

# Relationship Between Body Mass Index and High Cystatin Levels Among US Adults

Anoop Shankar, MD, PhD; Srinivas Teppala, MD, MPH

From the Department of Community Medicine, West Virginia University School of Medicine, Morgantown, WV

High cystatin C levels among patients without clinically recognized chronic kidney disease (CKD) may identify patients who are at preclinical stages of CKD. Higher body mass index (BMI) has been found to be associated with increased risk of CKD. However, the association between BMI and high cystatin C levels is not clear. The authors examined participants older than 20 years from the National Health and Nutrition Examination Survey 1999 to 2002 (N=2583, 50.2% women). BMI was categorized as <25 kg/m<sup>2</sup>, 25–29.9 kg/m<sup>2</sup>, and ≥30 kg/m<sup>2</sup>. Main outcome was high cystatin C (>1 mg/dL) among patients without clinically recognized CKD (estimated glomerular filtration rate <60 mL/min/1.73 m<sup>2</sup> or microalbuminuria). Higher BMI was positively associated with high cystatin C,

independent of age, sex, race-ethnicity, education, smoking, alcohol intake, cholesterol, and C-reactive protein levels. Compared with patients with BMI <25 kg/m<sup>2</sup> (referent), the multivariable odds ratio (95% confidence interval) of high cystatin C was 2.53 (1.79–3.58) (*P* trend <.0001 among patients with BMI ≥30 kg/m<sup>2</sup>). The association between BMI and high cystatin C persisted in subgroup analyses by sex, race-ethnicity, and among those without diabetes or hypertension. Among US adults without clinically recognized CKD, higher BMI levels were independently associated with high cystatin C levels. *J Clin Hypertens (Greenwich)*. 2011;13:925–930. ©2011 Wiley Periodicals, Inc.

Cystatin C is a novel marker of kidney function, considered to be more accurate than creatinine.<sup>1</sup> It has been proposed that high cystatin C levels (cystatin C levels >1 mg/dL) among patients without clinically recognized chronic kidney disease (CKD) may identify those who are at preclinical stages of CKD.<sup>2,3</sup> High cystatin C levels among patients without clinically recognized CKD have been shown to be associated with increased future risk of hypertension,<sup>4</sup> diabetes mellitus,<sup>5</sup> and CKD.<sup>2</sup> High cystatin C levels also have been shown to predict coronary heart disease,<sup>2,6</sup> stroke,<sup>2,6</sup> cardiovascular,<sup>2,6</sup> and all-cause mortality.<sup>2,6</sup>

Higher body mass index (BMI) has been found to be associated with increased risk of end-stage renal disease.<sup>7,8</sup> Recent studies have also shown that higher BMI is associated with earlier stages in the kidney disease continuum, including CKD.<sup>9–11</sup> However, the association between BMI and high cystatin C levels has not previously been studied in detail. Therefore, we examined the association between BMI and high cystatin C levels among patients without clinically recognized CKD in a large multiethnic sample of US adults.

## METHODS

The current study is based on data from the National Health and Nutrition Examination Survey (NHANES) 1999 to 2002. Detailed description of NHANES study

design and methods are available elsewhere.<sup>12–14</sup> In brief, NHANES included a stratified multistage probability sample representative of the civilian noninstitutionalized US population. Selection was based on counties, blocks, and 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. Patients 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 performed on a subset of participants, comprising patients 60 years or older (n=3234), in whom CKD is common, as well as a 25% random sample of those aged 12 to 59 years (n=6237).<sup>15</sup> All sampling was conducted by age-sex-race strata per National Center for Health Statistics recommendations. Weighted analyses showed that demographic factors were not significantly related to missing data after adjustment for design strata.<sup>15</sup>

The current study sample consisted of participants older than 20 years, among whom serum cystatin C was available (n=10,291). We excluded patients with clinically recognized CKD (n=938),<sup>16</sup> defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m<sup>2</sup> using the Modification of Diet in Renal Disease (MDRD) study equation,<sup>17</sup> or microalbuminuria, defined as a urinary albumin-creatinine ratio of at least 30 mg/g.<sup>16</sup> Since cardiovascular disease may be a confounder of the association between BMI and high cystatin C, we excluded patients with

**Address for correspondence:** Anoop Shankar, MD, PhD, Department of Community Medicine, West Virginia University School of Medicine, 1 Medical Center Drive, PO Box 9190, Morgantown, WV 26506-9190  
**E-mail:** ashankar@hsc.wvu.edu

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cardiovascular disease (n=637) from our analysis. From the resulting 8716 patients, we further excluded pregnant women (n=603) and also patients with missing data (n=5530) on covariates included in the multivariable model, including systolic or diastolic blood pressure (BP), BMI, or cholesterol levels. This resulted in 2583 participants (54.5% women), 492 of whom had high serum cystatin C levels (>1 mg/dL).

### Exposure Measurements

Age, sex, race/ethnicity, smoking status, alcohol intake (g/d), 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  $\geq 100$  cigarettes in their lifetime were considered never smokers; those who had smoked  $\geq 100$  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. 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.<sup>13,14</sup>

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, MA). 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 Association<sup>18</sup> as serum glucose  $\geq 126$  mg/dL after fasting for a minimum of 8 hours, a serum glucose  $\geq 200$  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. Seated systolic and diastolic BPs were measured using a mercury sphygmomanometer according to the American Heart Association and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) recommendations.<sup>19</sup> Up to 3 measurements were averaged for systolic and diastolic pressures. Patients were considered hypertensive if they reported current BP-reducing medication use and/or had systolic BPs  $\geq 140$  mm of Hg and/or diastolic BPs  $\geq 90$  mm of Hg.<sup>19</sup>

Creatinine was measured using the Jaffe kinetic alkaline picrate method performed on a Roche Hitachi 737 analyzer (Basel, Switzerland). The laboratory coefficient of variability ranged from 0.2% to 1.4%. Serum creatinine values in NHANES were calibrated to the standard creatinine values from the Cleveland Clinic Foundation 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 =  $0.960 \times \text{NHANES creatinine} - 0.184$ .<sup>20</sup> eGFR was estimated from serum creatinine using the 4-variable MDRD study equation as follows  $\text{eGFR} = 175 \times (\text{serum creatinine in mg/dL})^{-1.154} \times (\text{age in years})^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$ .<sup>15</sup> CKD was defined as an eGFR  $< 60$  mL/min/1.73 m<sup>2</sup>, consistent with National Kidney Foundation Kidney Disease Outcomes Quality Initiative<sup>16</sup>  $\geq$  stage 2 CKD.

Details of serum cystatin C measurement in NHANES have been described in detail elsewhere.<sup>15</sup> Serum from fasting blood samples was stored at  $-70^\circ\text{C}$  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 cycles,<sup>21</sup> but information about the stability of cystatin C at  $-70^\circ\text{C}$  for 12 or more years is currently 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 mg/L to 7.25 mg/L (17–543.0 nmol/L), is currently the most precise automated assay across the clinical concentration range.<sup>22</sup> Interassay coefficients of variation for the assay were 5.05% and 4.87% at mean concentrations of 0.97 mg/L and 1.90 mg/L (72.7 nmol/L and 142.3 nmol/L), respectively.

### Main Outcome of Interest: High Serum Cystatin C

Recent studies have demonstrated that high levels of serum cystatin C are associated with cardiovascular disease<sup>23,24</sup> and kidney outcomes, even in patients without CKD.<sup>2</sup> Consistent with these findings, high serum cystatin C, defined as serum cystatin C  $> 1$  mg/dL was the main outcome of interest in the current study.

### Statistical Analysis

BMI was analyzed both as a continuous variable as well as a categorical variable. For the analysis as a continuous variable, BMI values were log-transformed (base 2) as a result of their skewed distribution. We categorized BMI as normal weight ( $< 25$  kg/m<sup>2</sup>), overweight (25–29 kg/m<sup>2</sup>), and obese ( $\geq 30$  kg/m<sup>2</sup>). The odds ratio ([OR] 95% confidence interval [CI]) of high serum cystatin ( $> 1$  mg/dL) for each BMI category was calculated by taking patients with normal weight 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 (noncurrent, current), diabetes (absent, present), hypertension (absent, present), total cholesterol (mg/dL), and high-sensitivity CRP (mg/dL). Trends in the OR of high cystatin levels across increasing BMI were determined

by modeling BMI categories as an ordinal variable. We performed subgroup analyses by sex and race/ethnicity categories (non-Hispanic whites, non-Hispanic blacks, Mexican Americans, and others). In addition, we also performed a supplementary analysis after excluding patients with diabetes and hypertension from the entire cohort. Sample weights<sup>25</sup> that account for the unequal probabilities of selection, oversampling, and nonresponse 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; standard errors were estimated using the Taylor series linearization method.

## RESULTS

Baseline characteristics of the study population (Table I) included a mean age of 49.6 years, approximately half being women (50.2%), 74.0% being non-Hispanic whites, 20.8% having below high school education, 20.9% being current smokers, 8.0% having diabetes mellitus, and 35.4% having hypertension. Also, 28.5% of study patients were obese, 36.7% were overweight, and 34.9% had normal weight BMI. Among patients without clinically recognized CKD, 17.4% had a serum cystatin C level >1 mg/dL.

**TABLE I.** Baseline Characteristics of the Study Population<sup>a</sup>

Characteristics	Entire Cohort (N=2583)
Age, y	49.6±0.5
Women	50.2±1.0
Race/ethnicity	
Non-Hispanic whites	1268 (74.0)
Non-Hispanic blacks	482 (10.0)
Mexican Americans	652 (6.4)
Others	181 (9.6)
Education categories	
Below high school	899 (20.8)
High school	598 (26.9)
Above high school	1086 (52.3)
Smoking	
Never smoker	1313 (50.2)
Former smoker	776 (28.9)
Current smoker	494 (20.9)
Current alcohol drinker	1609 (68.0)
High-sensitivity C-reactive protein, mg/dL	0.4±0.013
Total cholesterol, mg/dL	201.6±1.2
Diabetes	310 (8.0)
Hypertension	1094 (35.4)
Serum cystatin C, mg/L	0.86±0.005
Body mass index categories	
Normal weight (<25 kg/m <sup>2</sup> )	811 (34.9)
Overweight (25–29 kg/m <sup>2</sup> )	998 (36.7)
Obese (BMI ≥30 kg/m <sup>2</sup> )	774 (28.5)
Serum cystatin >1 mg/dL	492 (17.4)

<sup>a</sup>Data presented are number (percentages) or mean ± standard error.

In Table II, there was a positive association between increasing BMI categories and the presence of high cystatin C in both the age-/sex-adjusted model and the multivariable-adjusted model. Models evaluating linear trend in this association were also statistically significant. The positive association was consistently present when BMI was analyzed as a continuous variable (per standard deviation increase).

We found that the positive association between increasing BMI categories and the presence of high cystatin C was consistently present among men as well as women (Table III) and among non-Hispanic whites, non-Hispanic blacks, and Mexican Americans and others (Table IV).

Since hypertension and diabetes are two of the main risk factors for kidney disease, we examined the association between increasing BMI categories and the presence of high cystatin C among study patients without diabetes mellitus and hypertension (Table V). We found a consistent positive association between BMI and high cystatin C. In a supplementary analysis, we examined the association between obesity and albuminuria, defined as a urinary albumin: creatinine ratio >300 mg/dL. We found that obesity was positively associated with albuminuria, with an OR of 3.02 (95% CI, 1.90–4.81) in the age-/sex-adjusted model and an OR of 1.66 (95% CI, 1.07–2.58) in the multivariable model.

## DISCUSSION

In a multiethnic sample of US adults who did not have clinically recognized CKD, we found increasing BMI levels to be positively associated with the presence of high cystatin C, defined as serum cystatin C levels >1 mg/dL. This association was found to be independent of age, sex, race-ethnicity, education, smoking, alcohol intake, cholesterol levels, and CRP levels. In addition, the observed association was consistently present in subgroups of sex and race-ethnicity and among apparently “healthy” study patients, defined as those without diabetes or hypertension. These results contribute to the literature on the role of adiposity in kidney disease development<sup>7–11</sup> by suggesting that higher BMI levels are associated with high cystatin C, a stage earlier in the kidney disease continuum, that has been shown to be linked with future risk of hypertension,<sup>4</sup> diabetes mellitus,<sup>5</sup> and cardiovascular<sup>2,6</sup> and all-cause mortality.<sup>2,6</sup>

The association between obesity and kidney disease may be mediated through multiple biologic mechanisms, including hormonal factors, inflammation, oxidative stress, and endothelial dysfunction.<sup>26,27</sup> Excess adiposity as evidenced by higher BMI levels may be related to activation of the sympathetic nervous system and the renin-angiotensin system, lipid deposition, hyperfiltration, and increased sodium absorption in the kidneys, resulting in a feedback loop where obesity-induced declines in kidney function lead to the development of hypertension, which results in further

**TABLE II. Association Between Body Mass Index Categories and High Cystatin (>1 mg/dL)**

Body Mass Index Categories, kg/m <sup>2</sup>	Sample Size (% With High Cystatin)	Age- and Sex-Adjusted OR (95% CI)	Multivariable-Adjusted OR (95% CI) <sup>a</sup>
Normal weight (<25)	811 (11.2)	1 (referent)	1 (referent)
Overweight (25–29)	998 (17.7)	1.44 (1.03–2.01)	1.56 (1.06–2.29)
Obese (≥30)	774 (24.5)	2.53 (1.91–3.36)	2.53 (1.79–3.58)
<i>P</i> trend		<.0001	<.0001
One SD (5.9 kg/m <sup>2</sup> ) Increase in BMI		1.08 (1.06–1.10)	1.08 (1.05–1.11)

Abbreviations: CI, confidence interval; OR, odds ratio; SD, standard deviation. <sup>a</sup>Adjusted for age (y), sex, 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 (noncurrent, current), diabetes (absent, present), hypertension (absent, present), total cholesterol (mg/dL), and C-reactive protein (mg/dL).

**TABLE III. Association Between Body Mass Index Categories and High Cystatin (>1 mg/dL) by Sex**

Body Mass Index Categories (kg/m <sup>2</sup> )	Men		Women	
	Sample Size (% With High Cystatin)	Multivariable-Adjusted OR (95% CI) <sup>a</sup>	Sample Size (% With High Cystatin)	Multivariable-Adjusted OR (95% CI) <sup>a</sup>
Normal weight (<25)	396 (14.8)	1 (referent)	415 (8.1)	1 (referent)
Overweight (25–29)	592 (19.0)	1.38 (0.86–2.21)	406 (16.0)	1.75 (1.17–2.61)
Obese (≥30)	328 (24.7)	1.74 (1.03–2.95)	446 (24.4)	3.71 (2.12–6.51)
<i>P</i> trend		.04		<.0001

<sup>a</sup>Adjusted for age (y), 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 (non-current, current), diabetes (absent, present), hypertension (absent, present), total cholesterol (mg/dL), and C-reactive protein (mg/dL).

**TABLE IV. Association Between Body Mass Index Categories and High Cystatin (>1 mg/dL) by Race/Ethnicity**

Body Mass Index categories (kg/m <sup>2</sup> )	Non-Hispanic Whites		Non-Hispanic Blacks		Mexican Americans and Others	
	Sample Size (% Cases)	Multivariable-Adjusted OR (95% CI) <sup>a</sup>	Sample Size (% Cases)	Multivariable-Adjusted OR (95% CI) <sup>a</sup>	Sample Size (% Cases)	Multivariable-Adjusted OR (95% CI) <sup>a</sup>
Normal weight (<25)	441 (13.0)	1 (referent)	129 (5.6)	1 (referent)	241 (5.6)	1 (referent)
Overweight (25–29)	478 (21.3)	1.58 (1.01–2.48)	168 (8.8)	1.28 (0.47–3.51)	352 (7.3)	2.30 (0.81–6.51)
Obese (≥30)	349 (27.1)	2.28 (1.57–3.31)	185 (19.1)	2.77 (0.74–10.42)	240 (15.6)	8.20 (3.05–22.05)
<i>P</i> trend		<.0001		.09		<.0001

<sup>a</sup>Adjusted for age (y), sex, education categories (below high school, high school, above high school), smoking (never, former, current), alcohol intake (noncurrent, current), diabetes (absent, present), hypertension (absent, present), total cholesterol (mg/dL), and C-reactive protein (mg/dL).

**TABLE V. Association Between Body Mass Index Categories and High Cystatin (>1 mg/dL), Excluding Those With Diabetes and Hypertension**

Body Mass Index Categories (kg/m <sup>2</sup> )	Sample Size (% cases)	Age- and Sex-Adjusted OR (95% CI)	Multivariable-Adjusted OR (95% CI) <sup>a</sup>
Normal weight (<25)	557 (9.7)	1 (referent)	1 (referent)
Overweight (25–29)	509 (13.5)	1.26 (0.79–2.00)	1.39 (0.81–2.39)
Obese (≥30)	304 (17.6)	2.04 (1.22–3.39)	2.29 (1.19–4.42)
<i>P</i> trend		.01	.02

<sup>a</sup>Adjusted for age (y), sex, 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 (noncurrent, current), total cholesterol (mg/dL), and C-reactive protein (mg/dL).

damage to the kidneys.<sup>28,29</sup> Pathways leading from obesity to diabetes have also been identified, including the development of insulin resistance,<sup>29</sup> which itself is an independent factor related to kidney disease.<sup>30</sup> Further research involving these mechanisms could provide a better understanding of the association between obesity, kidney disease, and potential mediating factors. Alternate explanations for the observed BMI-high cystatin C association include increased production of cystatin C by enlarged adipose tissue (ie, a reverse direction of association),<sup>31</sup> confounding by unmeasured factors, and the possibility that this is a chance finding.

Our findings are consistent with a previous study by Muntner and colleagues<sup>32</sup> that examined data from NHANES III conducted in 1988 to 1994. As we examined data from the more recent NHANES 1999 to 2002 survey, our results are based on a more contemporary US population sample. Furthermore, in the study by Muntner and associates,<sup>32</sup> in subgroup analyses, BMI was only weakly associated with high cystatin C in those without diabetes and hypertension. In contrast, in the current study, the magnitude of association between BMI and elevated cystatin C was high in the subgroup analysis that excluded patients with diabetes and hypertension, suggesting that the observed association is independent of diabetes and hypertension. Additionally, the consistency of our results in stratified analyses by sex and race-ethnicity suggest that these findings are less likely to be caused by chance or confounding.

Previous studies have shown that higher BMI is predictive of end-stage renal disease<sup>7,8</sup> and also earlier stages of kidney disease, such as CKD.<sup>9–11</sup> Our results extend this observation to high cystatin C levels, which could be considered a preclinical stage to CKD. Further, the clinical/public health implication of our finding is that lifestyle and behavioral interventions to reduce high BMI may be effective in preventing the development or delaying the progression of kidney disease.

## STRENGTHS AND LIMITATIONS

The main advantages of our study include its large sample size, representation of multiple racial-ethnic subgroups, standardized methods of data collection, and availability of data on confounders. The main study limitation is the cross-sectional nature of NHANES, which limits our ability to draw conclusions regarding the temporal nature of the observed association between higher BMI and cystatin C level.

## CONCLUSIONS

We have demonstrated that in a representative sample of US adults who did not have clinically recognized CKD, higher BMI levels were positively associated with high cystatin C, defined as serum cystatin C levels >1 mg/dL. This association was found to be independent of age, sex, race-ethnicity, education, smoking, alcohol intake, cholesterol levels, and CRP levels and

was consistently present in subgroups of sex and race-ethnicity. Further research is warranted to assess whether reducing BMI favorably affects elevated serum cystatin C and the development of CKD. These results suggest that higher BMI levels are associated with high cystatin C, an earlier stage in kidney disease, which is predictive of future risk of hypertension, diabetes mellitus, and cardiovascular and all-cause mortality.

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