate of

<60 mL/min/1.73 m^2 using the four-variable Modification of Diet in Renal Disease Study equation of Levey and colleagues [14]. Participants were evaluated again for a three-year follow-up visit from 2001-2003 (n = 926) and six-year follow-up visit from 2004-2006 (n = 844). Vital status was determined using data from the Mortality General Registry maintained by the Tuscany Region.

Blood samples were collected in the morning after a 12-h fast. Aliquots of plasma and serum were immediately obtained and stored at -80° C. The measure of plasma AGEs in this study was plasma carboxymethyl-lysine (CML), one of the better characterized AGEs that is found in the circulation and in high concentrations in tissue proteins [19]. CML was measured at enrollment using a competitive ELISA (AGE-CML ELISA, Microcoat, Penzberg, Germany) [2]. This assay has been validated [31], is specific, and shows no cross-reactivity with other compounds [2].

Variables are reported as medians (25^{th}, 75^{th} percentiles) or as percentages. Characteristics of subjects according whether or not they had chronic kidney disease were compared using Wilcoxon rank sum tests for continuous variables and chi-square tests for categorical variables. Age and body mass index were analyzed as categorical variables because the relationship between age, body mass index, and renal function was not linear. Univariate and multivariate logistic regression models were used to examine the relationship between plasma CML and chronic kidney disease. Variables that were significant in the univariate analyses were entered into the multivariate analyses. Univariate and multivariate linear regression models were used to examine the relationship between plasma CML and eGFR. Cox proportional hazards models were used to examine the relationship between plasma CML at enrollment and the categorical outcomes of incident chronic kidney disease and all-cause mortality. The statistical program used was SAS (SAS Institute, Cary, NC), with data analysis conducted by Kai Sun. The level of significance used in this study was $P < 0.05$.

Results

Of the 1,155 participants ≥65 years, seen at enrollment, 1,055 (91.3%) participated in the blood drawing. There were 1,012 (87.6%) participants who had plasma CML measurements available for this analysis at enrollment. The subjects who did not participate in the blood drawing were generally older and had greater comorbidity than the subjects who participated in the blood drawing, as reported elsewhere [21]. Of the 1,012 participants seen at enrollment, 1,008 had both plasma CML and eGFR measurements available at the enrollment visit. Of the 1,008 subjects, 735 (72.9%) had eGFR measurements available at the three-year follow-up visit, and 643 (63.8%) had eGFR measurements available at the six-year follow-up visit. Of the 1,012 subjects with CML measurements at enrollment, 96 died between enrollment and the three-year follow-up visit, and 130 died between the three-year and six-year follow-up visit, 73 refused participation in the three-year follow-up visit, 34 refused participation in the six-year follow-up visit, and 20 moved out of the study area.

The demographic and health characteristics of 1,008 adults with and without chronic kidney disease at enrollment are shown in Table 1. Overall, mean (SD) serum CML was 365 (110) ng/mL. Of 1,008 adults, 153 (15.2%) had chronic kidney disease. Those with chronic kidney disease were more likely to be older, female, non-smokers, and to have lower level of education, MMSE <24, congestive heart failure, stroke, depression, and cancer. There were no significant differences in body mass index or prevalence of hypertension, angina, peripheral artery disease, or diabetes mellitus between those with and without chronic kidney disease. The proportion of subjects with estimated glomerular filtration rate ≥90, 60-89, 30-59, 15-29, and <15 mL/min/1.73 m^2 was 17.9%, 67.4%, 14.8%, 0.4%, and 0.1%, respectively.

Separate multivariate logistic regression models were used to examine the cross-sectional relationship between plasma CML and chronic kidney disease at enrollment (Table 2). Plasma CML was significantly associated with increased odds of chronic kidney disease in models adjusting for age and sex, and additionally for education, smoking, and MMSE, and for chronic diseases (Table 2). After exclusion of participants who had diabetes, plasma CML was significantly associated with increased odds of chronic kidney disease in models adjusting for age and sex, and additionally for education, smoking, and MMSE, and for chronic diseases (Table 2). After exclusion of participants who were current smokers, plasma CML was significantly associated with increased odds of chronic kidney disease in models adjusting for age and sex, and additionally for education and MMSE, and for chronic diseases (Table 2).

The cross-sectional relationship between plasma CML and eGFR at enrollment was examined in univariate linear regression analyses shown in Table 3. Older age, sex, education, smoking, plasma CML, MMSE <24, congestive heart failure, depression, and cancer were associated with eGFR. Body mass index, hypertension, angina, peripheral artery disease, stroke, and diabetes mellitus were not associated with eGFR.

Separate multivariate linear regression models were used to examine the cross-sectional relationship between plasma CML and eGFR at enrollment (Table 4). Plasma CML was significantly associated with eGFR in separate models adjusting for age and sex, and additionally for education, smoking, and MMSE, and for chronic diseases. After exclusion of participants who had diabetes, plasma CML was significantly associated with eGFR in separate models adjusting for age and sex, and additionally for education, smoking, and MMSE, and for chronic diseases (Table 4). After exclusion of participants who were current smokers, plasma CML was significantly associated with eGFR in separate models adjusting for age and sex, and additionally for education and MMSE, and for chronic diseases (Table 4).

Of 855 participants who did not have chronic kidney disease at enrollment, 170 (19.9%) developed chronic kidney disease during the six years of follow-up. In multivariate Cox proportional hazards models, plasma CML (per 1 S.D.), was associated with incident chronic kidney disease, adjusting for age and sex (Hazards Ratio [H.R.] 1.15, 95% Confidence Interval [C.I.] 0.97-1.35, $P = 0.10$), adjusting additionally for education, smoking, and MMSE (H.R. 1.15, 95% C.I. 0.97-1.36, $P = 0.10$), and adjusting for the previous covariates and congestive heart failure, stroke, depression, and cancer (H.R. 1.15, 95% C.I. 0.97-1.36, $P = 0.10$).

After excluding participants with diabetes, of the 747 non-diabetic participants who did not have chronic kidney disease at enrollment, 140 (18.7%) developed chronic kidney disease during follow-up. In multivariate Cox proportional hazards models, plasma CML (per 1 S.D.), was associated with incident chronic kidney disease, adjusting for age and sex (Hazards Ratio [H.R.] 1.17, 95% Confidence Interval [C.I.] 0.97-1.40, $P = 0.09$), adjusting additionally for education, smoking, and MMSE (H.R. 1.16, 95% C.I. 0.97-1.40, $P = 0.10$), and adjusting for the previous covariates and congestive heart failure, stroke, depression, and cancer (H.R. 1.18, 95% C.I. 0.98-1.42, $P = 0.07$).

Of 855 participants who did not have chronic kidney disease at enrollment, 171 (20.0%) died during six years of follow-up. There was a strong competing risk of mortality during follow-up. Participants in the highest quartile of plasma CML compared to the lower three quartiles had higher all-cause mortality, adjusting for age and sex (H.R. 1.36, 95% C.I. 1.00-1.86, $P = 0.05$), adjusting additionally for education, smoking, and MMSE (H.R. 1.38, 95% C.I. 1.01-1.88, $P = 0.04$) and adjusting for the previous covariates and congestive heart failure, stroke, depression, and cancer (H.R. 1.44, 95% C.I. 1.03-2.02, $P = 0.03$).

There were 735 participants who had at least one or more eGFR measurements available from the six years of follow-up. The relationship between plasma CML at enrollment and eGFR at

3- and 6-year follow-up visits was examined in separate multivariate linear regression models (Table 5). Plasma CML was associated with eGFR at 3- and 6-year follow-up visits in models adjusting for age, sex, baseline eGFR, education, smoking, MMSE, and chronic diseases. After excluding participants with diabetes, plasma CML was associated with eGFR at 3- and 6-year follow-up visits in models adjusting for age, sex, baseline eGFR, education, smoking, MMSE, and chronic diseases (Table 5). After excluding participants who were current smokers, plasma CML was associated with eGFR at 3- and 6-year follow-up visits in models adjusting for age, sex, baseline eGFR, education, smoking, MMSE, and chronic diseases (Table 5). The relationships were generally stronger between plasma CML at baseline and eGFR at the 3 year follow-up visit compared with the 6-year follow-up visit.

Discussion

The present study shows that elevated plasma CML is independently associated with chronic kidney disease and eGFR in older adults living in the community. Elevated CML at baseline was an independent predictor of eGFR at three and six years' follow-up. To our knowledge, this is the first study to show that elevated circulating AGEs are an independent predictor of renal function in population-based study of community-dwelling men and women. Hyperglycemia is considered to increase the generation of endogenous AGEs, and the relationship between AGEs and renal disease has been studied extensively in patients with diabetes [26]. Another important new observation in the present study was that plasma CML was strongly associated with chronic kidney disease, eGFR, and eGFR at follow-up, even after excluding participants who had diabetes. These findings suggest that the potential adverse effects of AGEs on the kidney are applicable to the general population of older community-dwelling adults.

AGEs are metabolized and removed from the circulation by the kidney [10,16] but the kidney is also a site for accumulation of AGEs and AGE-related damage [20]. AGEs upregulate inflammation and the synthesis of fibronectin, laminin, and collagen IV in the kidney and promote glomerular sclerosis, fibrosis, and hypertrophy [27,30] and interstitial fibrosis [29]. The kidney is affected by AGEs, and declining renal function entails an increase in serum AGEs, thereby amplifying damage from AGEs [3].

Circulating AGEs are a modifiable risk factor, as AGEs can be lowered by dietary modification or pharmacological intervention. Plasma CML concentrations correlate well with dietary intake of AGEs [23,24]. Dietary intervention studies have shown that it is possible to lower serum or plasma CML concentrations substantially by restricting the intake of foods that are processed at high temperatures [17,24,25]. Elevated circulating AGEs could possibly be an epiphenomenon of impaired renal function, however, AGE inhibitors or AGE breakers can reduce systemic levels of AGEs, and treatment with pyridoxamine, an AGE inhibitor, has been shown to improve renal function in patients with diabetes [4,28] and in a diabetic animal model [6].

In the present study, among older adults without chronic kidney disease at enrollment, elevated plasma CML was predictive of incident chronic kidney disease, but the findings were of borderline significance. The findings may not have reached statistical significance because there was a strong competing risk of mortality in older adults who had elevated plasma CML. In older adults, reduced eGFR may be more likely to predict death than end-stage renal disease [18]. The interactions of CML, eGFR, and death should be explored in further detail in future studies. The mortality findings from the InCHIANTI study are being presented in greater detail in a separate paper.

The study has some limitations that include the use of the MDRD Study equation, which has not yet been validated in adults >70 years of age. The serum creatinine measurements in the present study were not standardized using the isotope dilution mass spectrometry-traceable MDRD Study equation [15]. Participants were only seen every three years, and some of the participants with elevated plasma CML may have developed chronic kidney disease before they died. CML is only one of many known AGEs, and the association between plasma CML and renal function does not imply that CML is the only AGE that could be associated with renal function. There are many other AGEs such as pentosidine, carboxyethyl-lysine, and hydroimidazolone AGEs [22] that could be measured and provide additional insight. The dietary intake of AGEs can only be assessed using specialized questionnaires that address the food preparation methods, and dietary intake of AGEs was not determined in the present study. However, the dietary intake of AGEs is moderately correlated with circulating CML concentrations [23].

In conclusion, elevated plasma CML was associated with chronic kidney disease and reduced renal function, and elevated plasma CML was an independent predictor of renal function. The relationships between elevated plasma CML and reduced renal function were strong in older community-dwelling men and women without diabetes. Clinical trials are needed in the future to determine whether dietary modification and/or pharmacological treatment with AGE inhibitors or AGE breakers can prevent the decline of renal function and reduce the incidence of chronic kidney disease.

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Table 1

Demographic and health characteristics of men and women, aged ≥65 years, with and without chronic kidney disease at enrollment in the InCHIANTI Study

Characteristic[1]		Chronic Kidney Disease N = 153		No Chronic Kidney Disease N = 855		*P*
		N	% or Median (25th, 75th percentile)	N	% or Median (25th, 75th percentile)	
Age, years	65-69	18	6.4	264	93.6	<0.0001
	70-74	29	10.7	242	89.3	
	75-79	34	16.3	175	83.7	
	80-84	33	29.0	81	71.0	
	85-89	24	28.9	59	71.1	
	≥90	15	30.6	34	69.4	
Sex	Male	39	8.9	400	91.1	<0.0001
	Female	114	20.0	455	80.0	
Education, years		152	5.0 (3.0, 5.0)	855	5.0 (4.0, 6.0)	<0.0001
Smoking status	Never	105	17.5	494	82.5	0.02
	Former	36	13.2	236	86.8	
	Current	12	8.8	125	91.2	
Body mass index (kg/m^2)		138	27.2 (24.1, 29.8)	808	27.2 (27.8, 27.2)	0.83
Serum creatinine (mg/dL)		153	1.1 (1.0, 1.3)	855	0.9 (0.8, 1.0)	<0.0001
Serum creatinine (μmol/L)		153	97 (88, 115)	855	80 (71, 88)	<0.0001
Estimated glomerular filtration rate (mL/min/1.73 m^2)		153	53.8 (48.5, 57.0)	855	76.3 (69.5, 87.0)	<0.0001
Plasma CML (ng/mL)		153	390 (323, 475)	855	344 (285, 413)	<0.0001
Mini-Mental Exam Score <24		62	40.5	229	26.8	0.0006
Hypertension		82	53.5	397	46.3	0.10
Angina		8	5.2	39	4.6	0.71
Peripheral artery disease		13	8.5	49	5.7	0.19
Congestive heart failure		19	12.4	35	4.1	<0.0001
Stroke		15	9.8	36	4.2	0.004
Diabetes mellitus		21	13.7	108	12.6	0.71
Depression		44	31.9	164	19.8	0.001
Cancer		20	13.1	45	5.3	0.0003

[1] Median (25th, 75th percentile) for continuous variables or percent of participants with specific characteristic as noted. For variables with multiple categories, row percentages are shown.

Table 2

Multivariate logistic regression models of the relation of plasma CML with prevalent chronic kidney disease in adults, aged ≥65 years, at enrollment in the InCHIANTI Study

		Model adjusted for age, sex			Model adjusted for age, sex, education, smoking, MMSE[2]			Model adjusted for age, sex, education, smoking, MMSE and chronic diseases[3]		
		OR	**95% CI**	***P***	**OR**	**95% CI**	***P***	**OR**	**95%CI**	***P***
Plasma CML[1,2] (ng/mL)	**All Subjects (n = 1008)**	1.57	1.32-1.86	<0.0001	1.56	1.32-1.85	<0.0001	1.53	1.27-1.84	<0.0001
	Subjects Without Diabetes (n = 879)	1.56	1.30-1.86	<0.0001	1.55	1.29-1.86	<0.0001	1.56	1.28-1.90	<0.0001
	Subjects Who Were Current Nonsmokers (n = 871)	1.51	1.27-1.81	<0.0001	1.51	1.27-1.81	<0.0001	1.46	1.20-1.78	0.0002

[1] Separate logistic regression models shown for plasma CML in which chronic kidney disease (defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2) is the dependent variable.

[2] Odds ratios expressed per 1 SD of plasma CML (1 SD = 110 ng/mL).

[3] Chronic diseases were congestive heart failure, stroke, depression, and cancer.

Table 3

Univariate relationships between plasma CML and other factors with estimated glomerular filtration rate in adults, aged ≥65 years, at enrollment in the InCHIANTI Study

Characteristic		Beta	SE	*P*
Age, years[1]	70-74	-2.78	1.42	0.05
	75-79	-5.76	1.52	0.0002
	80-84	-10.61	1.85	<0.0001
	85-89	-12.29	2.08	<0.0001
	≥90	-13.47	2.58	<0.0001
Sex, male		7.20	1.07	<0.0001
Education, years		0.44	0.16	0.006
Smoking status[2]	Former	2.63	1.25	0.04
	Current	4.75	1.62	0.004
Body mass index (kg/m^2)		-0.10	0.13	0.44
Plasma CML (ng/mL), per 1 SD		-3.91	0.52	<0.0001
Mini-Mental Exam Score <24		-5.43	1.18	<0.0001
Hypertension		0.08	1.98	0.94
Angina		-3.15	2.57	0.22
Peripheral artery disease		-3.44	2.26	0.13
Congestive heart failure		-10.58	2.39	<0.0001
Stroke		-2.63	2.47	0.29
Diabetes mellitus		1.55	1.62	0.34
Depression		-5.28	1.30	<0.0001
Cancer		-7.45	2.20	0.0007

[1] Reference category is age 65-69 years.

[2] Reference category is never a smoker.

Table 4

Separate multivariate linear regression models of the cross-sectional relationship of plasma CML with estimated glomerular filtration rate in adults, aged ≥65 years, at enrollment in the InCHIANTI Study

		Model adjusted for age, sex			Model adjusted for age, sex, education, smoking, MMSE			Model adjusted for age, sex, education, smoking, MMSE and chronic diseases[3]		
		Beta	**SE**	***P***	**Beta**	**SE**	***P***	**Beta**	**SE**	***P***
Plasma CML[1,2] (ng/mL)	**All Subjects (n = 1008)**	-3.29	0.51	<0.0001	-3.24	0.51	<0.0001	-2.77	0.51	<0.0001
	Subjects Without Diabetes (n = 879)	-3.20	0.53	<0.0001	-3.17	0.53	<0.0001	-2.98	0.54	<0.0001
	Subjects Who Were Current Nonsmokers (n = 871)	-3.32	0.56	<0.0001	-3.30	0.56	<0.0001	-2.73	0.56	<0.0001

[1] Separate multivariate linear regression models shown for plasma CML in which estimated glomerular filtration rate (mL/min/1.73 m^2) is the dependent variable.

[2] Beta expressed per 1 SD of plasma CML (1 SD = 110 ng/mL).

[3] Chronic diseases were congestive heart failure, stroke, depression, and cancer.

Table 5

Separate multivariate linear regression models of the relationship of plasma CML at enrollment with estimated glomerular filtration rate in adults, aged ≥65 years, at three and six years of follow-up in the InCHIANTI Study

A. Estimated GFR at Three-Year Follow-Up

		Model adjusted for age, sex, baseline eGFR			Model adjusted for age, sex, baseline eGFR, education, smoking, MMSE			Model adjusted for age, sex, baseline eGFR, education, smoking, MMSE and chronic diseases[3]		
		Beta	**SE**	***P***	**Beta**	**SE**	***P***	**Beta**	**SE**	***P***
Plasma CML[1,2] (ng/mL)	**All Subjects (n = 735)**	-2.62	0.61	<0.0001	-2.62	0.61	<0.0001	-2.54	0.61	<0.0001
	Subjects Without Diabetes (n = 648)	-2.76	0.65	<0.0001	-2.76	0.66	<0.0001	-2.71	0.65	<0.0001
	Subjects Who Were Current Nonsmokers (n = 619)	-2.56	0.66	0.0002	-2.51	0.66	0.0002	-2.43	0.65	0.0002

B. Estimated GFR at Six-Year Follow-Up

		Model adjusted for age, sex, baseline eGFR			Model adjusted for age, sex, baseline eGFR, education, smoking, MMSE			Model adjusted for age, sex, education, smoking, MMSE and chronic diseases[3]		
		Beta	**SE**	***P***	**Beta**	**SE**	***P***	**Beta**	**SE**	***P***
Plasma CML[1,2] (ng/mL)	**All Subjects (n = 643)**	-1.18	0.70	0.09	-1.16	0.70	0.10	-1.21	0.70	0.08
	Subjects Without Diabetes (n = 567)	-1.46	0.76	0.05	-1.43	0.76	0.06	-1.49	0.76	0.05
	Subjects Who Were Current Nonsmokers (n = 556)	-1.38	0.76	0.07	-1.39	0.76	0.06	-1.46	0.76	0.05

[1] Separate multivariate linear regression models shown for plasma CML in which estimated glomerular filtration rate (mL/min/1.73 m^2) is the dependent variable.

[2] Beta expressed per 1 SD of plasma CML (1 SD = 110 ng/mL).

[3] Chronic diseases were congestive heart failure, stroke, depression, and cancer.