Published in final edited form as:

J Am Soc Hypertens. 2011 ; 5(5): 378–384. doi:10.1016/j.jash.2011.03.003.

Relationship between serum cystatin C and hypertension among US adults without clinically recognized chronic kidney disease

Anoop Shankar¹ and Srinivas Teppala¹

¹Department of Community Medicine, West Virginia University School of Medicine, Morgantown, WV 26506

Abstract

Background—Previous animal studies have suggested that mild reductions in renal function, even before the development of clinically recognized chronic kidney disease (CKD), are associated with hypertension. However, few studies have examined this hypothesis in humans. We therefore examined the association between serum cystatin C levels and hypertension among subjects without clinically recognized CKD in a large multiethnic sample of US adults.

Methods—We examined the National Health and Nutrition Examination Survey 1999–2002 participants >20 years of age (n=2583, 54.5% women) without clinically recognized CKD (defined as an estimated glomerular filtration rate <60 mL/min/1.73 m² or microalbuminuria). Serum cystatin C levels were categorized into quartiles (<0.76 mg/L, 0.76–0.86 mg/L, 0.87–0.97 mg/L, >0.97 mg/L). Hypertension was defined as blood pressure (BP)-reducing medication use or having systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg.

Results—Higher serum cystatin C levels were found to be associated with hypertension in women, but not men. After adjusting for age, race-ethnicity, education, smoking, alcohol intake, body mass index, diabetes, total cholesterol and C-reactive protein, the odds ratio (95% confidence interval) of hypertension comparing quartile 4 of cystatin C to quartile 1 (referent) was 2.04 (1.13–3.69); p-trend=0.02 in women and 0.86 (0.53–1.41); p-trend=0.51 in men.

Conclusion—In a representative sample of US adults, mild reductions in kidney function as measured by higher serum cystatin C levels among subjects without clinically recognized CKD are associated with hypertension in women, but not men.

Keywords

Cystatin C; Hypertension; NHANES

© 2011 American Society of Hypertension. Published by Elsevier Inc. All rights reserved.

Correspondence to: Dr. Anoop Shankar, Department of Community Medicine, West Virginia University School of Medicine, P.O. Box 9190, Morgantown, WV 26506-9190; ashankar@hsc.wvu.edu; Tel: (304) 293-0199, Fax: (304) 293-6685.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Competing interest: There are no conflicts of interest related to this manuscript.

Guarantor statement: “The guarantor, AS, accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.”

Contributors: All the authors contributed to the intellectual development of this paper. AS had the original idea for the study, wrote the paper and is the guarantor. ST performed the statistical analyses and was involved in critical revisions to the manuscript.

Previous animal studies have suggested that mild reductions in renal function, even before the development of clinically recognized chronic kidney disease (CKD), are associated with hypertension^{1, 2}. Early stages of kidney disease may be associated with renal ischemia, stimulation of the renin-angiotensin-aldosterone axis and the sympathetic nervous system, all of which may contribute to the development of hypertension³. In previous studies, victims of fatal accidents who had primary hypertension were shown to have significantly lower number of nephrons compared to age, sex, height and weight matched normotensive controls⁴. Similarly, low birth weight, which has been shown to be associated with increased risk of hypertension later in life⁵ is also associated with reduced nephron number⁶.

Serum levels of Cystatin C are a measure of renal function that appears to be independent of age, sex, and lean muscle mass⁷. Only one study has examined the putative association between serum cystatin C levels and hypertension among subjects without clinical CKD and they found a positive association, consistent with previous animal studies⁸. However, more studies in humans are necessary to confirm the consistency of this finding. We therefore used data from the National Health and Nutritional Examination Survey (NHANES) 1999–2002 to examine the association between serum cystatin C levels and hypertension in a multiethnic sample of US adults without clinically recognized kidney disease.

METHODS

The current study is based on data from NHANES 1999–2002. Detailed description of NHANES study design and methods are available elsewhere^{9–11}. In brief, the NHANES survey included a stratified multistage probability sample representative of the civilian non-institutionalized US population. Selection was based on counties, blocks, households and individuals within households, and included the oversampling of non-Hispanic blacks and Mexican Americans in order to provide stable estimates of these groups. Subjects were required to sign a consent form before their participation, and approval was obtained from the Human Subjects Committee in the US Department of Health and Human Service.

To use a cost-efficient study design that allows for generalization to the US population while maximizing power, serum cystatin C measurement was done on a subset of participants consisting of all individuals 60 years or older ($n = 3,234$), in whom CKD is common, as well as a 25% random sample of those aged 12 to 59 years ($n = 6,237$)¹². All sampling was conducted by age-sex-race strata per NCHS recommendations. Weighted analyses showed that demographic factors were not significantly related to missing data after adjustment for design strata¹².

The current study sample consisted of participants aged greater than 20 years among whom serum cystatin C was available ($N=10,291$). We excluded subjects with clinically recognized CKD ($n=938$)¹³, defined as an estimated glomerular filtration rate <60 mL/min/1.73 m² using the Modification of Diet in Renal Disease (MDRD) study equation¹⁴ or microalbuminuria, defined as a urinary albumin-creatinine ratio of at least 30 mg/g¹³. From the resulting 9,353 subjects, we further excluded subjects with self-reported cardiovascular disease ($n=637$), pregnant women ($n=603$) and also subjects with missing data ($n=5,530$) on covariates included in the multivariable model, including systolic or diastolic blood pressure, body mass index (BMI), or cholesterol levels. This resulted in 2583 participants (54.5% women), 1094 of whom had hypertension.

Main Outcome of Interest: Hypertension

Seated systolic and diastolic blood pressures were measured using a mercury sphygmomanometer according to the American Heart Association and Seventh Joint National Committee (JNC7) recommendations¹⁵. Up to 3 measurements were averaged for

systolic and diastolic pressures. Patients were considered hypertensive if they reported current blood pressure-reducing medication use and/or had systolic blood pressures ≥ 140 mm of Hg and/or diastolic blood pressures ≥ 90 mm of Hg¹⁵.

Exposure Measurements

Age, gender, race/ethnicity, smoking status, alcohol intake (g/day), level of education, history of diabetes and oral hypoglycemic intake or insulin administration, and antihypertensive medication use were assessed using a questionnaire. Individuals who had not smoked ≥ 100 cigarettes in their lifetimes were considered never smokers; those who had smoked ≥ 100 cigarettes in their lifetimes were considered former smokers if they answered negatively to the question "Do you smoke now?" and current smokers if they answered affirmatively. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Rigorous procedures with quality control checks were used in blood collection and details about these procedures are provided in the NHANES Laboratory/Medical Technologists Procedures Manual^{10, 11}.

High sensitivity C-reactive protein (CRP) was analyzed using a modification of the Behring Latex-Enhanced CRP assay on the Behring Nephelometer Analyzer System (Behring Diagnostics, Westwood, Mass). Serum total cholesterol was measured enzymatically. Serum glucose was measured using the modified hexokinase method at the University of Missouri Diabetes Diagnostic Laboratory. Diabetes mellitus was defined based on the recent guidelines of the American Diabetes Association¹⁶ as a serum glucose ≥ 126 mg/dl after fasting for a minimum of 8 hours, a serum glucose ≥ 200 mg/dl for those who fasted < 8 hours before their NHANES visit, a glycosylated hemoglobin value $\geq 6.5\%$, or a self-reported current use of oral hypoglycemic medication or insulin.

Creatinine was measured using the Jaffe kinetic alkaline picrate method performed on a Roche Hitachi 737 analyzer. The laboratory coefficient of variability ranged from 0.2 to 1.4%. Serum creatinine values in NHANES III were calibrated to the standard creatinine values from the Cleveland Clinic Foundation (CCF) laboratory who used a Roche coupled enzymatic assay method that was traceable to an isotope dilution mass spectrometric method using the following Deming regression equation: Standard Creatinine = $0.960 \times \text{NHANES Creatinine} - 0.184$ ¹⁷. Glomerular filtration rate (eGFR) was estimated from serum creatinine using the 4-variable Modification of Diet in Renal Disease (MDRD) study equation as follows $\text{eGFR} = 175 \times (\text{serum creatinine in mg/dl})^{-1.154} \times (\text{age in years})^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$ ¹⁴. CKD was defined as an eGFR of < 60 mL/min/1.73 m², consistent with National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) $\geq$ Stage 2 chronic kidney disease¹³.

Details of serum cystatin C measurement in NHANES has been described in detail elsewhere¹². Serum from fasting blood samples was stored at -70°C until 2006, when cystatin C was measured at the Cleveland Clinical Research Laboratory. Serum cystatin C has been reported as robust to multiple freeze-thaw cycles¹⁸, but information about the stability of cystatin C at -70°C for 12 and more years currently is not available. Samples were assayed for cystatin C by using a particle-enhanced immunonephelometric assay (N Latex Cystatin C; Dade Behring, Deerfield, IL). This assay, with a range of 0.23 to 7.25 mg/L (17.2 to 543.0 nmol/L), is currently the most precise automated assay across the clinical concentration range¹⁹. Interassay coefficients of variation for the assay were 5.05% and 4.87% at mean concentrations of 0.97 and 1.90 mg/L (72.7 and 142.3 nmol/L), respectively.

Statistical Analysis

Serum cystatin C was analyzed both as a continuous variable as well as a categorical variable. For the analysis as a continuous variable, cystatin values were log transformed (base 2) as a result of their skewed distribution. We categorized serum cystatin C level as quartiles (<0.76 mg/L, 0.76–0.86 mg/L, 0.87–0.97 mg/L, >0.97 mg/L). The odds ratio [(OR) (95% confidence interval (CI))] of hypertension for each higher cystatin quartile was calculated by taking the lowest quartile as the referent, using multivariable logistic regression models. We used two models: the age and sex-adjusted model and the multivariable model, additionally adjusting for education categories (below high school, high school, above high school), smoking (never, former, current), alcohol intake (non-current, current), body mass index (non-obese, obese), diabetes (absent, present), total cholesterol (mg/dL) and high sensitivity C-reactive protein (mg/dL). Trends in the OR of hypertension across increasing serum cystatin C category were determined by modeling cystatin categories as an ordinal variable. We performed subgroup analyses by gender and BMI categories (<30 kg/m², and ≥30 kg/m²). Sample weights^{10, 11} that account for the unequal probabilities of selection, oversampling, and non-response were applied for all analyses using SUDAAN (version 8.0; Research Triangle Institute, Research Triangle Park, NC) and SAS (version 9.2; SAS Institute, Cary, NC) software; SEs were estimated using the Taylor series linearization method.

RESULTS

Table 1 presents the characteristics of the study population, by gender.

Table 2 presents the association between serum cystatin C levels and hypertension, by gender. In men, we found that cystatin C levels were not associated with hypertension (p-trend=0.51). In contrast, in women, we found a positive association between cystatin C levels and hypertension that persisted even after multivariable adjustment (p-trend=0.02); p-interaction for the cross-product gender×cystatin C quartile variable was <0.0001.

Table 3 presents the association between serum cystatin C levels and hypertension in women, by menopausal status. Cystatin C was found to be positively associated with hypertension in both premenopausal women and postmenopausal women.

Table 4 presents results for the association between estimated glomerular filtration rate (eGFR) and hypertension, by gender. Similar to earlier findings with cystatin C, in men, we found that decreasing eGFR levels were not associated with hypertension (p-trend=0.44). In contrast, in women, we found a positive association between eGFR levels and hypertension in both the age adjusted (p-trend=0.0005) and multivariable-adjusted models (p-trend=0.05).

Furthermore, we performed a supplementary analysis examining the association between cystatin C and hypertension after additionally adjusting for T4 and TSH levels in the multivariable model; the results were essentially similar but slightly attenuated in women. Among men, compared to quartile 1 (referent) of cystatin C, the OR (95% CI) of hypertension was 0.69 (0.25–1.91) for quartile 2, 0.83 (0.38–1.82) for quartile 3 and 0.89 (0.37–2.12) for quartile 4; p-trend=0.99. In women, compared to quartile 1 (referent) of cystatin C, the OR (95% CI) of hypertension was 1.93 (0.55–6.85) for quartile 2, 1.67 (0.56–4.99) for quartile 3 and 1.81 (1.01–3.24) for quartile 4; p-trend=0.034. In a second supplementary analysis, we examined whether obesity and metabolic syndrome were correlated with hypertension in men; we found that there was positive association between obesity and metabolic syndrome with hypertension. For obesity, we found that compared to men who were normal weight (BMI <25 kg/m²), the multivariable OR (95% CI) for hypertension was 2.21 (1.53–3.20) for overweight subjects (BMI 25–29.9 kg/m²), and 3.93

(2.41–6.41) for obese subjects (BMI >30kg/m²). Similarly for metabolic syndrome, compared to those without metabolic syndrome, the multivariable OR (95% CI) for hypertension was 3.91 (2.45–6.23) for men with metabolic syndrome.

DISCUSSION

In a nationally representative sample of US adults who were free of clinically recognized CKD, we found that serum cystatin C levels are positively associated with hypertension in women, but not men. The association in women appeared to be independent of age, race/ethnicity, education, smoking, alcohol intake, BMI, diabetes mellitus, total cholesterol and high sensitivity CRP levels. Furthermore, in additional analysis by menopausal status categories, the association among women appeared to be present in both premenopausal and menopausal women.

Relatively few previous studies examined the association between cystatin C levels and hypertension^{8, 20–22}. Among 906 participants in the Heart and Soul Study, Peralta et al. observed that systolic blood pressure was linearly associated with cystatin C (approximately 1.2 mm of Hg increase per 0.4 mg/L of cystatin C)²¹. In another case-control study involving 51 primary hypertension cases and 29 healthy control subjects, Ozer et al. concluded that cystatin C was more strongly associated with hypertension than other measures related to renal function such as creatinine clearance, serum uric acid, blood urea nitrogen, beta-2-microglobulin and urinary protein excretion²². Finally, in the Multi-Ethnic Study of Atherosclerosis (MESA), Kestenbaum et al. reported an overall positive association between serum cystatin C levels and hypertension⁸. After adjustment for established hypertension risk factors, the authors found that each 15-nmol/L increase in cystatin C was associated with a statistically significant 15% greater incidence of hypertension ($P = 0.017$)⁸. In general, results from our study are consistent with previous literature and support the conclusion of a positive association between serum cystatin C levels and hypertension.

In the current study, however, we found that serum cystatin C levels are positively associated with hypertension in women, but not men. Furthermore, the association among women appeared to be consistent in both premenopausal and postmenopausal women. Although the exact reason for these gender differences are not clear, several lines of recent evidence suggest that our results are plausible. First, in animal studies, estrogen has been shown to enhance the expression of cystatin C²³. Similarly, in population-based studies, free estradiol level has been shown to be positively associated with cystatin C levels²⁴. Subsequently, if cystatin C levels are associated with hypertension, it is possible that females may have a stronger association than men. Second, Fricker et al²⁵ recently demonstrated that hyperthyroidism, which is known to be more common in women and independently associated with a higher risk of hypertension²⁶, was associated with higher cystatin C levels²⁵. Therefore, we examined if our observed association was explained by hyperthyroidism. Our results showed an attenuation of the association between cystatin C and hypertension upon adjustment of T4 and TSH in the multivariable model suggesting that at least part of the observed association between cystatin C and hypertension is mediated by changes in thyroid function. Third, obesity and metabolic syndrome are known to be associated with elevated cystatin C levels²⁷ and are also risk factors for hypertension²⁸. Since women were more likely to be obese than men (32.8 % in women vs. 25.9% in men), the observed association between cystatin C and hypertension in women in the current study may be a consequence of the higher prevalence of obesity in women (32.8% in women vs. 25.9% in men). A final possibility is that our findings are due to chance or unmeasured confounding. Therefore, there is a need to examine such subgroup analysis in future studies.

The main strengths of our study include its population-based nature, inclusion of a representative multiethnic sample, adequate sample size, and the availability of data on confounders for multivariable adjustment. Furthermore, all data were collected following rigorous methodology, including a study protocol with standardized quality control checks. The main limitation of our study is the cross-sectional nature of NHANES, which precludes conclusions regarding the temporal nature of the association between serum cystatin C and hypertension.

In summary, in a nationally representative sample of adults, we found that serum cystatin C levels are positively associated with hypertension in women, but not men. Our results suggest that mild reductions in kidney function as measured by serum cystatin C even among subjects without clinically recognized CKD are associated with hypertension in women.

Acknowledgments

This study was funded by an American Heart Association National Clinical Research Program grant (AS).

References

1. Guyton AC, Coleman TG, Cowley AV Jr, Scheel KW, Manning RD Jr, Norman RA Jr. Arterial pressure regulation. Overriding dominance of the kidneys in long-term regulation and in hypertension. *Am J Med.* 1972 May; 52(5):584–594. [PubMed: 4337474]
2. Johnson RJ, Herrera-Acosta J, Schreiner GF, Rodriguez-Iturbe B. Subtle acquired renal injury as a mechanism of salt-sensitive hypertension. *N Engl J Med.* 2002 March 21; 346(12):913–923. [PubMed: 11907292]
3. Covic A, Gusbeth-Tatomir P. The role of the renin-angiotensin-aldosterone system in renal artery stenosis, renovascular hypertension, and ischemic nephropathy: diagnostic implications. *Prog Cardiovasc Dis.* 2009 November; 52(3):204–208. [PubMed: 19917331]
4. Keller G, Zimmer G, Mall G, Ritz E, Amann K. Nephron number in patients with primary hypertension. *N Engl J Med.* 2003 January 9; 348(2):101–108. [PubMed: 12519920]
5. Law CM, de SM, Osmond C, et al. Initiation of hypertension in utero and its amplification throughout life. *BMJ.* 1993 January 2; 306(6869):24–27. [PubMed: 8435572]
6. Luyckx VA, Brenner BM. Low birth weight, nephron number, and kidney disease. *Kidney Int Suppl.* 2005 August; 97:S68–S77. [PubMed: 16014104]
7. Coll E, Botey A, Alvarez L, et al. Serum cystatin C as a new marker for noninvasive estimation of glomerular filtration rate and as a marker for early renal impairment. *Am J Kidney Dis.* 2000 July; 36(1):29–34. [PubMed: 10873868]
8. Kestenbaum B, Rudser KD, de BI, et al. Differences in kidney function and incident hypertension: the multi-ethnic study of atherosclerosis. *Ann Intern Med.* 2008 April 1; 148(7):501–508. [PubMed: 18378946]
9. National Center for Health Statistics. [Accessed March 07, 2011] 1999–2000 National Health and Nutrition Examination Survey: survey operations manuals [article online]. 2010. Available at: www.cdc.gov/nchs/nhanes/nhanes1999-2000/current_nhanes_99_00.htm
10. National Center for Health Statistics. [Accessed March 07, 2011] Laboratory procedures used for NHANES 1999–2000. 2011. Available at: www.cdc.gov/nchs/nhanes/nhanes1999-2000/lab99_00.htm
11. National Center for Health Statistics. [Accessed March 07, 2011] Laboratory procedures used for NHANES 2000–2002. 2011. Available at: www.cdc.gov/nchs/nhanes/nhanes2001-2002/lab01_02.htm
12. Kottgen A, Selvin E, Stevens LA, Levey AS, Van LF, Coresh J. Serum cystatin C in the United States: the Third National Health and Nutrition Examination Survey (NHANES III). *Am J Kidney Dis.* 2008 March; 51(3):385–394. [PubMed: 18295054]

13. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002 February; 39(2 Suppl 1):S1–S266. [PubMed: 11904577]
14. Levey AS, Coresh J, Greene T, et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem.* 2007 April; 53(4):766–772. [PubMed: 17332152]
15. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension.* 2003 December; 42(6):1206–1252. [PubMed: 14656957]
16. Diagnosis and classification of diabetes mellitus. *Diabetes Care.* 2010 January.33 Suppl 1:S62–S69. [PubMed: 20042775]
17. Selvin E, Manzi J, Stevens LA, et al. Calibration of serum creatinine in the National Health and Nutrition Examination Surveys (NHANES) 1988–1994, 1999–2004. *Am J Kidney Dis.* 2007 December; 50(6):918–926. [PubMed: 18037092]
18. Kyhse-Andersen J, Schmidt C, Nordin G, et al. Serum cystatin C, determined by a rapid, automated particle-enhanced turbidimetric method, is a better marker than serum creatinine for glomerular filtration rate. *Clin Chem.* 1994 October; 40(10):1921–1926. [PubMed: 7923773]
19. Newman DJ, Cystatin C. *Ann Clin Biochem.* 2002 March; 39(Pt 2):89–104. [PubMed: 11928770]
20. Seco ML, Rus A, Sierra M, Caballero M, Borque L. Determination of serum cystatin C in patients with essential hypertension. *Nephron.* 1999; 81(4):446–447. [PubMed: 10095185]
21. Peralta CA, Whooley MA, Ix JH, Shlipak MG. Kidney function and systolic blood pressure new insights from cystatin C: data from the Heart and Soul Study. *Am J Hypertens.* 2006 September; 19(9):939–946. [PubMed: 16942937]
22. Ozer BA, Dursun B, Baykal A, Gultekin M, Suleymanlar G. Can cystatin C be a better marker for the early detection of renal damage in primary hypertensive patients? *Ren Fail.* 2005; 27(3):247–253. [PubMed: 15957539]
23. Slayden OD, Hettrich K, Carroll RS, Otto LN, Clark AL, Brenner RM. Estrogen enhances cystatin C expression in the macaque vagina. *J Clin Endocrinol Metab.* 2004 February; 89(2):883–891. [PubMed: 14764809]
24. Yi S, Selvin E, Rohrmann S, et al. Endogenous sex steroid hormones and measures of chronic kidney disease (CKD) in a nationally representative sample of men. *Clin Endocrinol (Oxf).* 2009 August; 71(2):246–252. [PubMed: 19178534]
25. Fricker M, Wiesli P, Brandle M, Schwegler B, Schmid C. Impact of thyroid dysfunction on serum cystatin C. *Kidney Int.* 2003 May; 63(5):1944–1947. [PubMed: 12675875]
26. American Association of Clinical Endocrinologists. Hyperthyroidism [article online]. 2006. Available at: www.aace.com/pub/thyroidbrochures/pdfs/Hyperthyroidism.pdf
27. de BI, Katz R, Fried LF, et al. Obesity and change in estimated GFR among older adults. *Am J Kidney Dis.* 2009 December; 54(6):1043–1051. [PubMed: 19782454]
28. Vigil L, Lopez M, Condes E, et al. Cystatin C is associated with the metabolic syndrome and other cardiovascular risk factors in a hypertensive population. *J Am Soc Hypertens.* 2009 May; 3(3): 201–209. [PubMed: 20409960]

Table 1

Baseline characteristics of the study population, by gender *

Characteristics	Men (n= 1316)	Women (n= 1267)
Age (years)	50.4 ± 0.6	54.5 ± 0.4
Race/Ethnicity (%)		
Non-Hispanic Whites	880 (74.0)	917 (75.5)
Non-Hispanic Blacks	340 (10.2)	316 (9.7)
Mexican Americans	400 (6.3)	420 (5.3)
Others	116 (9.4)	127 (9.4)
Education categories (%)		
Below high school	659 (22.1)	638 (23.9)
High school	376 (22.8)	449 (28.7)
Above high school	701 (52.1)	693 (47.3)
Smoking (%)		
Never smoker	691 (41.9)	1095 (57.7)
Former smoker	671 (34.0)	428 (25.2)
Current smoker	374 (24.1)	257 (17.1)
Alcohol intake (%)		
Current drinker	1152 (71.3)	931 (58.8)
Body mass index (BMI) (%)		
Non-Obese (<30 kg/m ²)	1286 (74.1)	1151 (67.2)
Obese (BMI ≥kg/m ²)	450 (25.9)	629 (32.8)
Diabetes (%)	292 (11.7)	270 (9.9)
High sensitivity C-reactive protein (mg/dL)	0.36 ± 0.02	0.49 ± 0.02
Total cholesterol (mg/dL)	198.83 ± 1.14	206.68 ± 1.47
Serum Cystatin C (mg/L)	0.960 ± 0.015	0.918 ± 0.009
Hypertension (%)	803 (38.5)	934 (45.8)

* Data presented are number (percentages) or mean values ± standard error (SE), as appropriate for the variable.

Table 2

Association between serum cystatin C levels and hypertension, by gender

Serum Cystatin C quartiles (mg/L)	Men			Women		
	Sample size (Hypertension %)	Age, adjusted OR (95% CI)*	Multivariable-adjusted OR (95% CI) [†]	Sample size Hypertension %	Age, adjusted OR (95% CI)*	Multivariable-adjusted OR (95% CI) [†]
Quartile 1 (<0.76)	295 (22.4)	1 (referent)	1 (referent)	396 (16.3)	1 (referent)	1 (referent)
Quartile 2 (0.76–0.86)	350 (30.5)	1.33 (0.78–2.24)	1.15 (0.68–1.95)	318 (39.9)	2.36 (1.39–4.03)	2.31 (1.35–3.98)
Quartile 3 (0.87–0.97)	337 (37.6)	1.40 (0.85–2.33)	1.20 (0.73–1.99)	289 (50.1)	2.51 (1.54–4.07)	2.29 (1.40–3.74)
Quartile 4 (>0.97)	334 (38.7)	1.07 (0.64–1.78)	0.86 (0.53–1.41)	264 (62.1)	2.94 (1.62–5.34)	2.04 (1.13–3.69)
p-trend		0.85	0.51		0.0004	0.02

* OR (95% CI): Odds Ratio (95% Confidence Interval)

[†] Adjusted for age (years), race-ethnicity (non-Hispanic whites, non-Hispanic blacks, Mexican Americans, others), education categories (below high school, high school, above high school), smoking (never, former, current), alcohol intake (absent, present), body mass index (non-obese, obese), diabetes (absent, present), total cholesterol (mg/dL), and C-reactive protein (mg/dL); p-interaction for the cross-product gender × cystatin C quartile variable was <0.0001

Table 3

Association between serum cystatin C levels and hypertension in women, by menopausal status

Serum Cystatin C tertiles (mg/L)	Sample size (Hypertension %)	Age, adjusted OR (95% CI)*	Multivariable-adjusted OR (95% CI)*†
Pre-menopausal women			
Tertile 1 (<0.78)	277 (9.0)	1 (referent)	1 (referent)
Tertile 2 (0.78–0.91)	140 (25.7)	3.15 (1.51–6.56)	2.83 (1.44–5.54)
Tertile 3 (>0.91)	82 (27.5)	2.27 (1.06–4.88)	1.56 (0.72–3.39)
p-trend		0.004	0.03
Menopausal women			
Tertile 1 (<0.78)	188 (38.2)	1 (referent)	1 (referent)
Tertile 2 (0.78–0.91)	259 (61.5)	1.90 (1.05–3.45)	1.80 (1.00–3.24)
Tertile 3 (>0.91)	321 (67.7)	2.09 (1.17–3.73)	1.51 (0.88–2.59)
p-trend		0.002	0.045

* OR (95% CI): Odds Ratio (95% Confidence Interval)

† Adjusted for age (years), race-ethnicity (non-Hispanic whites, non-Hispanic blacks, Mexican Americans, others), education categories (below high school, high school, above high school), smoking (never, former, current), alcohol intake (absent, present), body mass index (non-obese, obese), diabetes (absent, present), total cholesterol (mg/dL), and C-reactive protein (mg/dL)

Table 4

Association between estimated glomerular filtration rate* and hypertension, by gender

Glomerular Filtration Rate (ml/min/1.73 m ²)	Men			Women		
	Sample size (Hypertension %)	Age adjusted		Sample size (Hypertension %)	Age adjusted	
		OR (95% CI) [†]	Multivariable adjusted OR (95% CI) ^{‡‡}		OR (95% CI) [†]	Multivariable adjusted OR (95% CI) ^{‡‡}
Tertile 1 (>100)	465 (22.5)	1 (referent)	1 (referent)	344 (14.9)	1 (referent)	1 (referent)
Tertile 2 (80–100)	474 (36.6)	0.95 (0.74–1.21)	1.09 (0.72–1.65)	424 (35.6)	1.25 (0.77–2.03)	1.74 (0.94–3.20)
Tertile 3 (<80)	377 (41.5)	0.81 (0.59–1.10)	0.84 (0.53–1.32)	499 (61.3)	1.94 (1.24–3.04)	1.88 (1.02–3.47)
p-trend		0.18	0.44		0.0005	0.05

* eGFR was computed using Equation 2 from table 4 Stevens LA et al (*American Journal of Kidney Diseases*, 2008)

† OR (95% CI): Odds Ratio (95% Confidence Interval)

‡ Adjusted for age (years), race-ethnicity (non-Hispanic whites, non-Hispanic blacks, Mexican Americans, others), education categories (below high school, high school, above high school), smoking (never, former, current), alcohol intake (absent, present), body mass index (non-obese, obese), diabetes (absent, present), total cholesterol (mg/dL), and C-reactive protein (mg/dL)