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Differential Estimation of Chronic Kidney Disease Using Cystatin C Versus Creatinine-based Estimating Equations by Category of Body Mass Index

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Abstract

Background—Adiposity is associated with cystatin C. Cystatin C-based glomerular filtration rate (GFR) equations may result in the over-estimation of chronic kidney disease (CKD) prevalence at higher body mass index (BMI) levels.

Study Design—Cross-sectional

Setting and Participants—6,709 US adult NHANES III participants.

Factor—Body mass index

Outcome—Absolute percent difference in the prevalence of stage 3 or 4 CKD between creatinine- and cystatin C-based estimating equations by level of BMI.

Measurements—Normal weight, overweight, and obesity were defined as BMI levels of 18.5 to <25.0, 25 to <30.0, and ≥30 kg/m^2, respectively. Stage 3 or 4 CKD (eGFR of 15 to 59 ml/min/1.73m^2) was defined using the abbreviated creatinine-based Modification of Diet in Renal Disease equation ($eGFR_{MDRD}$); a cystatin C, age, sex, and race equation ($eGFR_{CysC,age,sex,race}$); a cystatin C only equation ($eGFR_{CysC}$); cystatin C≥1.12 mg/L (elevated cystatin C); and an equation incorporating serum creatinine, cystatin C, age, sex, and race ($eGFR_{Cr,CysC,age,sex,race}$).

Results—The differences in stage 3 or 4 CKD prevalence between $eGFR_{CysC,age,sex,race}$, $eGFR_{CysC}$, and elevated cystatin C, separately, and $eGFR_{MDRD}$ were larger at higher BMI levels. Specifically, compared to estimates derived using $eGFR_{MDRD}$, for normal weight, overweight, and obese participants, the prevalence of stage 3 or 4 CKD was 2.1%, 3.0%, and 6.5% higher, respectively, when estimated by $eGFR_{CysC,age,sex,race}$ (p-trend=0.005); 0.1%, 0.6%, 2.2% higher, respectively, for $eGFR_{CysC}$ (p-trend=0.028); 2.9%, 5.2%, and 9.5% higher, respectively, for

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elevated cystatin C (p-trend<0.001); and −0.1%, −0.4%, and 0.0% higher, respectively, for $eGFR_{Cr,CysC,age,sex,race}$ (p-trend=0.719).

Limitations—No gold standard measure of GFR was available.

Conclusions—BMI may influence the prevalence of stage 3 or 4 CKD when cystatin C-based equations are used.

In the identification, classification, and treatment of adults with chronic kidney disease (CKD), it is crucial to accurately estimate glomerular filtration rate (GFR). [1] The most widely used measure of kidney function is GFR estimated using the creatinine-based Modification in Diet and Renal Disease (MDRD) study formula.2 However, limitations associated with the use of serum creatinine have prompted interest in the use of other biomarkers for measuring kidney function.3, 4 Results from several studies suggest serum cystatin C may provide a more accurate estimate of GFR than serum creatinine alone, or GFR estimated by the MDRD study equation, especially among adults with estimated GFR ≥60 ml/min/1.73m^2.[5, 6] Stevens et al. recently derived three equations that incorporate cystatin C, all of which equally or more accurately, estimated measured GFR compared to the MDRD study formula.[7]

An ideal biomarker for estimating GFR should be freely filtered by the glomerular membrane without being reabsorbed, secreted or metabolized by the renal tubules.[8] Since cystatin C has a low molecular weight and is freely filtered by the glomerular membrane,[9] and because it is independent of muscle mass, it has been suggested as a better measure of GFR. However, several studies have demonstrated an association between cystatin C and BMI[10-12], even among individuals without CKD, raising the concern that cystatin C may be associated with adiposity independently of kidney function.[13, 14] The mechanism of the association between cystatin C and overweight and obesity is not clear; however, laboratory evidence has suggested that adipocytes secrete cystatin C.[15]

The purpose of the current analysis was to compare the estimation of GFR and prevalence of stage 3 or 4 CKD by cystatin C and creatinine-based equations, across BMI categories. We hypothesized that, due to the association of cystatin C with adiposity, the difference in the prevalence of CKD using cystatin C versus creatinine-based equations would be larger at progressively higher BMI categories.

METHODS

The Third National Health and Nutrition Examination Survey (NHANES III) was conducted between 1988 and 1994. A detailed description of the study participants and methods has been published elsewhere.[16] In brief, a stratified multi-stage probability design was employed to obtain a representative sample of the civilian non-institutionalized US general population. The study design included over-sampling of those who were very young, elderly, non-Hispanic black and Mexican-American to improve the precision of estimates in these groups.

Using stored serum specimens, cystatin C was measured on all NHANES III participants 60 years and older, as well as a random sample of those aged 12 to 59 years. Additionally, cystatin C was measured in all adult men and women with a serum creatinine ≥1.2 and 1.0 mg/dL, respectively. The current analysis was limited to adult NHANES III participants, aged 20 years or older, with serum cystatin C measurements. Participants were excluded from the current analysis if they were pregnant (n=71), missing a valid height and/or weight measurement (n=21), were underweight (BMI<18.5 kg/m^2; n=133), or had an estimated

GFR < 15 ml/min/1.73m^2 (based on the MDRD study equation; n=17). After these exclusions, the current analyses were based on the experience of 6709 participants.

NHANES III data were collected by administration of a standardized questionnaire during a home interview, followed by the completion of a detailed physical examination with collection of blood specimens at a mobile examination center or the participant's home. Of relevance to the current analysis, variables collected using questionnaires included age, race-ethnicity, sex, cigarette smoking, and leisure-time physical activity. Participants who reported having smoked more than 100 cigarettes during their lifetime and responded affirmatively to "Do you now smoke cigarettes?" were classified as current smokers. Being physically active was defined as participating in any leisure time physical activity or strength training in the month preceding the NHANES visit.

Body weight and height were measured according to a standard protocol. Height was measured with participants standing on the floor using a fixed stadiometer with a vertical backboard and movable headboard. Weight was taken by asking each participant to stand on the center of the platform of a Toledo digital scale while wearing underwear, a disposable gown, and foam slippers. BMI was calculated as weight in kilograms divided by height in meters squared and categorized into three categories (18.5 to <25 kg/m^2 - normal weight; 25 to <30 kg/m^2 – overweight; and ≥30 kg/m^2 – obese). Waist circumference was measured using a steel measuring tape to the nearest 0.1 cm at the high point of the iliac crest at minimal respiration when the participant was in a standing position. The examiner stood behind the participant, palpated the hip area for the right iliac crest, marked a horizontal line at the high point of the iliac crest, and crossed the line to indicate the midaxillary line of the body. Abdominal obesity was defined as waist circumference > 88 centimeters in women and > 102 centimeters in men[17].

Serum samples were obtained during the clinical examination. Serum creatinine was measured by the modified kinetic Jaffe reaction using a Roche Hitachi 737 analyzer (Roche Diagnostics Corporation, Indianapolis, Indiana) and re-calibrated in order to calculate estimated GFR (eGFR) using the 4-variable, IDMS-traceable, Modification of Diet in Renal Disease study equation: $eGFR_{MDRD}$ = 175 * serum creatinine [mg/dL]$^{-1.154}$ * age [years]$^{-0.203}$ * 0.742 [if female] * 1.210 [if black][18, 19]. Cystatin C was measured using an automated particle-enhanced nephelometric assay on the Dade Behring Nephelometer II. This assay maintains a range from 0.23 to 7.25 mg/L and intra- and inter-assay coefficients of variation of 2.0% to 3.0% and 3.2% to 4.4%, respectively. For the main analysis, cystatin C was used to calculate eGFR using the following formula: $eGFR_{CysC,age,sex,race}$ = 127.7 * cystatin C [mg/L]$^{-1.17}$ * age [years]$^{-0.13}$ * 0.91 [if female] * 1.06 [if black]. Individuals with an eGFR of 15 to 59 ml/min/1.73 m^2 were considered to have stage 3 or 4 CKD. For secondary analyses, the prevalence of stage 3 or 4 CKD was calculated using the cystatin C only equation ($eGFR_{CysC}$ = 76.7 * cystatin C [mg/L] $^{-1.19}$), serum cystatin C 1.12 mg/L (elevated cystatin C, the 99th percentile for adults 20 to 39 years of age without hypertension, diabetes mellitus or CKD), and an equation incorporating creatinine, cystatin C, age, sex and race ($eGFR_{Cr,CysC,age,sex,race}$ = 177.6 * serum creatinine [mg/dL]$^{-0.65}$ * cystatin C [mg/L]$^{-0.57}$ * age [years]$^{-0.20}$ * 0.82 [if female] * 1.11 [if black]).[7] Both the MDRD study formula and the cystatin C formulas were developed to predict measured GFR standardized to 1.73m^2 body surface area. eGFR levels > 200 ml/min/1.73m^2 were truncated at 200 ml/min/1.73m^2.

The protocol for NHANES III was approved by the National Center for Health Statistics of the Centers for Disease Control and Prevention Institutional Review Board. Informed consent was obtained from each NHANES III participant.

Statistical Analysis

Demographic characteristics, mean height, weight, and the prevalence of cigarette smoking and physical activity were calculated by BMI category (normal weight, overweight, and obese) for participants with and without stage 3 or 4 CKD defined using $eGFR_{MDRD}$ and $eGFR_{CysC,age,sex,race}$, separately. Using each equation, mean eGFR and the prevalence of stage 3 or 4 CKD were calculated by BMI category. Differences in mean eGFR, ($eGFR_{CysC,age,sex,race}$ minus $eGFR_{MDRD}$), within BMI category were calculated, with the statistical significance of the trend across BMI categories determined using linear regression. For all regression models assessing trends, the mean BMI (22.3, 27.2, and 34.7 kg/m^2 for normal weight, overweight, and obese, respectively) was included for each BMI category. Because the $eGFR_{CysC,age,sex,race}$ and $eGFR_{MDRD}$ prevalence estimates of stage 3 or 4 CKD were calculated on the same individuals, the prevalence estimates will not be independent. Furthermore, individuals with prevalent stage 3 or 4 CKD by both equations, and lack of prevalence by both equations, contributed no information to the analysis. To address these issues, we calculated the absolute percent difference in the prevalence of stage 3 or 4 CKD as the percentage of adults with stage 3 or 4 CKD by $eGFR_{CysC,age,sex,race}$ but not $eGFR_{MDRD}$ minus the percentage with stage 3 or 4 CKD by $eGFR_{MDRD}$ but not $eGFR_{CysC,age,sex,race}$. Since these are two independent groups, the standard errors for the difference in these prevalence estimates could be calculated directly. An example of this calculation is provided in the Appendix. The statistical significance of trends in the difference in the prevalence of CKD estimates across BMI categories was determined by modeling adults with stage 3 or 4 CKD by $eGFR_{CysC,age,sex,race}$ but not $eGFR_{MDRD}$ versus their counterparts with stage 3 or 4 CKD by $eGFR_{MDRD}$ but not $eGFR_{CysC,age,sex,race}$ by BMI category using logistic regression. Differences in the prevalence of stage 3 or 4 CKD between the $eGFR_{MDRD}$ and $eGFR_{CysC,age,sex,race}$ equations by BMI category were calculated for sub-groups defined by age (<70 and ≥70 years, the mean age of participants with stage 3 or 4 CKD by $eGFR_{MDRD}$), race-ethnicity (non-Hispanic whites, non-Hispanic blacks, and Mexican-Americans), and sex. In secondary analyses, differences in the prevalence of stage 3 or 4 CKD were compared between $eGFR_{MDRD}$ and eGFR derived using $eGFR_{CysC}$, elevated cystatin C, and $eGFR_{Cr,CysC,age,sex,race}$. Also, the differences in the prevalence of stage 3 or 4 CKD were compared between $eGFR_{MDRD}$ and eGFR derived using $eGFR_{CysC,age,sex,race}$, $eGFR_{CysC}$, elevated cystatin C, and $eGFR_{Cr,CysC,age,sex,race}$ by abdominal obesity.

Data were analyzed using SUDAAN (version 9.0; Research Triangle Institute, Research Triangle Park, NC) to account for the complex NHANES III sampling design including unequal probabilities of selection, over-sampling, non-response, and measurement of cystatin C in a sub-sample of NHANES III participants.

RESULTS

The prevalence of stage 3 or 4 CKD was 5.7% and 9.2% by $eGFR_{MDRD}$ and $eGFR_{CysC,age,sex,race}$, respectively. Defined using the $eGFR_{MDRD}$ or $eGFR_{CysC,age,sex,race}$, participants with stage 3 or 4 CKD were older, more likely to be women, non-Hispanic white, have a higher mean BMI, and were less likely to be current smokers and physically active than their counterparts without stage 3 or 4 CKD (Table 1).

Primary Analysis

Mean eGFR was lower, and the prevalence of stage 3 or 4 CKD was higher, at higher BMI categories using $eGFR_{MDRD}$ and $eGFR_{CysC,age,sex,race}$ (Table 2). The difference in mean eGFR and prevalence of stage 3 or 4 CKD between the two estimating equations was greater at progressively higher BMI categories. Specifically, the difference in eGFR

($eGFR_{CysC,age,sex,race}$ minus $eGFR_{MDRD}$) was +1.4, −1.9, and −5.4 ml/min/1.73m^2 for normal weight, overweight, and obese participants, respectively (p-trend<0.001). Compared to estimates derived using $eGFR_{MDRD}$, the prevalence of stage 3 or 4 CKD was 2.3%, 3.0%, and 6.4% higher for normal weight, overweight, and obese participants, respectively, when estimated by $eGFR_{CysC,age,sex,race}$ (p-trend=0.005).

Sub-group Analysis

A graded increase in the difference (i.e., $eGFR_{CysC,age,sex,race}$ minus $eGFR_{MDRD}$) in the estimates of stage 3 or 4 CKD prevalence across BMI categories was present among participants ≥ 70 years of age, men and women, and non-Hispanic Whites (Figure 1). Also, for participants <70 years of age and non-Hispanic blacks and Mexican-Americans, the difference in stage 3 or 4 CKD prevalence estimates was higher for obese compared with normal weight participants. Testing for interaction indicated that results were consistent by age group, sex, and race-ethnicity. The p-values for interaction were p=0.889 across age group, p=0.267 across gender, and p=0.61 and p=0.33 for non-Hispanic blacks and Mexican-Americans, respectively, compared to non-Hispanic whites.

Secondary analyses

Compared to stage 3 or 4 CKD defined by $eGFR_{MDRD}$, the prevalence of stage 3 or 4 CKD defined by $eGFR_{CysC}$ was 0.2%, 0.6%, 2.2% higher for normal weight, overweight, and obese participants, respectively (Table 3; p-trend=0.028). The differences (elevated cystatin C minus $eGFR_{MDRD}$) in stage 3 or 4 CKD prevalence estimates were 2.9%, 5.2%, 9.5% for normal weight, overweight, and obese participants, respectively (p-trend<0.001). In contrast, there was no difference in the estimates of stage 3 or 4 CKD prevalence by BMI categories between $eGFR_{MDRD}$ and $eGFR_{Cr,CysC,age,sex,race}$ ($eGFR_{Cr,CysC,age,sex,race}$ minus $eGFR_{MDRD}$; −0.1%, −0.4%, 0.0% for normal weight, overweight, and obese participants, respectively; p-trend=0.719). Similar to the trend observed with BMI, cystatin C-based equations demonstrated higher stage 3 or 4 CKD prevalence estimates in participants with, compared to those without, abdominal obesity. For example, the differences for $eGFR_{Cr,CysC,age,sex,race}$ minus $eGFR_{MDRD}$ in stage 3 or 4 CKD prevalence estimates were 6.3% and 1.4% for participants with and without abdominal obesity, respectively (p<0.001).

DISCUSSION

In the current analysis, the differences in the prevalence of stage 3 or 4 CKD, estimated using several cystatin C equations and the MDRD study equation were progressively larger at higher BMI categories. Among obese adults, the prevalence of stage 3 or 4 CKD was almost two-fold greater when estimated by $eGFR_{CysC,age,sex,race}$ versus $eGFR_{MDRD}$. These findings suggest cystatin C-based equations may result in the over-estimation of CKD prevalence, in overweight and obese adults.

Because it is not practical to measure GFR directly in clinical practice, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines recommend that creatinine-based estimating equations (such as the MDRD study equation or Cockcroft-Gault) be used to estimate GFR[1]. The accuracy of estimating GFR using various cystatin and creatine-based estimating equations was recently examined by Stevens et al.7 In a pooled analysis of adults with CKD, cystatin C alone and cystatin C with age, race and sex provided an estimation of GFR that was as accurate as a creatinine-based estimating equation. The authors suggested that cystatin C is a better measure of GFR because it is independent of muscle mass. That report did not present sub-group analyses by BMI category. However, the impact of BMI on cystatin C-based prediction equations, in the

context of CKD, may be limited since the prevalence of obesity is likely to be lower in a disease-based sample.20

Cystatin C is produced at a steady rate by all types of nucleated cells in the body and is, thus, found in detectable amounts in most body fluids. Its low molecular mass allows it to be freely filtered by the glomerular membrane in the kidney.[21] Several researchers have hypothesized that serum cystatin C may be a better marker of GFR as it is independent of body composition;[21-24] however, this generally refer to muscle mass and not to body fat. Our study suggests that cystatin C may not be independent of adiposity.

Cystatin C has been associated with overweight and obesity in previous population-based research studies. In a cross-sectional analysis of the NHANES III population without CKD, 13 a graded association between BMI categories and elevated cystatin C was reported. Specifically, compared to normal weight, overweight, class I obesity, and class II-III obesity, were associated with a 1.46, 2.36, and 2.82 greater odds of cystatin C ≥ 1.09 mg/L (p for trend <0.001). In an analysis of the NHANES III population older than 60 years that included persons with CKD,[12] higher BMI was associated with a statistically significant increased odds ratio of elevated cystatin C (≥1.12 mg/L). The reported multivariable adjusted odds ratios between BMI and elevated cystatin C in these two NHANES III studies were not adjusted for eGFR. In a population-based sample of 8,058 adults in Groningen, The Netherlands, a significant correlation ($r=0.22$; $p<0.001$) was present between body weight and serum cystatin C independent of creatinine clearance.11 Also, Fried and colleagues10 demonstrated that mean BMI was significantly associated with increasing levels of cystatin C in a study of 2,135 elderly men and women. However, a multivariable adjusted association was not reported. It is also possible that obesity leads to CKD25, a reduction in GFR, and elevations in serum creatinine and cystatin C. Hsu et al conducted a study among 320,252 adult members of Kaiser Permanente who volunteered for screening health checkups between 1964 and 1985 and linked them to the US Renal Data registry through 2000. A strong, independent association of increasing BMI with end-stage renal disease was present in this study. Because the current study did not have a gold standard measure of GFR or longitudinal measures of BMI, we were not able to explore whether the differences in estimation of GFR by creatinine versus cystatin C-based equations could be a result of decreased kidney function due to increasing BMI .

The mechanism underlying an association between BMI and cystatin C remains unclear. Adipose tissue secretes endocrine and paracrine hormones and thus plays a vital role in metabolism and homeostasis.[26, 27] The growth of adipose tissue is the consequence of increased accumulation of lipids in the adipocytes as well as new adipocytes formed from precursor cells.[28] These “preadipocytes” become mature adipocytes when exposed to a multitude of inhibitory and stimulatory factors. Laboratory studies have examined the expression of cathepsin S as a new biomarker of adiposity and have demonstrated that human adipose tissue secretes and expresses cathepsin S which is upregulated in obesity.[29] Cystatin C regulates cathepsin S activity by acting as an endogenous inhibitor. In a recent laboratory study, researchers examined the effect of cathepsin S on adipogenesis by studying the effects of inhibition of cathepsin S using cystatin C in human preadipocytes. This study showed that cystatin C secretion increased and cathepsin S decreased during pre-adipocyte differentiation suggesting a possible role of cystatin C in adipogenesis.[28]

The evidence of an association between cystatin C and overweight and obesity raises the concern that the estimation of kidney function using cystatin C-based equations may result in biased estimation of GFR and CKD prevalence, in overweight and obese adults. Without a gold standard measurement of GFR, our study could not address this directly. However, we did show a significant trend in increasing differences in CKD prevalence estimated by

cystatin C and creatinine-based equations increased with increasing BMI. It is unlikely that this trend is due to bias in the MDRD formula at higher BMI levels since studies have shown that adiposity is associated with CKD estimation by cystatin C-based equations but not creatinine-based equations[30]. Given the high prevalence of overweight and obesity in US adults, this finding has important implications. Data from the NHANES 2005-2006 indicate that over a third of US adults (72 million Americans) are obese.[31] While cystatin C has been advocated as a measure of GFR that is independent of muscle mass, the current data suggest that cystatin C may not be independent of body fat and may lead to the overestimation of CKD among overweight and obese persons.

In contrast to the other estimating equations, there was no difference in stage 3 or 4 CKD prevalence estimates across BMI categories between $eGFR_{Cr,CysC,age,sex,race}$ and $eGFR_{MDRD}$. Thus, $eGFR_{Cr,CysC,age,sex,race}$ appears to not have a substantial bias across BMI categories while benefiting in precision from addition of cystatin C to serum creatinine, age, sex and race. In a previous report, the $eGFR_{Cr,CysC,age,sex,race}$ equation successfully estimated GFR within 30% of measured GFR for 89% of patients screened for CKD, compared to 81% for $eGFR_{CysC}$, 83% for $eGFR_{CysC,age,sex,race}$ and 85% for $eGFR_{MDRD}$. Equations using both serum creatinine and cystatin C may provide more accurate estimate of the overall burden of CKD than other published cystatin C-based estimating equations, especially among populations with a high percentage of overweight and obese adults.

There are limitations to the current analysis that warrant mention. The lack of a gold standard measurement of GFR means we are unable to determine whether there is a bias, or the extent of any bias, in the estimation of GFR using these equations. For example, it is possible that equations using serum creatinine overestimate GFR, equations using cystatin C underestimate GFR or, more likely, the answer is somewhere in between but cannot be assessed due to the lack of a gold-standard. However, this bias is unlikely to affect BMI groups differentially. Secondly, only a single measurement of serum creatinine and cystatin C was obtained. Ideally, the presence of CKD would be defined based on at least two serum measurements over a period of several months due to intra-individual variation.[32]

These limitations are balanced by the strengths of NHANES III, which included a large multi-ethnic sample of US adults. NHANES III also incorporated an over-sampling of older individuals to ensure valid estimates could be obtained for this population sub-group. This is important because of the higher prevalence of CKD at older age and the growing number of older adults in the US population. As previously reported, NHANES III response rates were high, missing data were rare and data were collected by trained staff, following a standardized protocol.[16]

In conclusion, data from the current study demonstrated a greater difference in CKD prevalence, estimated by cystatin C versus creatinine-based equations, at higher BMI categories. However, no such trend across BMI categories was present when an equation that incorporated serum creatinine and cystatin C was compared to a creatinine-based equation. The impact of overweight and obesity on cystatin C-based equations requires further research.

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Appendix

Example of the process used to calculate the difference in the prevalence of stage 3 or 4 chronic kidney disease using two estimating equations ($eGFR_{cysC,age,sex,race}$ minus $eGFR_{MDRD}$).

		$eGFR_{MDRD}$		
		Yes	**No**	**Total**
$eGFR_{cysC,age,sex,race}$	Yes	3.1% (0.3)	3.4% (0.4)	6.5% (0.7)
	No	1.1% (0.2)	92.4% (0.7)	93.5% (0.7)
	Total	4.2% (0.4)	95.8% (0.4)	100%

Numbers in table represent percent (standard error)

The difference in stage 3 or 4 chronic kidney disease was calculated as the percent of individuals with stage 3 or 4 CKD by $eGFR_{cysC,age,sex,race}$ but not $eGFR_{MDRD}$ (shaded circle: 3.4%) minus the percent with stage 3 or 4 CKD by the $eGFR_{MDRD}$ equation but not the $eGFR_{cysC,age,sex,race}$ equation (unshaded circle:1.1%). The difference in this example is 2.3%.

The standard error of the difference between these two percentages was calculated as the square root of the sum of the variance for each percentage (square root of 0.4*0.4 + 0.2*0.2). The standard error of the difference in this example is 0.4.

Data presented in this example are for normal weight individuals (see table 2).

REFERENCES

1. Levey AS, Coresh J, Balk E, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med Jul 15;2003 139(2): 137–147. [PubMed: 12859163]
2. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D, Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med Mar 16;1999 130(6):461–470. [PubMed: 10075613]
3. Rule AD, Larson TS, Bergstralh EJ, Slezak JM, Jacobsen SJ, Cosio FG. Using serum creatinine to estimate glomerular filtration rate: accuracy in good health and in chronic kidney disease. Ann Intern Med Dec 21;2004 141(12):929–937. [PubMed: 15611490]

4. Rule AD, Bergstralh EJ, Slezak JM, Bergert J, Larson TS. Glomerular filtration rate estimated by cystatin C among different clinical presentations. Kidney Int Jan;2006 69(2):399–405. [PubMed: 16408133]
5. Laterza OF, Price CP, Scott MG. Cystatin C: an improved estimator of glomerular filtration rate? Clin Chem May;2002 48(5):699–707. [PubMed: 11978596]
6. Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. Am J Kidney Dis Aug;2002 40(2):221–226. [PubMed: 12148093]
7. Stevens LA, Coresh J, Schmid CH, et al. Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. Am J Kidney Dis Mar;2008 51(3):395–406. [PubMed: 18295055]
8. Levin A, Stevens LA. Executing change in the management of chronic kidney disease: perspectives on guidelines and practice. Med Clin North Am May;2005 89(3):701–709. [PubMed: 15755474]
9. Madero M, Sarnak MJ, Stevens LA. Serum cystatin C as a marker of glomerular filtration rate. Curr Opin Nephrol Hypertens Nov;2006 15(6):610–616. [PubMed: 17053476]
10. Fried LF, Lee JS, Shlipak M, et al. Chronic kidney disease and functional limitation in older people: health, aging and body composition study. J Am Geriatr Soc May;2006 54(5):750–756. [PubMed: 16696739]
11. Knight EL, Verhave JC, Spiegelman D, et al. Factors influencing serum cystatin C levels other than renal function and the impact on renal function measurement. Kidney Int Apr;2004 65(4): 1416–1421. [PubMed: 15086483]
12. Kottgen A, Selvin E, Stevens LA, Levey AS, Van Lente F, Coresh J. Serum cystatin C in the United States: the Third National Health and Nutrition Examination Survey (NHANES III). Am J Kidney Dis Mar;2008 51(3):385–394. [PubMed: 18295054]
13. Muntner P, Winston J, Uribarri J, Mann D, Fox CS. Overweight, obesity, and elevated serum cystatin C levels in adults in the United States. Am J Med Apr;2008 121(4):341–348. [PubMed: 18374694]
14. Stevens LA, Greene T, Li C, et al. Factors Other Thank GFR Influencing Serum Cystatin. J Am Soc Nephrol 2007;18:547A–548A. abstract.
15. Kratchmarova I, Kalume DE, Blagoev B, et al. A proteomic approach for identification of secreted proteins during the differentiation of 3T3-L1 preadipocytes to adipocytes. Mol Cell Proteomics Mar;2002 1(3):213–222. [PubMed: 12096121]
16. National Center for Health Statistics. Plan and Operation of the Third National Health and Nutrition Examination Survey, 1988-1994. Vol. 1994:1. US Dept of Health and Human Services publication; Washington, D.C.: p. 94-1308.
17. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). Jama May 16;2001 285(19):2486–2497. [PubMed: 11368702]
18. Coresh J, Astor BC, McQuillan G, et al. Calibration and random variation of the serum creatinine assay as critical elements of using equations to estimate glomerular filtration rate. Am J Kidney Dis May;2002 39(5):920–929. [PubMed: 11979335]
19. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med Aug 15;2006 145(4):247–254. [PubMed: 16908915]
20. Kalantar-Zadeh K, Block G, Humphreys MH, Kopple JD. Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. Kidney Int Mar;2003 63(3):793–808. [PubMed: 12631061]
21. Filler G, Bokenkamp A, Hofmann W, Le Bricon T, Martinez-Bru C, Grubb A. Cystatin C as a marker of GFR--history, indications, and future research. Clin Biochem Jan;2005 38(1):1–8. [PubMed: 15607309]
22. Jones CY, Jones CA, Wilson IB, et al. Cystatin C and Creatinine in an HIV Cohort: The Nutrition for Healthy Living Study. Am J Kidney Dis Jun;2008 51(6):914–24. [PubMed: 18455851]

23. Bokenkamp A, Domanetzki M, Zinck R, Schumann G, Byrd D, Brodehl J. Cystatin C--a new marker of glomerular filtration rate in children independent of age and height. Pediatrics May; 1998 101(5):875–881. [PubMed: 9565418]
24. Shlipak MG, Sarnak MJ, Katz R, et al. Cystatin C and the risk of death and cardiovascular events among elderly persons. N Engl J Med May 19;2005 352(20):2049–2060. [PubMed: 15901858]
25. Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS. Body mass index and risk for end-stage renal disease. Ann Intern Med Jan 3;2006 144(1):21–28. [PubMed: 16389251]
26. Kahn BB, Flier JS. Obesity and insulin resistance. J Clin Invest Aug;2000 106(4):473–481. [PubMed: 10953022]
27. MacDougald OA, Mandrup S. Adipogenesis: forces that tip the scales. Trends Endocrinol Metab Jan-Feb;2002 13(1):5–11. [PubMed: 11750856]
28. Taleb S, Cancello R, Clement K, Lacasa D. Cathepsin s promotes human preadipocyte differentiation: possible involvement of fibronectin degradation. Endocrinology Oct;2006 147(10): 4950–4959. [PubMed: 16825321]
29. Taleb S, Lacasa D, Bastard JP, et al. Cathepsin S, a novel biomarker of adiposity: relevance to atherogenesis. Faseb J Sep;2005 19(11):1540–1542. [PubMed: 15985526]
30. Young JA, Hwang SJ, Sarnak MJ, et al. Association of visceral and subcutaneous adiposity with kidney function. Clin J Am Soc Nephrol Nov;2008 3(6):1786–1791. [PubMed: 18815239]
31. Ogden CL, Carroll MD, McDowell MA, Flegal KM. Obesity Among Adults in the United States -- No Statistically Significant Change Since 2003-2004. 2007 NCHS Data Brief.
32. Myers GL, Miller WG, Coresh J, et al. Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. Clin Chem Jan;2006 52(1):5–18. [PubMed: 16332993]

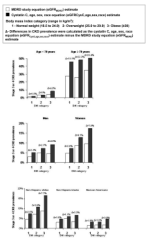

Figure 1.
Difference in the prevalence of stage 3 or 4 chronic kidney disease using the age, sex, race and cystatin C equation ($eGFR_{CysC,age,sex,race}$) and the Modification of Diet in Renal Disease (MDRD) study equation ($eGFR_{MDRD}$) by body mass index for demographic subgroups.

Table 1

Characteristics of adults with and without stage 3 or 4 chronic kidney disease (CKD) based on the Modification of Diet in Renal Disease (MDRD) study equation and the cystatin C, age, sex, and race equation

	$eGFR_{MDRD}$		**$eGFR_{CysC,age,sex,race}$**	
	Without Stage 3 or 4 CKD (n=5791)	**Stage 3 or 4 CKD (n=918)**	**Without Stage 3 or 4 CKD (n=5134)**	**Stage 3 or 4 CKD (n=1575)**
Age, years	43.5 (0.7)	69.7 (1.0)	42.3 (0.7)	71.5 (0.9)
Women, %	50.5	62.7	50.0	63.2
Non-Hispanic white, %	82.4	90.9	82.1	90.8
Non-Hispanic black, %	11.9	7.6	12.2	7.1
Mexican American, %	5.7	1.5	5.8	2.1
Body mass index, kg/m^2	26.8 (0.2)	27.8 (0.2)	26.7 (0.2)	28.4 (0.3)
Current cigarette smokers, %	29.3	13.4	29.5	17.8
Physically active, %	79.1	68.3	79.8	65.3

$eGFR_{MDRD}$ was derived from an equation including creatinine, age, sex, race

$eGFR_{CysC,age,sex,race}$ was derived from an equation including cystatin C, age, sex, race

Numbers in table are mean (standard error) or percentage

All comparisons between the stage 3 or 4 CKD and no stage 3 or 4 CKD groups are significant ($p<0.001$)

Table 2

Mean estimated glomerular filtration rate (eGFR) and prevalence of stage 3 or 4 chronic kidney disease (CKD) calculated using the Modification of Diet in Renal Disease (MDRD) study equation and the cystatin C age, sex, race equation by body mass index

	Body mass index category (range, kg/m^2)			
	Normal weight (18.5 - 24.9)	**Overweight (25.0 – 29.9)**	**Obesity (≥30.0)**	**P-Trend**
Mean (SE) eGFR, ml/min/1.73m^2				
$eGFR_{CysC,age,sex,race}$ *	96.5 (1.0)	88.8 (0.9)	84.1 (1.3)	
$eGFR_{MDRD}$ **	95.2 (0.9)	90.7 (0.9)	89.5 (1.1)	
Difference				
$eGFR_{CysC,age,sex,race}$ estimate minus $eGFR_{MDRD}$ estimate	1.4 (1.0)	−1.9 (0.9)	−5.4 (1.0)	0.0009
Stage 3 or 4 CKD prevalence † , % (SE)				
$eGFR_{CysC,age,sex,race}$	6.5 (0.7)	9.5 (0.8)	13.8 (1.5)	
$eGFR_{MDRD}$	4.2 (0.3)	6.5 (0.5)	7.4 (0.7)	
Difference				
$eGFR_{CysC,age,sex,race}$ estimate minus $eGFR_{MDRD}$ estimate	2.3 (0.4)	3.0 (0.7)	6.4 (1.2)	0.005

SE – standard error

* $eGFR_{CysC,age,sex,race}$ was derived from an equation including cystatin C, age, sex, race

** $eGFR_{MDRD}$ was derived from an equation including creatinine, age, sex, race

† Percent prevalence of stage 3 or 4 CKD was defined by either $eGFR_{CysC,age,sex,race}$ or $eGFR_{MDRD}$

Table 3

Prevalence of stage 3 or 4 chronic kidney disease calculated using the Modification of Diet in Renal Disease (MDRD) study equation and other cystatin C-based estimates, by body mass index

	Body mass index category (range, kg/m^2)			
	Normal weight (18.5 - 24.9)	**Overweight (25.0 − 29.9)**	**Obesity (≥30.0)**	**P-Trend**
Stage 3 or 4 CKD prevalence, % (SE)				
$eGFR_{cysC}$	4.3 (0.5)	7.1 (0.7)	9.6 (1.1)	
$eGFR_{MDRD}$	4.2 (0.3)	6.5 (0.5)	7.4 (0.7)	
Difference				
$eGFR_{cysC}$ estimate minus $eGFR_{MDRD}$ estimate	0.2 (0.3)	0.6 (0.7)	2.2 (0.8)	0.03
Stage 3 or 4 CKD prevalence, % (SE)				
Elevated cystatin C	7.1 (0.7)	11.7 (1.0)	16.9 (1.8)	
$eGFR_{MDRD}$	4.2 (0.3)	6.5 (0.5)	7.4 (0.7)	
Difference				
Elevated cystatin C estimate minus $eGFR_{MDRD}$ estimate	2.9 (0.5)	5.2 (0.9)	9.5 (1.4)	0.0009
Stage 3 or 4 CKD prevalence, % (SE)				
$eGFR_{creat, cysC, age, sex, race}$	4.1 (0.4)	6.1 (0.6)	7.4 (0.8)	
$eGFR_{MDRD}$	4.2 (0.4)	6.5 (0.6)	7.4 (0.7)	
Difference				
$eGFR_{creat, cysC, age, sex, race}$ estimate minus $eGFR_{MDRD}$	−0.1 (0.3)	−0.4 (0.4)	0.0 (0.4)	0.7

SE − Standard error

Prevalence of stage 3 or 4 CKD was defined by estimated glomerular filtration rate (eGFR):

$eGFR_{cysC}$ was derived from an equation including only cystatin C.

$eGFR_{MDRD}$ was derived from an equation including creatinine, age, sex, and race.

Elevated cystatin C was defined as cystatin C ≥ 1.12 mg/L (the 99th percentile for adults 20 to 39 years of age without hypertension, diabetes mellitus or CKD).

$eGFR_{creat, cysC, age, sex, race}$ was derived from an equation including creatinine, cystatin C, age, sex, and race.

Table 4

Prevalence of stage 3 or 4 chronic kidney disease calculated using the Modification of Diet in Renal Disease (MDRD) study equation and other cystatin C-based estimates, by abdominal obesity

	Abdominal obesity*		
	No	**Yes**	**P-Value**
Stage 3 or 4 CKD prevalence, % (SE)			
$eGFR_{CysC,age,sex,race}$	4.5 (0.5)	15.6 (1.2)	
$eGFR_{MDRD}$	3.1 (0.3)	9.4 (0.7)	
Difference			
$eGFR_{CysC,age,sex,race}$ estimate minus $eGFR_{MDRD}$ estimate	1.4 (0.3)	6.2 (0.9)	0.002
Stage 3 or 4 CKD prevalence, % (SE)			
$eGFR_{cysC}$	3.4 (0.3)	11.6 (0.9)	
$eGFR_{MDRD}$	3.1 (0.3)	9.4 (0.7)	
Difference			
$eGFR_{cysC}$ estimate minus $eGFR_{MDRD}$ estimate	0.3 (0.3)	2.2 (0.7)	0.012
Stage 3 or 4 CKD prevalence, % (SE)			
Elevated cystatin C	5.7 (0.6)	18.0 (1.5)	
$eGFR_{MDRD}$	3.1 (0.3)	9.4 (0.7)	
Difference			
Elevated cystatin C estimate minus $eGFR_{MDRD}$ estimate	2.6 (0.5)	8.6 (1.1)	<0.001
Stage 3 or 4 CKD prevalence, % (SE)			
$eGFR_{creat,\ cysC,\ age,\ sex,\ race}$	2.9 (0.3)	9.1 (0.8)	
$eGFR_{MDRD}$	3.1 (0.3)	9.4 (0.7)	
Difference			
$eGFR_{creat,\ cysC,\ age,\ sex,\ race}$ estimate minus $eGFR_{MDRD}$	−0.2 (0.2)	−0.3 (0.5)	0.93

SE – Standard error

Prevalence of stage 3 or 4 CKD was defined by estimated glomerular filtration rate (eGFR):

$eGFR_{cysC}$ was derived from an equation including only cystatin C.

$eGFR_{MDRD}$ was derived from an equation including creatinine, age, sex, and race.

Elevated cystatin C was defined as cystatin C ≥ 1.12 mg/L (the 99^{th} percentile for adults 20 to 39 years of age without hypertension, diabetes mellitus or CKD).

$eGFR_{creat,\ cysC,\ age,\ sex,\ race}$ was derived from an equation including creatinine, cystatin C, age, sex, and race.

*Abdominal obesity (waist circumference > 88 cm for women; > 102 cm for men)