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Renal Function and Nonvertebral Fracture Risk in Multiethnic Women: the Women's Health Initiative (WHI)

Kristine E. Ensrud, MD, MPH^{1,2,3}, Kamil Barbour, PhD⁴, Muna T. Canales, MD, MS^{5,6}, Michelle E. Danielson, PhD⁴, Robert M. Boudreau, PhD⁴, Douglas C. Bauer, MD⁷, Andrea Z. LaCroix, PhD⁸, Areef Ishani, MD, MS^{1,3}, Rebecca D. Jackson, MD⁹, John A. Robbins, MD¹⁰, and Jane A. Cauley, DrPH⁴

¹Department of Medicine, University of Minnesota, Minneapolis, MN

²Division of Epidemiology & Community Health, University of Minnesota, Minneapolis, MN

³Center for Chronic Disease Outcomes Research, VA Medical Center, Minneapolis, MN

⁴Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA

⁵Department of Medicine, University of Florida, Gainesville, FL

⁶Department of Medicine, Malcolm-Randal Veterans Affairs Medical Center, Gainesville, FL

⁷Department of Medicine, University of California at San Francisco, San Francisco, CA

⁸Division of Public Health Sciences, WHI Clinical Coordinating Center, Fred Hutchinson Cancer Research Center, Seattle, WA

⁹Department of Medicine, Ohio State University, Columbus, OH

¹⁰Department of Medicine, University of California – Davis, Sacramento, CA

Abstract

Purpose—Determine whether renal function is associated with fracture risk within racial/ethnic groups.

Methods—Nested case-control study. Among 93,673 postmenopausal women, incident nonvertebral fractures identified in 362 Black, 183 Hispanic, 110 Asian, and 45 American Indian women. Random sample of 395 White women with incident nonvertebral fracture was chosen. One non-fracture control for each case selected (matched on age, race/ethnicity and blood draw date). Cystatin C levels measured using baseline serum; estimated glomerular filtration rate calculated (eGFR_{cys-c}).

Results—Each 1 SD increase in cystatin C was associated with a 1.2-fold increased risk of fracture among White women (adjusted OR 1.23, 95% CI 1.04–1.46). The OR of fracture was 1.16 (95% CI, 0.85–1.58) among women with eGFR_{cys-c} 60–90 mL/min/1.73m² and 2.46 (95% CI 1.16–5.21) among those with eGFR_{cys-c} <60 mL/min/1.73m² compared to referent group (eGFR_{cys-c} >90 mL/min/1.73m²) (p-trend=0.05). Association was reduced after adjustment for cytokine TNFα soluble receptors (OR 1.62, 95% CI 0.59–4.46 for eGFR_{cys-c} <60 mL/min/1.73m²). Among Blacks, there was an association between cystatin C and fracture risk (OR per 1 SD increase 1.15, 95% CI 1.00–1.32); after adjustment, this association was modestly attenuated,

Corresponding Author: Kristine E. Ensrud, MD, MPH, One Veterans Drive (111-0), Minneapolis, MN 55417, Phone: 612-467-5841; Fax: 612-467-2284, ensru001@umn.edu.

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but not significant. There was no evidence of significant associations among Hispanic, Asian, or American Indian women.

Conclusion—Postmenopausal White women with mild renal dysfunction are at increased risk of nonvertebral fracture. Effects of renal function on chronic inflammation may mediate this association. Reduced renal function may increase fracture risk among Black women, but there was little evidence to support this association among other racial/ethnic groups.

Keywords

chronic kidney disease; fracture; renal function; ethnic groups

INTRODUCTION

Older age and female gender are associated with a higher prevalence of chronic kidney disease (CKD).[1] There is also some evidence that the prevalence of CKD in the United States varies by race/ethnicity. While data from specific non-White minority populations is limited, non-Hispanic Blacks compared with non-Hispanic Whites appear more likely to have severe CKD (stage 4–5 as defined by estimated glomerular filtration rate (eGFR) <30 mL/min per 1.73m²), but less likely to have moderate (Stage 3) CKD (eGFR 30–59 mL/min per 1.73m²).[1–4] Variability in CKD prevalence estimates across racial/ethnic groups may be due to several factors including differences between White and nonwhite populations in the rate of progression from CKD to end-stage renal disease (ESRD), differences between populations in survival rates among those with advanced stages of CKD[4], or choice of formula used to estimate GFR.[5]

Older age and female gender are also associated with a higher prevalence of osteoporosis and related fractures. Among postmenopausal women, fracture risk varies by race/ethnicity. Black women have 50% lower rates of hip[6] and all fractures[7] compared with White women. In addition, rates of hip fracture are 25% lower among Hispanic and Asian women in comparison to that among White women.[8] While fractures rates are highest among postmenopausal White women, the number of fractures over time is estimated to increase 72% in Blacks, 160% in Hispanics and 155% in Asians.[9] Thus, the share of the costs attributable to fractures among non-White persons is predicted to increase from 12% to 21%.[9] Among postmenopausal women, a prior study has examined clinical risk factors for fracture according to race/ethnicity[10], but little is known about associations between biochemical determinants and fracture risk by race/ethnicity.

Several prior retrospective cohort studies have reported increased rates of hip and other fractures in patients with ESRD.[11–13] More recent investigations have also reported an association between moderate reductions in renal function (e.g. Stage 3 CKD assessed using either serum creatinine and cystatin C-based eGFR formulas) and an increased risk of hip fracture among postmenopausal and older women.[14–16] However, all of these studies were conducted in predominantly white women and none examined the association between renal function and risk of fractures at sites other than the hip or spine. One prior small prospective study examined the association between renal function (as assessed by serum creatinine-based eGFR formulas) and risk of all clinical (nonvertebral and clinical vertebral) fractures. This study was limited to postmenopausal white women and found no evidence of an association after adjustment for age alone.[17]

To determine whether mild reductions in renal function are associated with an increased risk of fractures among postmenopausal women within multiple racial/ethnic groups, we conducted a case-control study nested within the prospective Women's Health Initiative Observational Study (WHI-OS) and examined the associations between serum cystatin C

levels (and eGFR using a cystatin C-based eGFR formula) and risk of nonvertebral fractures in White, Black, Hispanic, Asian and American Indian women enrolled in WHI-OS.

METHODS

Study Population

The WHI-OS is a prospective cohort study that enrolled 93,676 women ages 50–79 years from 1994 to 1998 at 40 clinical centers in the United States. Study methods have been described in detail elsewhere.[18] Briefly, women were eligible if they were postmenopausal, unlikely to move or die within 3 years, not enrolled in the WHI Clinical Trial, and not currently participating in any other clinical trial. The study was approved by Human Subjects Review Committees at each participating institution. All participants provided written informed consent.

Race/Ethnicity

Information on race or ethnicity was obtained by self-report at baseline and was reported as “White” (not of Hispanic origin); “Black” (not of Hispanic origin); “Hispanic/Latino” (Mexican, Cuban, Puerto Rican, Central American, or South American); “Asian or Pacific Islander” (Chinese, Indo-Chinese, Korean, Japanese, Pacific Islander, Vietnamese); “American Indian” (including Alaskan Native), or “Other.” Women reporting “Other” race/ethnicity (n = 2,229) were excluded from this analysis.

Fracture Ascertainment

Women were sent questionnaires annually to report any hospitalization and other outcomes including fractures. Hip fractures were verified by review of medical records and confirmed by blinded central adjudicators.[19] While ascertainment of nonhip fractures in WHI-OS was based on self-report alone, 80% of self-reported nonhip fractures in the WHI Clinical Trials were confirmed by physician review of medical records, suggesting that the self-report of such fractures is reasonably accurate.[20]

Selection of Case and Control Samples

This analysis is a case-control study nested within the prospective design of WHI-OS. All self-reported cases of fracture in WHI-OS as of August 2006 were selected as potential cases. We excluded from this analysis women reporting current use at baseline of hormone therapy, bisphosphonates, or selective estrogen receptor modulators; those reporting “Other” race/ethnicity; those self-reporting incident fractures of the spine, coccyx, fingers, toes, face, skull, or sternum; those with adjudicated incident hip fractures from a pathologic cause; those missing important covariates (e.g., height, weight or fracture history); and those with insufficient serum.

After these exclusions, a total of 7,116 fracture cases and 37,713 controls (out of 93,676 total participants in WHI-OS) were potentially eligible for this analysis. Of the 7,116 women with fracture, 726 reported Black, Hispanic, Asian or American Indian race/ethnicity. We included in this analysis a total of 700 minority women with fracture and sufficient serum (362 Black; 183 Hispanic; 110 Asians and 45 American Indian women) and a random sample of 395 White women from the 6,416 fracture cases among White women.

One control was selected for each case from the risk set corresponding to the time of the case’s event. All participants (cases included) were part of the risk set until they experienced a fracture event or until their last contact; participants were censored from the analysis if they were lost to follow-up or in the event of death. Controls were matched by age at screening (± 1 year), race/ethnicity (White, Black, Hispanic, Asian, American Indian), and

date of baseline blood draw (± 92 days). Race/ethnicity status was matched exactly, and age and draw dates were selected based on a criteria to minimize an overall distance measure. All matching factors were weighted equally during the selection process. The controls were chosen to have follow-up time at least as long as the cases event time. Seventeen unmatched cases during the first run were subsequently matched by age at screening (± 2 years), race/ethnicity, and draw date (± 365 days).

Thus, there were 1,095 fracture cases and 1,095 controls for a total of 2,190 women in this analysis. The average (SD) follow-up time in years from baseline to the minimum of the last follow-up date as of August 31, 2006 was 8.60 (1.61) among cases and 8.65 (1.61) among controls.

Assessment of Renal Function and Other Laboratory Parameters

A 12-hour fasting serum sample was obtained at the baseline exam, processed and stored at -70°C according to strict quality control procedures.[21] Serum cystatin C levels were determined using a BN100 nephelometer (Dade Behring Inc., Deerfield, IL) using a particle-enhanced immunonephelometric assay.[22] The assay range is 0.30 to 10.00 mg/L with intra-assay coefficients of variation (CVs) ranging from 2.0 to 2.8% and inter-assay CVs from 2.3 to 3.1%. For calculation of eGFR, we used the CKD epidemiology equation ($\text{eGFR}_{\text{cys-c}} = 76.7 \times \text{cystatin C}^{-1.19}$) which was derived from a pooling of cohorts that used iothalamate clearance as the criterion standard.[23]

Categories of eGFR were Whole (1–84) parathyroid hormone (PTH) in plasma was measured using an immunoradiometric assay (Scantibodies Laboratory, Inc., Santee, CA) utilizing a polyclonal 1–84 antibody with a tendency to bind in the N terminal region and polyclonal 1–84 antibody with a tendency to bind in the C terminal region. The use of these antibodies guarantees that only whole PTH is detected. For serum 25-hydroxyvitamin D [25(OH)D], a radioimmunoassay was used with DiaSorin reagents (Stillwater, MN). Markers of chronic inflammatory processes were assessed by serum levels of pro-inflammatory cytokine soluble receptors (IL-6 sR, TNF α sR1, and TNF α sR2) measured using ELISA kits (R&D systems, Minneapolis, MN) due to previously reported findings concerning the associations between inflammatory markers and fracture risk in older adults. [24]

Other Measurements

All covariates were ascertained at baseline. Data were collected on education, cigarette smoking, alcohol intake, health status, history of specific medical conditions including prior fractures, physical activity, general health status, diet, falls, and medications. Current use of prescription medications and dietary supplements including calcium/vitamin D preparations was recorded by clinic interviewers by direct inspection of medicine containers. Generic and brand names of prescription medications were entered into the WHI database and assigned drug codes using Medispan software. Dietary intakes of calcium and vitamin D were assessed using a semi-quantitative food frequency questionnaire.[25] Physical activity was classified on the basis of frequency and duration of walking and mild, moderate and strenuous activities in the prior week. Kilocalories of energy expended in a week was calculated (metabolic equivalent (MET) score=kcal hours/week/kg).[26] Weight was measured on a balance beam scale with the participant dressed in indoor clothing without shoes. Height was measured using a wall-mounted stadiometer. Body mass index was calculated as weight/height (kg/m^2).

Statistical Analysis

Baseline characteristics between fracture cases and matched control participants within each race/ethnicity group were compared using chi-square and t tests. To further assess potential confounders, we also examined baseline characteristics according to quartiles of cystatin C among control subjects within each race/ethnicity group and performed tests for linear trend.

Renal function was expressed as a continuous variable (cystatin C level), quartiles of cystatin C (cutpoints determined from distribution of cystatin C among all control subjects; quartiles were weighted based on the number of participants in each racial/ethnicity group that the controls were sampled from) and categories of eGFR_{cys-c} (<60, 60–90 and >90 mL/min per 1.73m²). [27] We assessed the association between renal function and incident nonvertebral fracture using conditional logistic regression models that retained the matched case-control design (age, race/ethnicity, blood draw data). Odds ratios (OR) and 95% confidence intervals (CI) were calculated per standard deviation (SD) increase in cystatin C and for women in each quartile of cystatin C using women in quartile 1 as the referent group. In addition, the OR with 95% CI of fracture was estimated for women with an eGFR_{cys-c} 60–90 mL/min per 1.73m², and those with an eGFR_{cys-c} <60 mL/min per 1.73m² using women with an eGFR_{cys-c} >90 mL/min per 1.73m² as the referent group. [27] Associations were first examined without any additional adjustment (cases and controls matched on age, blood draw date and racial/ethnicity). Candidate covariates included those characteristics associated with case-control status or cystatin C level among control subjects in at least 1 of the 5 racial/ethnic groups: educational level, smoking status, alcohol use, health status, treated diabetes mellitus, history of selected medical conditions (previous fracture, myocardial infarction, stroke), current thiazide use, falls in past 12 months, and body mass index. Within each racial/ethnic group, a backward stepwise elimination procedure was performed and $p = 0.05$ was used as a cut-off level for retention of covariates in the adjusted model. To examine biological mechanisms that might underlie the independent association observed between renal function and fracture among White women, models in White women were further adjusted for calcitropic hormones (PTH, 25(OH)D) and markers of chronic inflammation (cytokine soluble receptors: IL-6 sR, TNF α sR1, and TNF α sR2).

Given the specific number of fracture cases and controls within each race/ethnicity group and alpha level (Type 1 error) of 0.05, the odds ratio per 1 SD increase in serum cystatin C detectable in adjusted models with 80% power was 1.11 among Whites, 1.11 among Blacks, 1.17 among Hispanics, 1.21 among Asians, and 1.35 among American Indians.

RESULTS

The mean age of subjects varied across race/ethnicity groups and ranged from 62.6 years among Black women to 66.2 years among White women (Table 1). Within each race/ethnicity group, cases and controls were well matched on age. Characteristics of fracture cases and controls within each specific race/ethnicity group are given in Table 1. Among White women, fracture cases were more likely to report diabetes, prior history of fracture, and had lower average eGFR_{cys-c}. Among Black women, fracture cases were more likely to be past smokers and report a prior history of fracture. Mean cystatin C level was higher in fracture cases vs. controls among both White and Black women, but the difference was not quite significant (p for comparison between cases and controls 0.06 among White women and 0.07 among Black women). Among Hispanic women the only difference that reached significance was a prior history of fracture which was more common among fracture cases. Among Asian women and among American Indian women, there were no differences between fracture cases and controls that reached significance. In control subjects, the proportion of women with an eGFR_{cys-c} <60 mL/min per 1.73m² was 3.5% among Whites,

2.2% among Blacks, 4.4% among Hispanics, 2.7% among Asians, and 4.4% among American Indians.

Characteristics according to quartiles of cystatin C among control subjects within each race/ethnicity group are given in Table 2. Among White women, older age, lower education, less frequent alcohol consumption, poorer health status, lower physical activity, and higher BMI were associated with higher cystatin C levels. White women with higher cystatin C were also more likely to be non-smokers and report treated diabetes. In general, similar associations were observed among Black women. In addition, Black women with higher cystatin C were more likely to report a history of myocardial infarction, stroke and current thiazide use. Among Hispanic women, older age, less frequent alcohol consumption, poorer health status, and higher BMI were associated with higher cystatin C levels. There were smaller numbers of control subjects in the remaining racial/ethnic groups and power to detect differences between quartiles of cystatin C was lower. Among Asian women, older age, lower education and poorer health status (p-trend 0.06) were associated higher cystatin C levels. Among American Indian women, the only characteristic associated with higher cystatin C levels (p-trend 0.06) was recurrent (2 or more) falls in the past year.

In unadjusted models (matched on age, blood draw date and race/ethnicity), each 1 SD increase in cystatin C was associated with a 1.2-fold (OR 1.20, 95% CI 1.03–1.41) increased risk of nonvertebral fracture among White women (Table 3). This association was not altered after further adjustment for previous fracture history (the only covariate retained after the backwards elimination procedure). In addition, the association persisted after excluding women with hip fracture (n=19) and their controls from the analysis; the adjusted OR (95% CI) of nonhip nonvertebral fracture per 1 SD increase in cystatin C was 1.24 (95% CI 1.04–1.48) (p=0.02). Women in the highest quartile of cystatin C (>0.94 mg/L) had 1.7-fold higher risk of nonvertebral fracture (multivariable OR 1.71, 95% CI 1.09–2.70) compared with those in the lowest quartile (<0.75 mg/L); the risk of nonvertebral fracture was intermediate in magnitude among women in quartile 2 and among women in quartile 3 (p-trend 0.02), though the comparisons with quartile 1 (referent group) did not reach significance. Compared with women with an $eGFR_{cys-c} > 90$ mL/min per $1.73m^2$ (referent group), the adjusted OR (95% CI) of nonvertebral fracture was 1.16 (0.85–1.58) among women with an $eGFR_{cys-c}$ 60–90 mL/min per $1.73m^2$ and 2.45 (1.16–5.21) among women with an $eGFR_{cys-c} < 60$ mL/min per $1.73m^2$ (p-trend 0.05). Additional adjustment for calcitropic hormones (PTH, 25(OH)D) or IL-6sR did not alter the association, but it was reduced after adjustment for cytokine soluble receptors TNF α sR1 or TNF α sR2, individually or in combination (Table 4). After adjustment for TNF sR1 and TNF sR2, the OR for $eGFR_{cys-c} < 60$ mL/min per $1.73m^2$ was 1.62 (95% CI 0.59–4.46). Mean levels of these three soluble receptors increased in a graded manner with increasing quartile of cystatin C among White control subjects (p trend <0.01) (results not shown).

Among Black women, higher serum cystatin C levels appeared to be similarly associated (unadjusted OR per 1 SD increase 1.15, 95% CI 1.00–1.48) (p=0.06) with an increased risk of nonvertebral fracture (Table 3). The association was modestly attenuated and not significant after further adjustment for previous fracture history, the only covariate retained after the backwards elimination procedure (adjusted OR per 1 SD increase 1.12, 95% CI 0.98–1.30 (p=0.11). There was no evidence for an interaction between cystatin C and health status or cystatin C and BMI (<30 kg/m² vs. ≥ 30 kg/m²) for prediction of nonvertebral fracture risk among Black women (p for interaction terms = 0.62). Black women with an $eGFR_{cys-c} < 60$ mL/min per $1.73m^2$ compared with those with an $eGFR_{cys-c} > 90$ mL/min per $1.73m^2$ appeared to have a 2-fold higher risk of nonvertebral fracture, but the 95% CI overlapped 1.00 (adjusted OR 2.06, 95% CI 0.87–4.87).

Among each of the three other race/ethnicity groups (Hispanic, Asian, and American Indians), there were no significant associations between renal function and fracture; 95% CI around point estimates of associations widely overlapped 1.00 (Table 3).

CONCLUSION

In this prospective nested case-control study, White women with mild reductions in renal function as manifested by higher cystatin C or lower $\text{eGFR}_{\text{cys-c}}$ had an increased risk of nonvertebral fracture over the following 8 years. The association, albeit not at the level of significance, appeared to be similar in direction and magnitude among Black women. While power to detect associations was lower among other racial/ethnic groups in this study, renal function was not significantly related to the risk of fracture among Hispanic, Asian, or American Indian women.

The findings among White women in this study are in agreement with those of a prior case-control study (397 incident hip fracture cases [380 in White women] and 397 matched controls) nested within the same (WHI-OS) cohort[15] that reported a higher risk of hip fracture among women with higher cystatin C levels and those with lower $\text{eGFR}_{\text{cys-c}}$. In the present study, the association between higher cystatin C levels and increased risk of nonvertebral fractures in White women persisted despite excluding hip fracture cases and their controls from the analysis. Thus, these results extend those of the previous WHI-OS study and suggest that the association between reduced renal function and fracture among White women is not limited to an increased risk of hip fracture. An independent association between lower serum creatinine-based eGFR ($<60 \text{ mL/min per } 1.73\text{m}^2$) and increased risk of hip fracture has also been reported among a cohort of older White women.[14] In addition, the magnitude of the association between cystatin C level and nonvertebral fracture in this study was similar to that observed between cystatin C and incident hip fracture in a cohort of predominantly White elderly women.[16] However, these results stand in contrast with those of a prior small prospective study of 427 White postmenopausal women that found no evidence that women with modest reductions in renal function (as assessed by serum creatinine or eGFR using serum creatinine-based equations) had a higher age-adjusted risk of clinical fractures.[17]

In this study of healthy postmenopausal women without severe or endstage kidney disease, the magnitude of associations between measures of renal function (higher cystatin C levels or lower $\text{eGFR}_{\text{cys-c}}$) and risk of nonvertebral fracture were similar among Black as compared with White women, but none of the associations among Black women reached the level of significance. While power to detect an association between cystatin C and fracture was similar among White and Black women, power to detect an association between reduced $\text{eGFR}_{\text{cys-c}}$ and fracture among Black women was lower as an $\text{eGFR}_{\text{cys-c}} <60 \text{ mL/min per } 1.73\text{m}^2$ was less common among Black compared with White women. Previous studies have also reported that moderate CKD ($\text{eGFR}_{\text{cys-c}} 30\text{--}59 \text{ mL/min per } 1.73\text{m}^2$) is less prevalent among Black compared with White populations.[1–4]

Among the three remaining smaller race/ethnicity groups (Hispanic, Asian and American Indians), none of the associations between renal function and fracture were significant. Confidence intervals around the point estimates of associations widely overlapped the null hypothesis of no association. A prior cross-sectional study among 659 Japanese women seeking an evaluation for osteoporosis at a metabolic bone disorders clinic reported that women with lower creatinine clearance calculated using the serum creatinine-based Cockcroft-Gault equation, but not lower serum creatinine-based eGFR calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation, were more likely to have a radiographically identified vertebral fracture.[28] Inconsistencies in results among

the Asian women in this study and those of the study in Japanese women may be in part related to differences in study design, study populations (e.g., selected population versus population-based cohort and degree of ethnic admixture), measures of renal function, and choice of fracture outcome. In particular, cross-sectional studies examining associations yield weaker evidence for causality and are more prone to biases than prospective cohort studies such as WHI-OS.

Discrepancies in the findings concerning the association between renal function and fracture according to race/ethnicity in this study may exist for a number of reasons. Although we included all fracture cases in minority women, we had limited power to detect the association between serum cystatin C and fracture among Hispanic, Asian, and American Indian women. In addition, the participants were healthy postmenopausal women without severe or endstage chronic kidney disease and few women had evidence of mild to moderate renal dysfunction as manifested by an $eGFR_{cys-c} < 60$ mL/min per $1.73m^2$. It is possible that threshold for renal dysfunction indicative of increased fracture risk varies by race/ethnicity. Finally, direct measures of GFR were not available and we relied on serum cystatin C and eGFR using a cystatin C-based equation to provide estimates of renal function. The most widely used Modification of MDRD formula[29] uses serum creatinine to estimate GFR. However, serum creatinine levels are influenced by muscle mass and tubular secretion and true GFR levels may differ between individuals despite the same serum creatinine level. In addition, the MDRD formula was derived in middle-aged non-diabetic adults with chronic kidney disease and adjusts for age, black race and gender, although no adjustment is made for other nonwhite racial/ethnic groups. Serum cystatin C, produced by most nucleated cells and free filtered at the glomerulus, has advantages over serum creatinine as a marker of GFR. Since muscle mass is not a major determinant of cystatin C levels, its use to estimate GFR may lead to more congruent estimates of CKD across racial/ethnic groups. While it is true that the independence of cystatin C from muscle mass and other demographic factors such as race/ethnicity is not as great as originally hypothesized[30], differences in CKD estimates among women across four racial/ethnic groups[5] were substantially attenuated with the use of the cystatin C-based GFR prediction equation without race and gender coefficients vs. use of the MDRD formula. Differences in mean cystatin C levels and $eGFR_{cys-c}$ across race/ethnicity groups in this cohort may reflect racial differences in kidney function or ethnic differences in how cystatin C approximates GFR.

Several biological mechanisms may underlie an association between mild to moderate renal dysfunction and increased fracture risk among postmenopausal women. Abnormalities in calcium, phosphorus, and vitamin D metabolism that occur in even mild renal insufficiency among postmenopausal women and older adults may lead to decreased formation of active vitamin D (1,25-dihydroxyvitamin D) by the kidney, resulting in decreased fractional calcium absorption, secondary hyperparathyroidism, greater bone resorption, and higher fracture rates.[31,32] However, the association between renal function and fracture observed among White women in this study persisted despite adjustment for calcitropic hormones. Some, but not all prospective studies, have reported an association between lower vitamin D status and increased fracture risk[33,34] and the association between PTH levels and fracture risk among healthy older adults is controversial.[35,36] Moderate impairment in renal function has also been associated with higher levels of inflammatory factors and homocysteine, as well as anemia.[37–39] Our findings suggest that the effect of renal function on chronic inflammatory processes as assessed by levels of TNF α cytokine soluble receptors may in part mediate the association between renal function and fracture observed among White women. While these results need confirmation in future studies, a prior prospective study in older adults[24] reported independent associations of higher levels of inflammatory markers (including cytokine soluble receptors TNF sR1 and TNF sR2) with increased fracture risk. However, this study did not evaluate the effect of renal function on

these associations. In addition, CKD may be a marker for poorer health status and frailty[40] that may increase risk of falls and related fractures, though a prior investigation from this cohort reported that adjustment for markers of bone resorption and formation, frailty and co-morbid conditions, 25(OH) D, hemoglobin, or homocysteine did not entirely explain the association between reduced renal function and increased hip fracture risk.[15]

Strengths of this study include the large, diverse cohort of well-characterized postmenopausal women with representation of five different race/ethnicity groups, consideration of several candidate potential confounding variables in the analysis, consideration of underlying biological mediators, choice of nonvertebral fracture as the outcome, and use of cystatin C as a measure of renal function. However, this study has several limitations. Participants were healthy postmenopausal women with a low prevalence of CKD as defined by an $eGFR_{cys-c} < 60$ mL/min per $1.73m^2$ and we were unable to evaluate the association between moderate to severe CKD and fracture risk among race/ethnicity groups. Power to detect modest associations between renal dysfunction and fracture was limited among Hispanic, Asian, and American Indian women. No measure of bone mineral density was available. Finally, given our observational design, the possibility of residual confounding cannot be eliminated.

In conclusion, postmenopausal White women with $eGFR_{cys-c} < 60$ mL/min per $1.73m^2$ are at increased risk of nonvertebral fracture and a similar association may exist among Black women. There was little evidence to support an association between renal function and nonvertebral fracture risk among other racial/ethnic groups in this cohort. Additional prospective studies among other cohorts of minority women are needed to accurately and precisely determine the association between renal function and risk of fracture among non-White women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. United States Renal Data System. 2009 Annual Data Report. Atlas of Chronic Kidney Disease. 2010; 1 <http://www.usrds.org/adr.htm>.
2. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis*. 2003; 41:1–12. [PubMed: 12500213]
3. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van LF, Levey AS. Prevalence of chronic kidney disease in the United States. *JAMA*. 2007; 298:2038–2047. [PubMed: 17986697]
4. McClellan W, Warnock DG, McClure L, Campbell RC, Newsome BB, Howard V, Cushman M, Howard G. Racial differences in the prevalence of chronic kidney disease among participants in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Cohort Study. *J Am Soc Nephrol*. 2006; 17:1710–1715. [PubMed: 16641151]
5. Kramer H, Palmas W, Kestenbaum B, Cushman M, Allison M, Astor B, Shlipak M. Chronic kidney disease prevalence estimates among racial/ethnic groups: the Multi-Ethnic Study of Atherosclerosis. *Clin J Am Soc Nephrol*. 2008; 3:1391–1397. [PubMed: 18550650]

6. Farmer ME, White LR, Brody JA, Bailey KR. Race and sex differences in hip fracture incidence. *Am J Public Health.* 1984; 74:1374–1380. [PubMed: 6507690]
7. Baron JA, Karagas M, Barrett J, Kniffin W, Malenka D, Mayor M, Keller RB. Basic epidemiology of fractures of the upper and lower limb among Americans over 65 years of age. *Epidemiology.* 1996; 7:612–618. [PubMed: 8899387]
8. Silverman SL, Madison RE. Decreased incidence of hip fracture in Hispanics, Asians, and blacks: California Hospital Discharge Data. *Am J Public Health.* 1988; 78:1482–1483. [PubMed: 3177728]
9. Burge R, King A, Solomon D, Tosteson A, Wong J, Dawson-Hughes B. Osteoporosis fractures and costs by race/ethnicity and gender in the USA. *J Bone Miner Res.* 2005; 20:S87.
10. Cauley JA, Wu L, Wampler NS, Barnhart JM, Allison M, Chen Z, Jackson R, Robbins J. Clinical risk factors for fractures in multi-ethnic women: the Women's Health Initiative. *J Bone Miner Res.* 2007; 22:1816–1826. [PubMed: 17638574]
11. Alem AM, Sherrard DJ, Gillen DL, Weiss NS, Beresford SA, Heckbert SR, Wong C, Stehman-Breen C. Increased risk of hip fracture among patients with end-stage renal disease. *Kidney Int.* 2000; 58:396–399. [PubMed: 10886587]
12. Ball AM, Gillen DL, Sherrard D, Weiss NS, Emerson SS, Seliger SL, Kestenbaum BR, Stehman-Breen C. Risk of hip fracture among dialysis and renal transplant recipients. *JAMA.* 2002; 288:3014–3018. [PubMed: 12479766]
13. Ramsey-Goldman R, Dunn JE, Dunlop DD, Stuart FP, Abecassis MM, Kaufman DB, Langman CB, Salinger MH, Sprague SM. Increased risk of fracture in patients receiving solid organ transplants. *J Bone Miner Res.* 1999; 14:456–463. [PubMed: 10027911]
14. Ensrud KE, Lui LY, Taylor BC, Ishani A, Shlipak MG, Stone KL, Cauley JA, Jamal SA, Antonucci DM, Cummings SR. Renal function and risk of hip and vertebral fractures in older women. *Arch Intern Med.* 2007; 167:133–139. [PubMed: 17242313]
15. LaCroix AZ, Lee JS, Wu L, Cauley JA, Shlipak MG, Ott SM, Robbins J, Curb JD, Leboff M, Bauer DC, Jackson RD, Kooperberg CL, Cummings SR. Cystatin-C, renal function, and incidence of hip fracture in postmenopausal women. *J Am Geriatr Soc.* 2008; 56:1434–1441. [PubMed: 18662213]
16. Fried LF, Biggs ML, Shlipak MG, Seliger S, Kestenbaum B, Stehman-Breen C, Sarnak M, Siscovick D, Harris T, Cauley J, Newman AB, Robbins J. Association of kidney function with incident hip fracture in older adults. *J Am Soc Nephrol.* 2007; 18:282–286. [PubMed: 17167115]
17. McCarthy JT, Rule AD, Achenbach SJ, Bergstralh EJ, Khosla S, Melton LJ III. Use of renal function measurements for assessing fracture risk in postmenopausal women. *Mayo Clin Proc.* 2008; 83:1231–1239. [PubMed: 18990322]
18. Hays J, Hunt JR, Hubbell FA, Anderson GL, Limacher M, Allen C, Rossouw JE. The Women's Health Initiative recruitment methods and results. *Ann Epidemiol.* 2003; 13:S18–S77. [PubMed: 14575939]
19. Curb JD, McTiernan A, Heckbert SR, Kooperberg C, Stanford J, Nevitt M, Johnson KC, Proulx-Burns L, Pastore L, Criqui M, Daugherty S. Outcomes ascertainment and adjudication methods in the Women's Health Initiative. *Ann Epidemiol.* 2003; 13:S122–S128. [PubMed: 14575944]
20. Chen Z, Kooperberg C, Pettinger MB, Bassford T, Cauley JA, LaCroix AZ, Lewis CE, Kipersztok S, Borne C, Jackson RD. Validity of self-report for fractures among a multiethnic cohort of postmenopausal women: results from the Women's Health Initiative observational study and clinical trials. *Menopause.* 2004; 11:264–274. [PubMed: 15167305]
21. Anderson GL, Manson J, Wallace R, Lund B, Hall D, Davis S, Shumaker S, Wang CY, Stein E, Prentice RL. Implementation of the Women's Health Initiative study design. *Ann Epidemiol.* 2003; 13:S5–17. [PubMed: 14575938]
22. Erlandsen EJ, Randers E, Kristensen JH. Evaluation of the Dade Behring N Latex Cystatin C assay on the Dade Behring Nephelometer II System. *Scand J Clin Lab Invest.* 1999; 59:1–8. [PubMed: 10206092]
23. Stevens LA, Coresh J, Schmid CH, Feldman HI, Froissart M, Kusek J, Rossert J, Van LF, Bruce RD III, Zhang YL, Greene T, Levey AS. 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.* 2008; 51:395–406. [PubMed: 18295055]

24. Cauley JA, Danielson ME, Boudreau RM, Forrest KY, Zmuda JM, Pahor M, Tylavsky FA, Cummings SR, Harris TB, Newman AB. Inflammatory markers and incident fracture risk in older men and women: the Health Aging and Body Composition Study. *J Bone Miner Res.* 2007; 22:1088–1095. [PubMed: 17419681]
25. Patterson RE, Kristal AR, Tinker LF, Carter RA, Bolton MP, Agurs-Collins T. Measurement characteristics of the Women's Health Initiative food frequency questionnaire. *Ann Epidemiol.* 1999; 9:178–187. [PubMed: 10192650]
26. Manson JE, Greenland P, LaCroix AZ, Stefanick ML, Mouton CP, Oberman A, Perri MG, Sheps DS, Pettinger MB, Siscovick DS. Walking compared with vigorous exercise for the prevention of cardiovascular events in women. *N Engl J Med.* 2002; 347:716–725. [PubMed: 12213942]
27. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002; 39:S1–266. [PubMed: 11904577]
28. Kaji H, Yamauchi M, Yamaguchi T, Shigematsu T, Sugimoto T. Mild renal dysfunction is a risk factor for a decrease in bone mineral density and vertebral fractures in Japanese postmenopausal women. *J Clin Endocrinol Metab.* 2010; 95:4635–4642. [PubMed: 20631017]
29. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med.* 2003; 139:137–147. [PubMed: 12859163]
30. 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; 51:385–394. [PubMed: 18295054]
31. Francis RM, Peacock M, Barkworth SA. Renal impairment and its effects on calcium metabolism in elderly women. *Age Ageing.* 1984; 13:14–20. [PubMed: 6422710]
32. Vieth R, Ladak Y, Walfish PG. Age-related changes in the 25-hydroxyvitamin D versus parathyroid hormone relationship suggest a different reason why older adults require more vitamin D. *J Clin Endocrinol Metab.* 2003; 88:185–191. [PubMed: 12519850]
33. Agency for Healthcare Research and Quality. [Accessed 19 April 2010] Effectiveness and safety of vitamin D in relation to bone health. 2007. <http://www.ahrq.gov/clinic/tp/vitadtp.htm>
34. Agency for Healthcare Research and Quality. [Accessed 19 April 2010] Vitamin D and calcium: a systematic review of health outcomes. 2009. <http://www.ahrq.gov/clinic/tp/vitadcaltp.htm>
35. Sakuma M, Endo N, Oinuma T, Hayami T, Endo E, Yazawa T, Watanabe K, Watanabe S. Vitamin D and intact PTH status in patients with hip fracture. *Osteoporos Int.* 2006; 17:1608–1614. [PubMed: 16874442]
36. von Muhlen DG, Greendale GA, Garland CF, Wan L, Barrett-Connor E. Vitamin D, parathyroid hormone levels and bone mineral density in community-dwelling older women: the Rancho Bernardo Study. *Osteoporos Int.* 2005; 16:1721–1726. [PubMed: 15928802]
37. Astor BC, Muntner P, Levin A, Eustace JA, Coresh J. Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988–1994). *Arch Intern Med.* 2002; 162:1401–1408. [PubMed: 12076240]
38. Francis ME, Eggers PW, Hostetter TH, Briggs JP. Association between serum homocysteine and markers of impaired kidney function in adults in the United States. *Kidney Int.* 2004; 66:303–312. [PubMed: 15200438]
39. Shlipak MG, Fried LF, Crump C, Bleyer AJ, Manolio TA, Tracy RP, Furberg CD, Psaty BM. Elevations of inflammatory and procoagulant biomarkers in elderly persons with renal insufficiency. *Circulation.* 2003; 107:87–92. [PubMed: 12515748]
40. Odden MC, Chertow GM, Fried LF, Newman AB, Connelly S, Angleman S, Harris TB, Simonsick EM, Shlipak MG. Cystatin C and measures of physical function in elderly adults: the Health, Aging, and Body Composition (HABC) Study. *Am J Epidemiol.* 2006; 164:1180–1189. [PubMed: 17035344]

Table 1

Baseline Characteristics of Fracture Cases and Controls by Ethnic Group

	White			Black			Hispanic			Asian/Pacific Islander			American Indian		
	Control (n=395)	Case (n=395)	P	Control (n=362)	Case (n=362)	P	Control (n=183)	Case (n=183)	P	Control (n=110)	Case (n=110)	P	Control (n=45)	Case (n=45)	P
Age, mean (SD), yrs	66.2 (7.3)	66.2 (7.3)	0.95	62.6 (7.7)	62.6 (7.7)	0.99	62.9 (7.4)	62.9 (7.5)	0.97	65.3 (7.6)	65.3 (7.6)	0.99	63.6 (7.3)	63.6 (7.4)	0.99
Education, %	--	--	0.86	--	--	0.25	--	--	0.09	--	--	0.71	--	--	0.81
High school or less	25.3	23.8	--	30.8	26.5	--	44.5	46.1	--	23.6	28.2	--	35.6	40.0	--
School after high school	34.1	35.7	--	34.5	40.1	--	35.7	26.4	--	31.8	28.2	--	42.2	35.6	--
College degree or higher	40.6	40.5	--	34.7	33.4	--	19.8	27.5	--	44.6	43.6	--	22.2	24.4	--
Smoking status, %	--	--	0.44	--	--	0.03	--	--	0.66	--	--	0.78	--	--	0.78
Never	51.3	55.2	--	54.7	46.4	--	61.6	66.1	--	79.8	78.0	--	53.3	51.4	--
Past	43.1	38.6	--	33.7	43.0	--	29.4	26.6	--	14.7	18.4	--	35.6	32.5	--
Current	5.6	6.2	--	11.6	10.6	--	9.0	7.3	--	5.5	3.6	--	11.1	16.1	--
Alcohol use, %	--	--	0.43	--	--	0.53	--	--	0.54	--	--	0.88	--	--	0.88
Never	10.9	13.2	--	20.9	17.3	--	20.7	26.4	--	44.5	47.3	--	27.3	22.2	--
Former	17.8	20.9	--	31.9	36.1	--	26.8	26.4	--	17.3	16.3	--	22.7	20.0	--
<7 drinks/wk	59.1	55.2	--	42.7	42.6	--	45.2	42.1	--	32.7	29.1	--	40.9	53.4	--
7 drinks/wk	12.2	10.7	--	4.5	4.0	--	7.3	5.1	--	5.5	7.3	--	9.1	4.4	--
Health status, %	--	--	0.15	--	--	0.72	--	--	0.67	--	--	0.57	--	--	0.57
Excellent to very good	65.1	58.7	--	36.3	33.7	--	37.3	35.8	--	58.2	43.6	--	40.9	44.2	--
Good	29.3	33.7	--	41.1	41.9	--	37.3	34.6	--	33.6	40.9	--	36.4	41.9	--
Fair to poor	5.6	7.6	--	22.6	24.4	--	25.4	29.6	--	8.2	15.5	--	22.7	13.9	--
Physical activity, median (IQR), METs/wk	8.8 (3–28)	8.4 (3–18)	0.36	6.3 (1–15)	4.9 (1–15)	0.28	6.4 (2–18)	7.0 (2–17)	0.92	10.0 (4–26)	10.6 (3–19)	0.94	7.5 (2–15)	7.5 (1–14)	0.94
Treated diabetes mellitus, %	2.8	6.1	0.02	11.3	16.1	0.06	7.7	12.0	0.16	2.7	8.2	0.06	11.1	26.7	0.06
History of fracture, %	36.0	56.2	0.01	22.5	32.7	0.01	23.8	40.4	0.01	20.0	26.4	0.26	36.4	52.3	0.13
History of myocardial infarction, %	1.8	3.0	0.40	5.8	4.4	0.39	1.7	1.6	0.50	3.6	0.0	1.00	13.3	13.3	1.00
History of stroke, %	0.3	1.8	0.07	4.7	4.7	1.00	4.4	2.7	0.39	3.6	3.6	0.68	6.8	4.4	0.68
Hormone therapy use, %	--	--	0.69	--	--	0.50	--	--	0.70	--	--	0.06	--	--	0.06
Past	25.8	27.1	--	19.6	17.7	--	21.3	19.7	--	34.6	28.2	--	37.8	20.0	--
Never	74.2	72.9	--	80.4	82.3	--	78.7	80.3	--	65.4	71.8	--	62.2	80.0	--
Current thiazide use, %	6.6	2.9	0.66	9.7	8.8	0.70	1.6	2.2	0.70	1.8	1.4	1.00	6.7	4.4	1.00
Oral daily glucocorticoid use, %	0.8	2.0	0.22	1.7	3.3	0.15	0.6	1.9	0.34	1.8	0.0	0.34	1.6	3.4	0.34

	White			Black			Hispanic			Asian/Pacific Islander			American Indian		
	Control (n=395)	Case (n=395)	P	Control (n=362)	Case (n=362)	P	Control (n=183)	Case (n=183)	P	Control (n=110)	Case (n=110)	P	Control (n=45)	Case (n=45)	P
Falls in past 12 mo, %	--	--	0.61	--	--	0.44	--	--	0.45	--	--	0.34	--	--	0.34
None	68.3	65.0	--	69.8	65.2	--	60.1	54.0	--	77.3	70.9	--	64.5	53.3	--
1	18.3	20.4	--	17.2	20.0	--	23.1	24.7	--	11.8	20.0	--	24.4	24.5	--
2	13.4	14.6	--	13.0	14.8	--	16.8	21.3	--	10.9	9.1	--	11.1	22.2	--
BMI, mean (SD), kg/m ²	27.3 (5.7)	27.7 (5.6)	0.33	30.4 (6.8)	30.5 (6.3)	0.88	28.4 (6.7)	29.5 (6.7)	0.12	24.5 (6.1)	24.8 (5.1)	0.87	29.7 (6.9)	29.4 (6.6)	0.87
Total dietary Ca intake ^a , median (IQR), mg/day	759 (522–1078)	739 (528–1049)	0.57	500 (306–753)	516 (325–848)	0.25	596 (399–974)	652 (423–910)	0.70	511 (327–747)	486 (298–757)	0.97	667 (385–1028)	679 (459–908)	0.97
Cystatin C level, mean (SD), mg/L	0.88 (0.20)	0.91 (0.26)	0.06	0.83 (0.17)	0.86 (0.17)	0.07	0.85 (0.17)	0.85 (0.20)	0.76	0.80 (0.23)	0.78 (0.16)	0.57	0.89 (0.26)	0.90 (0.28)	0.87
eGFR _{cys-c} ^b , mean (SD), mL/min/1.73m ²	94.2 (20.3)	91.1 (20.3)	0.03	99.8 (22.8)	97.8 (23.9)	0.23	98.0 (20.7)	98.4 (24.0)	0.85	106.4 (23.6)	108.8 (24.2)	0.97	94.5 (22.1)	94.3 (23.7)	0.97
eGFR _{cys-c} category, %, mL/min/1.73m ²	0.13			0.13			0.78			0.78			0.78		
>90	58.2	54.2		64.9	64.4		66.1	63.4		80.0	82.7		60.0	64.4	
60–90	38.2	39.0	32.9	30.7	29.5	32.8	17.3	15.5	35.6		28.9				
<60	3.5	6.6	2.2	5.0	4.4	3.8	2.7	1.8	4.4	6.7					

^aDietary plus supplements

^b $\text{eGFR}_{\text{cys-c}} = 7.67 \times (\text{cystatin C})^{-1.19}$

Abbreviations: IQR, interquartile range; METs, metabolic equivalent score; BMI, body mass index; Ca, calcium; eGFR, estimated glomerular filtration rate

Table 2
Baseline Characteristics According to Quartiles^a of Cystatin C^b among Control Subjects within Each Ethnic Group

	Q ^c	White (n=790)			Black (n=724)			Hispanic (n=366)			Asian/Pacific Islander (n=220)			American Indian (n=90)		
		Value	p-trend	Value	Value	p-trend	Value	Value	p-trend	Value	Value	p-trend	Value	Value	p-trend	Value
Age, mean (SD), yrs	1	63.2 (7.7)	<0.001	59.7 (6.4)	61.4 (7.3)	<0.001	60.4 (6.6)	63.7 (7.6)	0.001	64.1 (7.3)	65.4 (8.6)	0.04	61.8 (9.0)	61.2 (6.6)	0.12	61.2 (6.6)
	2	65.5 (7.0)														
	3	66.1 (6.9)		64.5 (7.4)			61.8 (7.0)			66.2 (5.8)			65.9 (5.6)			
	4	69.5 (6.5)		66.4 (8.1)			66.6 (6.9)			68.5 (7.4)			65.4 (6.6)			
High school education or less, %	1	8.8	<0.001	26.1	0.04	45.5	0.32	23.1	0.02	23.1	23.1	0.02	23.1	23.1	0.33	23.1
	2	26.0		23.9			38.2			22.6			40.0			40.0
	3	22.6		32.9			37.1			20.0			27.3			27.3
	4	41.8		43.6			59.5			29.4			54.6			54.6
Current smoker, %	1	7.9	0.02	14.4	0.05	12.7	0.77	3.9	0.73	7.7	7.7	0.73	7.7	7.7	0.99	7.7
	2	3.1		11.2			9.6			10.0			20.0			20.0
	3	6.7		12.5			11.8			0.0			0.0			0.0
	4	4.9		6.5			0.0			5.9			18.0			18.0
7 alcoholic drinks/wk, %	1	18.7	0.005	3.6	0.001	12.7	0.03	5.8	0.13	5.8	5.8	0.13	7.7	7.7	0.79	7.7
	2	13.4		6.6			5.7			6.5			0.0			0.0
	3	9.7		2.7			2.9			0.0			9.1			9.1
	4	7.8		5.1			5.4			5.9			20.0			20.0
Fair to poor health status, %	1	4.4	0.004	17.0	0.001	22.6	0.001	7.7	0.06	16.7	16.7	0.06	16.7	16.7	0.79	16.7
	2	5.2		16.3			20.8			3.2			30.0			30.0
	3	1.9		25.7			31.4			10.0			18.2			18.2
	4	10.8		35.1			30.6			17.7			27.3			27.3
Physical activity, median (IQR), METs/wk	1	14.0 (5.0–26.3)	<0.001	7.2 (1.5–16.7)	0.09	5.9 (1.3–11.3)	0.53	10.8 (3.8–27.7)	0.79	8.8 (5.3–21.3)	8.8 (5.3–21.3)	0.79	8.8 (5.3–21.3)	8.8 (5.3–21.3)	0.53	8.8 (5.3–21.3)
	2	10.2 (2.3–19.9)		6.7 (2.9–15.8)		7.9 (2.9–18.8)		10.5 (3.5–21.3)		4.0 (1.5–7.0)	4.0 (1.5–7.0)		4.0 (1.5–7.0)	4.0 (1.5–7.0)		4.0 (1.5–7.0)
	3	10.3 (4.8–19.5)		6.0 (1.3–15.7)		6.4 (1.0–19.8)		15.4 (10.0–18.5)		10.8 (1.3–21.8)	10.8 (1.3–21.8)		10.8 (1.3–21.8)	10.8 (1.3–21.8)		10.8 (1.3–21.8)
	4	3.9 (1.3–14.1)		3.8 (0.8–11.5)		7.3 (0.8–16.4)		10.8 (7.0–20.8)		5.0 (1.8–15.0)	5.0 (1.8–15.0)		5.0 (1.8–15.0)	5.0 (1.8–15.0)		5.0 (1.8–15.0)
Treated diabetes mellitus, %	1	0.0	0.006	9.8	0.08	9.1	0.94	1.9	0.67	7.7	7.7	0.67	7.7	7.7	0.93	7.7

Q ^c	White (n=790)			Black (n=724)			Hispanic (n=366)			Asian/Pacific Islander (n=220)			American Indian (n=90)		
	Value	p-trend	Value	Value	p-trend	Value	Value	p-trend	Value	Value	p-trend	Value	Value	p-trend	Value
2	1.0		7.5			7.3			6.5			20.0			
3	3.9		11.7			2.9			0.0			9.1			
4	5.8		17.7			10.5			0.0			9.1			
History of fracture, %	1	39.3	0.89	21.4	0.57	17.3	0.19	0.93	25.0	0.93	0.67	30.8	0.67		
	2	30.9		21.7		29.4			9.7			60.0			
	3	38.8		22.7		12.5			10.0			27.3			
	4	37.4		25.0		35.1			29.4			30.0			
History of myocardial infarction, %	1	1.1	0.69	2.7	0.03	0.0	0.11	0.12	1.9	0.12	0.07	30.8	0.07		
	2	3.1		4.3		1.9			3.2			0.0			
	3	0.0		9.1		0.0			0.0			10.0			
	4	2.9		8.9		5.4			11.8			18.2			
History of stroke, %	1	1.1	0.16	0.0	0.03	3.6	0.59	0.12	1.9	0.12	0.68	0.0	0.68		
	2	0.0		7.5		3.6			3.2			10.0			
	3	0.0		5.2		5.7			0.0			18.2			
	4	0.0		7.6		5.4			11.8			0.0			
Past hormone therapy use, %	1	29.7	0.11	15.2	0.17	23.6	0.63	0.49	34.6	0.49	0.49	46.2	0.49		
	2	26.8		20.2		21.8			25.8			30.0			
	3	28.9		22.1		17.1			50.0			45.5			
	4	18.5		22.8		21.1			41.2			27.3			
Current thiazide use, %	1	4.4	0.17	3.6	0.001	0.0	0.57	0.92	0.0	0.92	0.49	15.4	0.49		
	2	5.2		8.5		3.6			6.5			0.0			
	3	7.7		11.7		0.0			0.0			0.0			
	4	8.7		17.7		2.6			0.0			9.1			
Oral daily glucocorticoid use, %	1	1.1	0.86	0.9	0.73	1.8	0.97	0.57	1.9	0.57	--	0.0	--		
	2	0.0		3.2		1.8			3.2			0.0			
	3	1.0		0.0		0.0			0.0			0.0			
	4	1.0		2.5		2.6			0.0			0.0			
2 falls in past 12 mo, %	1	11.2	0.50	14.3	0.77	7.8	0.08	0.47	7.7	0.47	0.06	0.0	0.06		

Q ^c	White (n=790)			Black (n=724)			Hispanic (n=366)			Asian/Pacific Islander (n=220)			American Indian (n=90)		
	Value	p-trend		Value	p-trend		Value	p-trend		Value	p-trend		Value	p-trend	
2	10.3			8.7			18.9			19.4			10.0		
3	16.5			13.7			25.0			0.0			18.2		
4	15.2			15.6			18.9			11.8			18.2		
BMI, mean (SD), kg/m ²	1	25.2 (4.4)	<0.001	29.0 (6.2)	0.001		26.6 (5.6)	0.02		23.4 (4.4)	0.32		27.8 (5.1)	0.11	
	2	25.9 (4.1)		30.0 (6.8)			28.6 (8.3)			26.5 (8.6)			29.5 (8.1)		
	3	27.0 (5.2)		31.0 (6.4)			29.4 (5.5)			23.1 (3.5)			28.8 (5.7)		
	4	30.7 (6.8)		32.1 (7.3)			29.9 (6.4)			25.3 (5.8)			32.8 (8.3)		
Total dietary Ca intake ^d , median (IQR), mg/day	1	831 (561–1226)	0.16	536 (317–807)	0.52		636 (383–1014)	0.18		521 (336–809)	0.55		952 (495–1377)	0.15	
	2	730 (441–1078)		511 (307–741)			697 (421–1059)			468 (327–677)			682 (406–968)		
	3	762 (598–1073)		441 (230–723)			550 (380–1107)			432 (280–733)			385 (286–796)		
	4	731 (496–983)		537 (346–751)			580 (331–743)			561 (255–688)			546 (339–1041)		

^aQuartile cutpoints: 0.75, 0.84, and 0.94 mg/L across all ethnic groups

^bRange of cystatin C levels (mg/L) by ethnicity/race: White (0.53–2.42); Black (0.42–1.85); Hispanic (0.53–1.61); Asian/Pacific Islander (0.51–2.54); American Indian (0.57–2.19)

^cN in each quartile by ethnicity/race: White (167, 188, 202, 233); Black (226, 178, 149, 171); Hispanic (113, 96, 74, 83); Asian/Pacific Islander (108, 53, 27, 32); American Indian (24, 22, 20, 24)

^dDietary plus supplements

Abbreviations: IQR, interquartile range; METs, metabolic equivalent score; BMI, body mass index; Ca, calcium

Table 3
Association between Renal Function and Risk of Fracture According to Ethnic Group

Odds Ratio (95% CI) by Measure of Renal function											
Ethnic Group	Per 1 SD increase in Cystatin C	P	Quartile of Cystatin C				Category of eGFR _{cys-c} (mL/min/1.73m ²) ^e				
			Q1	Q2	Q3	Q4	p-trend	>90	60–90	<60	p-trend
White											
Unadjusted (n=790)	1.20 (1.03–1.41)	0.02	1.00 (referent)	1.17 (0.75–1.83)	1.19 (0.77–1.84)	1.61 (1.04–2.48)	0.03	1.00 (referent)	1.13 (0.84–1.52)	2.15 (1.05–4.41)	0.09
Multivariate ^a (n=790)	1.23 (1.04–1.46)	0.02	1.00 (referent)	1.21 (0.76–1.93)	1.26 (0.80–1.97)	1.71 (1.09–2.70)	0.02	1.00 (referent)	1.16 (0.85–1.58)	2.46 (1.16–5.21)	0.05
Black											
Unadjusted (n=724)	1.15 (1.00–1.32)	0.06	1.00 (referent)	0.89 (0.59–1.33)	0.95 (0.60–1.48)	1.17 (0.74–1.84)	0.48	1.00 (referent)	0.95 (0.68–1.34)	2.20 (0.94–5.13)	0.39
Multivariate ^a (n=724)	1.12 (0.98–1.30)	0.11	1.00 (referent)	0.86 (0.57–1.29)	0.88 (0.55–1.39)	1.12 (0.71–1.77)	0.60	1.00 (referent)	0.94 (0.67–1.32)	2.06 (0.87–4.87)	0.49
Hispanic											
Unadjusted (n=366)	1.04 (0.84–1.29)	0.73	1.00 (referent)	0.71 (0.41–1.23)	1.13 (0.63–2.05)	1.18 (0.63–2.22)	0.45	1.00 (referent)	1.16 (0.73–1.85)	0.97 (0.30–3.09)	0.67
Multivariate ^a (n=366)	1.04 (0.83–1.30)	0.76	1.00 (referent)	0.69 (0.39–1.20)	1.22 (0.66–2.26)	1.17 (0.62–2.23)	0.42	1.00 (referent)	1.55 (0.72–1.86)	0.90 (0.28–2.97)	0.72
Asian/Pacific Islander											
Unadjusted (n=220)	0.85 (0.60–1.21)	0.37	1.00 (referent)	0.64 (0.32–1.30)	1.53 (0.64–3.65)	0.87 (0.38–1.97)	0.95	1.00 (referent)	0.85 (0.41–1.80)	0.65 (0.11–3.89)	0.55
Multivariate ^b (n=220)	0.75 (0.50–1.12)	0.16	1.00 (referent)	0.54 (0.26–1.13)	1.39 (0.56–3.45)	0.59 (0.24–1.44)	0.42	1.00 (referent)	0.71 (0.32–1.56)	0.49 (0.08–3.24)	0.29
American Indian											
Unadjusted (n=90)	1.04 (0.69–1.57)	0.86	1.00 (referent)	1.46 (0.45–4.74)	0.84 (0.21–3.46)	1.52 (0.43–5.38)	0.69	1.00 (referent)	0.76 (0.29–1.96)	1.27 (0.19–8.31)	0.85
Multivariate ^c (n=90)	1.04 (0.69–1.57)	0.86	1.00 (referent)	1.46 (0.45–4.74)	0.84 (0.21–3.46)	1.52 (0.43–5.38)	0.69	1.00 (referent)	0.76 (0.29–1.96)	1.27 (0.19–8.31)	0.85

Matched on age, blood draw date, and race/ethnicity

^a Adjusted for history of fracture

^b Adjusted for health status

^c Same as unadjusted model

^d Quartile cutpoints: 0.75, 0.84, and 0.94 mg/L

^e eGFR_{cys-c} = 7.67 x (cystatin C)^{−1.19}

Abbreviations: eGFR, estimated glomerular filtration rate

Table 4

Effect of Calcitropic Hormones and Inflammatory Markers on Association between Renal Function and Risk of Fracture among White Women

	Odds Ratio (95% CI) by Measures of Renal function						
	N	Per 1 SD increase in Cystatin C	P	Category of eGFR _{cyst-c} (mL/min/1.73m ²)			p-trend
				>90	60–90	<60	
Base Model ^a	790	1.23 (1.04–1.46)	0.02	1.00 (referent)	1.16 (0.85–1.58)	2.46 (1.16–5.21)	0.05
Base Model + 25(OH)D and PTH	790	1.22 (1.03–1.45)	0.02	1.00 (referent)	1.16 (0.85–1.58)	2.44 (1.14–5.21)	0.06
Base Model + IL-6sR	786	1.22 (1.02–1.46)	0.03	1.00 (referent)	1.16 (0.84–1.59)	2.27 (1.05–4.90)	0.08
Base Model + TNF-sR1	782	1.09 (0.85–1.40)	0.49	1.00 (referent)	1.03 (0.72–1.47)	1.64 (0.60–4.48)	0.68
Base Model + TNF-sR2	786	1.06 (0.85–1.32)	0.63	1.00 (referent)	0.97 (0.68–1.39)	1.40 (0.57–3.48)	0.87
Base Model + TNF-sR1 and TNF-sR2	774	1.07 (0.83–1.37)	0.59	1.00 (referent)	0.98 (0.68–1.43)	1.62 (0.59–4.46)	0.81
Base Model + TNF-sR1, TNF-sR2, IL-6sR, 25(OH)D and PTH	772	1.08 (0.84–1.39)	0.57	1.00 (referent)	0.99 (0.68–1.43)	1.59 (0.57–4.42)	0.82

^aMatched on age, blood draw date, and race/ethnicity; adjusted for history of fracture

Abbreviations: eGFR, estimated glomerular filtration rate