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Differences in Kidney Function and Incident Hypertension: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Background—Kidney disease and hypertension commonly coexist, yet the direction of their association is still debated.

Objective—To evaluate whether early kidney dysfunction, measured by serum cystatin C levels and urinary albumin excretion, predates hypertension in adults without clinically recognized kidney or cardiovascular disease.

Design—Observational cohort study using data from 2000 to 2005.

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Reproducible Research Statement: *Study protocol:* The complete MESA protocol is available online at www.mesanhlbi.org/moreinfo.aspx. *Statistical code:* Statistical code for these analyses is available from Dr. Kestenbaum (brk@u.washington.edu). *Data set:* The MESA data are available for researchers with a MESA sponsor and approved manuscript proposal. A list of participating institutions and principal investigators can be found at www.mesanhlbi.org/institutions.aspx.

Setting—The MESA (Multi-Ethnic Study of Atherosclerosis), a community-based study of subclinical cardiovascular disease in adults age 45 to 84 years.

Participants—2767 MESA participants without prevalent hypertension, cardiovascular disease, or clinically recognized kidney disease (an estimated glomerular filtration rate <60 mL/min per 1.73 m^2 or microalbuminuria).

Measurements—Cystatin C was measured by using a nephelometer, and urinary albumin and creatinine were measured from a spot morning collection. The primary outcome was incident hypertension, defined as systolic blood pressure of at least 140 mm Hg, diastolic blood pressure of at least 90 mm Hg, or use of an antihypertensive medication.

Results—During a median follow-up of 3.1 years, 19.7% of the cohort (545 participants) developed hypertension. After adjustment for established hypertension risk factors, each 15-nmol/L increase in cystatin C was associated with a statistically significant 15% greater incidence of hypertension ($P = 0.017$). The highest sex-specific quartile of urinary albumin–creatinine ratio was associated with a statistically insignificant 16% greater incidence of hypertension ($P = 0.192$) compared with the lowest quartile. No statistical evidence suggested a multiplicative interaction.

Limitations—Unmeasured characteristics may have confounded observed associations of kidney markers with hypertension. Follow-up was relatively short. Hypertension that may have occurred between study visits or hypertension that was not captured by standard cuff measurements may have been missed.

Conclusion—Differences in kidney function, indicated by cystatin C levels, are associated with incident hypertension among individuals without clinical kidney or cardiovascular disease. These population-based findings complement experimental work implicating early kidney damage in the pathogenesis of essential hypertension.

The kidneys play a central role in the regulation of blood pressure (1,2). Although most individuals with established kidney disease have hypertension, the direction of the association between kidney dysfunction and elevated blood pressure remains controversial (3–7).

Evidence suggests that early disturbances in kidney function may contribute to the development of hypertension. Transplantation of kidneys from Dahl and other hypertensive rat species transfers hypertension to recipient animals (8). Renal ischemia in early stages of kidney disease stimulates the renin–angiotensin–aldosterone and sympathetic nervous systems, which promotes sodium retention and increase peripheral resistance (9,10). Evidence links low birthweight, a surrogate marker for reduced nephron number, with a greater risk for hypertension later in life (11). Accident victims with essential hypertension have a documented decrease in nephron number compared with matched control participants (12).

The evaluation of early differences in kidney function has been hampered by the imprecision of traditional serologic methods and estimating equations (13). Cystatin C is an alternative marker of kidney function. It correlates with formal measurements of glomerular filtration and is more precise than serum creatinine levels in detecting early kidney dysfunction (14,15). Urinary albumin excretion is a complementary marker to renal filtration and partially reflects hemodynamic disturbances within the glomerulus. We evaluated serum cystatin C levels and the urinary albumin–creatinine ratio separately and in combination as predictors of incident hypertension in a multiethnic, community-based cohort without clinically recognized kidney or cardiovascular disease.

Methods

Study Population

The MESA (Multi-Ethnic Study of Atherosclerosis) is a community-based study of subclinical cardiovascular disease among 6814 adults age 45 to 84 years (16). Between 2000 and 2002, the MESA researchers recruited participants from 6 communities: Forsyth County, North Carolina; northern Manhattan and Bronx, New York; the city of Baltimore and Baltimore County, Maryland; St. Paul, Minnesota; Chicago, Illinois; and Los Angeles County, California. The MESA researchers sampled eligible participants by self-reported race or ethnicity to create a cohort that was 38% white; 28% African American; 22% Hispanic; and 12% Asian, primarily of Chinese descent. The MESA researchers excluded participants if they had a previous diagnosis of cardiovascular disease (that is, physician-diagnosed heart attack, angina, stroke, transient ischemic attack, heart failure, or atrial fibrillation; were taking nitroglycerin; or had had angioplasty, coronary artery bypass grafting, valve replacement, pacemaker or defibrillator implantation, or any surgery on the heart or arteries.)

We excluded MESA participants with baseline hypertension from our current analysis. Baseline hypertension was defined by any of the following criteria: systolic blood pressure of at least 140 mm Hg, diastolic blood pressure of at least 90 mm Hg, the use of medication for hypertension, or a self-reported history of hypertension. To focus the analyses on clinically unrecognized differences in kidney function, we excluded participants with clinical kidney disease, defined as an estimated glomerular filtration rate (GFR) less than 60 mL/min per 1.73 m^2, or microalbuminuria, defined as a urinary albumin–creatinine ratio of at least 25 mg/g for women or 17 mg/g for men (17,18). We calculated estimated GFR by using the 4-variable Modification of Diet in Renal Disease equation (19). Participants with an estimated GFR greater than 90 mL/min per 1.73 m^2 were examined separately in sensitivity analyses. Finally, we excluded participants who did not return for any follow-up MESA examinations. Figure 1 shows a flow diagram of the study participants.

Ascertainment of Exposure Variables

The Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, Vermont) measured baseline cystatin C by using the BN II nephelometer (Dade Behring, Deerfield, Illinois) (20) and measured baseline urinary albumin–creatinine ratio on a single spot morning collection by using nephelometry and the rate-Jaffe reaction, respectively. The coefficient of variation for cystatin C is 7.7%; cystatin C levels are stable through multiple freeze–thaw cycles (21). We reported the urinary albumin–creatinine ratio as milligrams of albumin per gram of creatinine, which correlates with milligrams of albumin obtained from a 24-hour urine collection (22,23). Studies have suggested that urinary albumin–creatinine ratio values are higher in women because of lower creatinine excretion; therefore, we analyzed the values as sex-specific quartiles (18).

Ascertainment of Outcome

The MESA personnel assessed blood pressure and medication use during each MESA examination, each of which was conducted 18 months apart. They obtained 3 seated blood pressure measurements 5 minutes apart by using an automated sphygmomanometer. We calculated the mean of the second 2 measurements for analysis. The MESA personnel asked participants to bring all medications to each examination, and they assessed medication use by taking a medication inventory (24). We defined incident hypertension as systolic blood pressure of at least 140 mm Hg, diastolic blood pressure of at least 90 mm Hg, or the use of any antihypertensive medication during the second or third MESA follow-up examination (25). Because angiotensin-converting enzyme inhibitors and angiotensin II antagonists may

be prescribed to individuals with diabetes but without hypertension, sensitivity analyses explored associations after excluding participants with diabetes. We also explored a second outcome, a clinically meaningful increase in blood pressure, defined as an increase in systolic blood pressure of at least 10 mm Hg, an increase in diastolic blood pressure of at least 5 mm Hg, or the introduction of an antihypertensive medication during follow-up.

Ascertainment of Covariates

We assessed covariates at the MESA baseline examination. Diabetes was defined as a reported history of diabetes, the use of any diabetes medication, or a fasting blood glucose level of at least 7 mmol/L (≥ 126 mg/dL) (26). Impaired fasting glucose was defined by a fasting glucose level of 5.6 to 6.99 mmol/L (100 to 125 mg/dL) without diabetes (26). The MESA investigators used a questionnaire to obtain histories of alcohol use and smoking. We analyzed smoking as the number of reported pack-years and alcohol use as the mean number of alcoholic drinks consumed per week. The MESA investigators obtained laboratory values after an 8- to 12-hour overnight fast. The Laboratory for Clinical Biochemistry Research measured high-sensitivity C-reactive protein levels by using the BN II nephelometer.

Statistical Analysis

We tabulated baseline participant characteristics by quartiles of cystatin C and urinary albumin–creatinine ratio. We calculated risk time as the elapsed time from the baseline to the third MESA examination, unless a participant developed hypertension at the second examination or was lost to follow-up before the third examination, in which case we calculated risk time as the elapsed time from the baseline to the second examination.

We calculated unadjusted hypertension rates as the number of events divided by person-years at risk, and we examined hypertension rates according to race or ethnicity, sex, and quartiles of cystatin C and urinary albumin–creatinine ratio. We used Poisson (log-link) regression to model the incidence rate ratio of hypertension as a function of predictor covariates with robust variance estimation and an offset for follow-up time (27). We selected a 15-nmol/L increment in cystatin C levels for continuous analyses because it corresponded approximately to the intraquartile range for cystatin C. Variables that might be related to kidney function or hypertension were selected a priori (Table 1) and were added in blocks to progressive nested models. We used a Wald test to calculate *P* values and 95% CIs for model covariates and to evaluate the statistical significance of interactions. We used complete case analysis to handle missing data.

Searching MEDLINE from July 2007 through January 2008 did not yield any new references to the relationship of cystatin C levels with incident hypertension.

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Results

Of the 6814 MESA participants, we excluded 3508 because of baseline hypertension, 151 because of an estimated GFR less than 60 mL/min per 1.73 m^2, and 182 because of microalbuminuria (Figure 1). In addition, we excluded 43 participants because of a missing cystatin C value or urinary albumin–creatinine ratio, 1 for an implausible cystatin C value, and 162 for not returning for future follow-up visits. These 162 participants had cystatin C

levels (63.6 vs. 62.2 nmol/L) and urinary albumin–creatinine ratios (5.6 vs. 5.2 mg/g) similar to those of included participants. After exclusions, we analyzed 2767 participants.

The study population had a mean age of 58 years and a mean estimated GFR of 84 mL/min per 1.73 m^2. A total of 1832 participants (66%) had a baseline systolic blood pressure less than 120 mm Hg and baseline diastolic blood pressure less than 80 mm Hg; 537 (20%) had a baseline systolic blood pressure of 120 to 129.9 mm Hg or baseline diastolic blood pressure of 80 to 84.9 mm Hg; and 398 (14%) had a baseline systolic blood pressure of 130 to 139.9 mm Hg or baseline diastolic blood pressure of 85 to 89.9 mm Hg.

Serum cystatin C levels were normally distributed, whereas urinary albumin–creatinine ratios were skewed to the right. The intraquartile range for the urinary albumin–creatinine ratio was 2.8 to 6.3 mg/g; 90% of participants had ratios less than 10 mg/g. Higher cystatin C levels were associated with older age and traditional cardiovascular risk factors, whereas lower cystatin C levels were associated with Asian ethnicity (Table 1). Similar to cystatin C, greater urinary albumin–creatinine ratios were associated with older age and greater baseline systolic blood pressure. In contrast to cystatin C, greater ratios were associated with female sex, Asian and Hispanic ethnicity, and diabetes. The urinary albumin–creatinine ratio was not associated with serum cystatin C level in this study population without clinical kidney disease ($P = 0.65$).

After the baseline examination, 2418 participants (87.4%) returned for both MESA follow-up examinations, 173 (6.3%) for only the second examination, and 176 (6.4%) for only the third examination. During a median follow-up of 3.1 years, 19.7% of the cohort (545 participants) developed hypertension. Incident hypertension was more common with older age and among African-American participants (9.5 events per 100 person-years [CI, 8.1 to 11.1 events per 100 person-years]) than among Hispanic (6.8 events per 100 person-years [CI, 5.7 to 8.0 events per 100 person-years]), white (5.6 events per 100 person-years [CI, 4.9 to 6.4 events per 100 person-years]), and Asian (5.0 events per 100 person-years [CI, 3.8 to 6.5 events per 100 person-years]) participants. Among a subset of 274 participants whose incident hypertension was diagnosed by blood pressure measurements alone (without use of antihypertensive medication), 87% had isolated systolic hypertension.

Higher serum cystatin C levels and urinary albumin–creatinine ratio were associated with greater unadjusted incident hypertension rates during follow-up (Table 2). In contrast, serum creatinine levels within the normal range were not statistically associated with incident hypertension after adjustment for age, race, and sex. Serum creatinine levels of 61 to 91 μmol/L (0.8 to 1.19 mg/dL) and 92 to 114 μmol/L (1.2 to 1.5 mg/dL) were associated with 20% and 21% lower risks for hypertension ($P = 0.056$ and 0.23, respectively) compared with levels less than 61 μmol/L (<0.8 mg/dL).

After adjustment for age, race, and sex, higher cystatin C levels were associated with greater incident hypertension rates within each urinary albumin–creatinine ratio quartile (Figure 2). Observed associations of cystatin C and urinary albumin–creatinine ratio with hypertension were attenuated by adjustment for demographic characteristics, body mass index, diabetes, and baseline blood pressure (Table 2). After adjustment, the association between urinary albumin and hypertension was notably attenuated. Inclusion of additional adjustment covariates did not further alter the magnitude of the observed associations and increased the proportion of missing data in the analyses. After full adjustment, higher cystatin C quartiles remained statistically associated with incident hypertension. The highest cystatin C quartile, levels greater than 67.5 nmol/L, was associated with a statistically significant 31% greater adjusted incidence of hypertension compared with the lowest quartile. No evidence indicated a multiplicative interaction among cystatin C levels, urinary albumin–creatinine

ratios, and incident hypertension. Other covariates that were statistically associated with incident hypertension included older age, African-American race, diabetes (but not impaired fasting glucose), and greater baseline systolic blood pressure.

After adjustment for established hypertension risk factors, each linear 15-nmol/L increase in cystatin C was associated with a 15% greater incidence of hypertension ($P = 0.017$). The second study outcome, a clinically meaningful increase in blood pressure, occurred in 1320 participants (48%). Associations of cystatin C with this outcome were weaker: After adjustment, each 15-nmol/L increase in cystatin C was associated with a 6% greater incidence of a clinically meaningful increase in blood pressure ($P = 0.051$).

Exclusion of 398 participants with borderline high blood pressure at baseline, defined as systolic blood pressure of at least 130 mm Hg or diastolic blood pressure of at least 85 mm Hg, resulted in a modest increase in the magnitude of the association between cystatin C and hypertension (18% greater incidence per 15-nmol/L increase [$P = 0.019$]) and between the urinary albumin–creatinine ratio and hypertension (33% greater incidence comparing the highest with the lowest sex-specific quartile [$P = 0.053$]). Similarly, associations of both cystatin C and urinary albumin–creatinine ratio with hypertension were qualitatively strengthened when analyses were restricted to participants with an estimated GFR of at least 90 mL/min per 1.73 m^2. Associations of cystatin C levels with incident hypertension were similar among participants with and those without diabetes and across subgroups defined by baseline blood pressure category, age, race or ethnicity, and sex ($P > 0.20$ for all interactions) (Figure 3).

Discussion

We found higher cystatin C levels to be associated with a greater incidence of hypertension, independent of known risk factors, in a multiethnic cohort without clinically apparent kidney or cardiovascular disease. Associations between the urinary albumin–creatinine ratio and hypertension were attenuated by adjustment for baseline blood pressure and other covariates, and we found no evidence for a synergistic interaction between cystatin C and the urinary albumin–creatinine ratio on the risk for incident hypertension. These findings suggest that early variation in kidney function in persons without clinically recognized kidney disease might play a role in the pathogenesis of essential hypertension.

Hypertension is present in most individuals with chronic kidney disease, and hypertensive nephropathy accounts for about 25% of the population with end-stage renal disease in the United States (28,29). Chronic elevation in blood pressure promotes damage to the intrarenal vasculature, leading to intimal and medial thickening, renal ischemia, and glomerulosclerosis (30). Although hypertension clearly contributes to the progression of established kidney disease, available evidence also suggests that early kidney damage contributes to the development of hypertension, creating a vicious circle of kidney injury and blood pressure dysregulation. Epidemiologic studies have identified low birthweight, a surrogate marker of lower functional renal mass, as a risk factor for essential hypertension later in life (31,32), although recognized limitations of birthweight studies diminish the impact of these findings (33). Provocative autopsy studies have demonstrated significantly fewer nephrons in accident victims with essential hypertension than in matched control participants (12). Cyclosporine, an agent that causes renal ischemia by directly constricting the afferent renal arteriole, leads to sodium retention and chronic hypertension (34). Moreover, in spontaneously hypertensive rat models, the degree of renal arteriolar narrowing predicts the extent of future hypertension (35). Taken together, existing data suggest a unifying hypothesis in which early reductions in GFR, whether congenital or acquired because of sympathetic excess, renal arteriolosclerosis, or tubulointerstitial disease,

lead to an adverse physiologic state in which higher blood pressures are needed to maintain sodium balance (5). Although provocative, this theory has not been directly tested in population-based human studies, in part because of difficulty in evaluating early kidney dysfunction with traditional serologic methods and estimating equations (13). In this multiethnic cohort without clinically detectable kidney disease, we show a direct association between lower GFR (estimated by higher cystatin C levels) and a greater risk for future hypertension independent of traditional risk factors and other potential determinants of cystatin C.

Albuminuria represents a manifestation, distinct from renal filtration, of hemodynamic and endothelial changes within the renal glomerulus. In our normotensive study population, the urinary albumin–creatinine ratio within the clinically normal range was not related to cystatin C levels. The urinary albumin–creatinine ratio was associated with greater unadjusted risks for hypertension, but we did not observe these associations in models that fully adjusted for potential confounding factors. Cystatin C may be a more relevant marker of hypertension risk than urinary albumin excretion among relatively healthy, middle-aged adults. However, a single spot measurement of the urinary albumin–creatinine ratio is only a surrogate for daily urinary albumin excretion and thus may obscure potential associations of albuminuria and hypertension. Moreover, baseline blood pressure may reside in the causal pathway between albuminuria and incident hypertension, leading to possible overadjustment in more comprehensive models. Two previous studies have reported associations of urinary albumin–creatinine ratio with incident hypertension below the threshold for microalbuminuria (36,37). In the Prevention of Renal and Vascular End Stage Disease (PREVEND) study, timed urinary albumin excretion rates as low as 6.5 mg/d were associated with a greater risk for hypertension during follow-up (36). In contrast to our findings, that study also detected a statistically significant interaction among urinary albumin excretion, estimated GFR, and hypertension risk. In the Framingham Heart Study, higher spot urinary albumin–creatinine ratios within the normal range were associated with a greater risk for incident hypertension (37). The MESA sample differs from that of other studies because it is ethnically diverse, includes measurements of cystatin C, and does not include persons with prevalent cardiovascular disease.

Our data do not address potential causes of early variation in kidney function among individuals without clinical albuminuria in the general population. Baseline associations of smoking, body mass index, blood pressure, and C-reactive protein levels with greater cystatin C levels indicate that these factors may play a role in early kidney damage; however, associations of cystatin C with hypertension persisted after adjustment for these factors. Lower serum cystatin C levels and hypertension rates were observed among Asian participants; this finding warrants further investigation. Despite contrasts in serum cystatin C levels by race, associations of cystatin C levels with hypertension were consistent across racial or ethnic groups. Proposed potential explanations for variation in kidney function are congenital differences in nephron number and acquired exposure to heavy metals, such as lead, which can cause nonproteinuric kidney disease (38).

Strengths of our study are the use of a community-based, ethnically diverse cohort without preexisting cardiovascular or kidney disease and uniform measurements of cystatin C, urinary albumin–creatinine ratio, and multiple hypertension risk factors. Limitations include a relatively short follow-up, ascertainment of the outcome at discrete time points, potential for residual confounding by unmeasured characteristics, and possible misclassification of hypertension and urinary albumin excretion. We may have missed transient hypertension that may have occurred between study visits and hypertension that developed after follow-up. The MESA study personnel ascertained baseline hypertension status from 3 measurements on a single occasion, suggesting that some participants with prevalent

hypertension were inadvertently included in the analyses. This concern is mitigated to some extent by sensitivity analyses demonstrating persistent associations of kidney disease markers with incident hypertension after participants with borderline-high blood pressure at baseline were excluded and by analyses that adjusted for baseline blood pressure. Previous studies have postulated that cystatin C levels may be influenced by factors other than kidney function, such as age, sex, smoking history, body mass index, and inflammation, motivating adjustment for these factors in the analyses (39). Other unmeasured factors unrelated to kidney disease may be associated with the kidney predictor variables and hypertension. For example, uric acid, a novel predictor of hypertension, was not measured in MESA. The relationship between uric acid levels and either cystatin or urinary albumin–creatinine ratio within the normal range is unknown.

In summary, we report an association of early kidney dysfunction, estimated by serum cystatin C levels, with incident hypertension in a community-based, multiethnic cohort without clinically recognized kidney or cardiovascular disease. These findings suggest that early renal impairment may play a role in the pathogenesis of essential hypertension among the general population.

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Figure 1. Study flow diagram
GFR = glomerular filtration rate; MESA = Multi-Ethnic Study of Atherosclerosis.

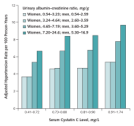

Figure 2. Incident hypertension rates within quartiles of serum cystatin C and sex-specific urinary albumin–creatinine ratio

Results are adjusted for age, race, and sex.

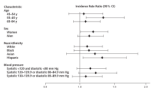

Figure 3. Association of each 15-nmol/L increase in serum cystatin C level with incident hypertension within subgroups

Table 1
Baseline Characteristics, by Serum Cystatin C Level*

Characteristic	Serum Cystatin C Level			
	30.7–53.9 nmol/L (*n* = 645)	**54.0–59.9 nmol/L (*n* = 662)**	**60.0–67.4 nmol/L (*n* = 742)**	**67.5–131.1 nmol/L (*n* = 718)**
Mean age (SD), *y*	54.3 (7.9)	56.4 (8.3)	58.3 (8.9)	62.7 (10.1)
Female, *n (%)*	439 (68.1)	353 (53.3)	341 (46.0)	309 (43.0)
White, *n (%)*	238 (36.9)	264 (39.9)	324 (43.7)	357 (49.7)
Chinese American, *n (%)*	133 (20.6)	96 (14.5)	80 (10.8)	59 (8.2)
African American, *n (%)*	144 (22.3)	154 (23.3)	154 (20.8)	122 (17.0)
Hispanic, *n (%)*	130 (20.2)	148 (22.4)	184 (24.8)	180 (25.1)
Mean smoking history (SD), *pack-years*	7.2 (13.5)	9.3 (17.7)	9.3 (16.4)	13.1 (21.7)
Mean alcohol intake (SD), *drinks/wk*	2.4 (4.8)	2.4 (5.0)	2.6 (5.1)	2.5 (5.7)
No diabetes, *n (%)*	470 (72.9)	481 (72.7)	515 (69.4)	476 (66.3)
Impaired fasting glucose, *n (%)*	129 (20.0)	146 (22.1)	188 (25.3)	200 (27.9)
Diabetes, *n (%)*	46 (7.1)	35 (5.3)	39 (5.3)	42 (5.8)
NSAID use, *n (%)*	106 (16.4)	121 (18.3)	134 (18.1)	120 (16.7)
COX-2 inhibitor use, *n (%)*	19 (2.9)	23 (3.5)	33 (4.4)	42 (5.8)
Oral estrogen use, *n (%)*	128 (19.9)	116 (17.5)	83 (11.2)	60 (8.4)
Thyroid medication use, *n (%)*	27 (4.2)	39 (5.9)	47 (6.3)	4.6 (6.4)
Mean BMI (SD), kg/m^2	25.7 (4.2)	26.7 (4.7)	27.5 (4.9)	28.7 (5.6)
Mean systolic blood pressure (SD), *mm Hg*	110.7 (13.3)	114.4 (12.6)	114.6 (12.3)	115.0 (12.9)
Mean diastolic blood pressure (SD), *mm Hg*	67.3 (9.1)	69.7 (8.5)	69.4 (8.2)	68.1 (8.8)
Mean LDL cholesterol level (SD)				
mmol/L	2.98 (0.78)	3.11 (0.81)	3.14 (0.81)	3.09 (0.83)
mg/dL	115.0 (30.1)	120.2 (31.1)	121.1 (31.1)	119.2 (32.1)
Mean HDL cholesterol level (SD)				
mmol/L	1.47 (0.43)	1.36 (0.40)	1.32 (0.38)	1.23 (0.33)
mg/dL	56.7 (16.7)	52.5 (15.4)	50.9 (14.7)	47.3 (12.9)
Mean C-reactive protein level (SD), *mg/L*	2.6 (4.5)	2.9 (4.7)	3.0 (4.6)	4.0 (6.6)
Mean urinary albumin–creatinine ratio (SD), *mg/g*	5.5 (3.9)	5.0 (3.4)	5.0 (3.5)	5.5 (4.0)

Characteristic	Serum Cystatin C Level			
	30.7–53.9 nmol/L (*n* = 645)	**54.0–59.9 nmol/L (*n* = 662)**	**60.0–67.4 nmol/L (*n* = 742)**	**67.5–131.1 nmol/L (*n* = 718)**
Mean serum creatinine level (SD)				
μmol/L	62.7 (10.9)	67.9 (11.5)	70.8 (11.6)	74.5 (12.9)
mg/dL	0.7 (0.1)	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)
Mean estimated GFR (SD), *mL/min per 1.73 m²*	91.4 (15.2)	86.4 (14.1)	83.1 (13.1)	77.6 (13.1)

* BMI = body mass index; COX-2 = cyclooxygenase-2; GFR = glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NSAID = nonsteroidal anti-inflammatory drug.

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Table 2

Unadjusted and Adjusted Incidence Rates of Hypertension

Quartile	Unadjusted Hypertension Rate per 100 Person-Years	Adjusted Incidence Rate Ratio (95% CI)			
		Model 1 (*n* = 2778)*	Model 2 (*n* = 2778)†	Model 3 (*n* = 2778)‡	Model 4 (*n* = 2621)§
Cystatin C					
1	4.59	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
2	6.20	1.25 (0.97–1.62)	1.24 (0.96–1.60)	1.11 (0.87–1.43)	1.09 (0.83–1.41)
3	6.55	1.27 (0.99–1.63)	1.21 (0.94–1.55)	1.13 (0.89–1.44)	1.12 (0.87–1.45)
4	8.86	1.45 (1.13–1.87)	1.33 (1.04–1.71)	1.35 (1.05–1.73)	1.31 (1.00–1.71)
P value for trend	<0.001	0.005	0.044	0.017	0.038
Sex-specific urinary albumin–creatinine ratio					
1	5.01	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
2	4.68	1.01 (0.77–1.31)	1.00 (0.77–1.29)	0.90 (0.70–1.16)	0.86 (0.66–1.12)
3	6.97	1.45 (1.14–1.85)	1.40 (1.10–1.79)	1.16 (0.92–1.46)	1.14 (0.89–1.45)
4	9.88	1.81 (1.43–2.28)	1.56 (1.23–1.98)	1.16 (0.93–1.46)	1.16 (0.92–1.46)
P value for trend	<0.001	<0.001	<0.001	0.057	0.061
***P* value for interaction‖**	0.43	0.123	0.27	0.149	0.115

*Adjusted for age, race and ethnicity, sex, serum cystatin C level, and urinary albumin–creatinine ratio.

†Same adjustments as model 1, but also adjusted for body mass index and diabetes status (normal, impaired fasting glucose, or diabetes).

‡Same adjustments as model 1, but also adjusted for baseline systolic and diastolic blood pressure.

§Same adjustments as model 1, but also adjusted for pack-years of smoking, alcohol use, hours of weekly conditioning, education level, income, health insurance status, nonsteroidal anti-inflammatory drug use, cyclooxygenase-2 inhibitor use, oral estrogen use, low-density lipoprotein and high-density lipoprotein cholesterol levels, and C-reactive protein level.

‖Between cystatin C quartile and sex-specific urinary albumin–creatinine ratio quartile.