Kidney Function and Prevalent and Incident Frailty


Summary

Background and objectives Kidney disease is associated with physiologic changes that may predispose to frailty. This study sought to investigate whether lower levels of kidney function were associated with prevalent or incident frailty in Cardiovascular Health Study (CHS) participants.

Design, setting, participants, & measurements CHS enrolled community-dwelling adults age ≥65 years between 1989–1990 and 1992–1993. To examine prevalent frailty, included were 4150 participants without stroke, Parkinson disease, prescribed medications for Alzheimer disease or depression, or severely impaired cognition. To examine incident frailty, included were a subset of 3459 participants without baseline frailty or development of exclusion criteria during follow-up. The primary predictor was estimated GFR (eGFR) calculated using serum cystatin C (eGFRcys). Secondary analyses examined eGFR using serum creatinine (eGFRSCr). Outcomes were prevalent frailty and incident frailty at 4 years of follow-up. Frailty was ascertained on the basis of weight loss, exhaustion, weakness, slowness, and low physical activity.

Results The mean age was 75 years and the median eGFRcys was 73 ml/min per 1.73 m². Among participants with an eGFRcys <45 ml/min per 1.73 m², 24% had prevalent frailty. In multivariable analysis and compared with eGFRcys ≥90 ml/min per 1.73 m², eGFRcys categories of 45–59 (odds ratio [OR], 1.80; 95% confidence interval [CI], 1.17 to 2.75) and 15–44 (OR, 2.28; 95% CI, 1.72 to 2.75) were associated with higher odds of frailty, whereas 60–75 (OR, 1.44; 95% CI, 0.76 to 1.70) was not. In multivariable analysis, eGFRcys categories of 60–75 (incidence rate ratio [IRR], 1.72; 95% CI, 1.07 to 2.75) and 15–44 (IRR, 2.28; 95% CI, 1.23 to 4.22) were associated with higher incidence of frailty whereas 45–59 (IRR, 1.53; 95% CI, 0.90 to 2.60) was not. Lower levels of eGFRSCr were not associated with a higher risk of prevalent or incident frailty.

Conclusions In community-dwelling elders, lower eGFRcys was associated with a higher risk of prevalent and incident frailty whereas lower eGFRSCr was not. These findings highlight the importance of considering non-GFR determinants of kidney function.

Introduction

CKD affects a large segment of the aged population (1), and older adults may be more vulnerable to the metabolic and hormonal disturbances associated with kidney disease. Although CKD is known to affect cardiovascular disease risk, in older adults it has also been associated with noncardiovascular complications, poor physical functioning, and unsuccessful aging (2–5). Of interest is whether kidney function is independently associated with frailty, defined as a lack of physiologic reserve. Identifying and clearly delineating whether kidney function is associated with frailty are important for the clinical care of older adults living with CKD. Frailty is also a strong risk factor for the development of disability and death (6).

Few studies have examined whether kidney function is independently associated with frailty, and these studies have been limited by the use of serum creatinine–based estimates of kidney function, the examination of a referred population, and/or the use of modified frailty criteria (7–9). The misclassification of kidney function with use of serum creatinine is a particular concern for examining frailty because unintentional weight loss, poor physical function, and weakness are more likely to be associated with low muscle mass and low serum creatinine independent of kidney function, therefore obscuring the relation between kidney function and frailty.

In this study, we examined whether lower levels of kidney function, as estimated by serum cystatin C, were associated with the risk of prevalent or incident frailty in Cardiovascular Health Study (CHS) participants. In secondary analyses, we examined the association between kidney function, as estimated by serum creatinine, and prevalent or incident frailty.

Materials and Methods

Study Population

The CHS is a prospective cohort study of adults 65 years and older living in the community. Participants were initially recruited between 1989 and 1990 from Forsyth County, North Carolina; Sacramento County,
California; Washington County, Maryland; and Pittsburgh, Pennsylvania. An additional 687 African American participants were enrolled between 1992 and 1993. To be eligible participants had to provide informed consent; had to intend to remain within the enrollment area for at least 3 years; and could not be institutionalized, using a wheelchair within the home, receiving chemotherapy or radiation for cancer, or receiving hospice care. The study design and recruitment have been described in detail (10,11). The CHS was approved by institutional review boards at each participating clinical center and the University of Washington coordinating center. Participants provided informed consent.

To examine the association between kidney function and prevalent frailty, we restricted the CHS cohort to participants who presented for the year 3 (1992–1993) evaluation. We chose year 3 as the baseline to ensure equal length of follow-up for incident frailty between the original cohort enrolled at year 0 (1989–1990) and the African American cohort enrolled at year 3 (1992–1993). We further excluded participants for the following: Parkinson disease, stroke, prescribed medications for Parkinson disease, Alzheimer disease or depression, a Mini-Mental State Examination score <18, or a modified Mini-Mental State Examination score <60; these exclusion criteria were applied to be consistent with the exclusion criteria used to validate the frailty phenotype in CHS (6). We further excluded patients with fewer than three frailty components measured, missing serum cystatin C or baseline estimated GFR (eGFR) (calculated using serum cystatin C [eGFR_{cys}] <15 ml/min per 1.73 m². To examine the incidence of frailty, the cohort was further restricted to those without baseline frailty and those without interval development of the exclusion criteria used to validate the frailty phenotype between years 3 and 7 of the study.

Figure 1. | Cohort selection. The selection of Cardiovascular Health Study participants to examine the association between kidney function and prevalent frailty. eGFR_{cys}, estimated GFR using cystatin C; MMSE, Mini-Mental State Examination; 3MSE, modified Mini-Mental State Examination.
Data Collection

Extensive baseline data were collected, including information on age, sex, self-reported race, coexisting illnesses, body composition, habits, medications, laboratory measures, and physical and cognitive function. Participants underwent semi-annual evaluation by telephone contact alternating with comprehensive annual examinations. Details regarding measures, data collection, and laboratory specimen collection and processing have previously been described in detail (10,12,13).

Exposure and Outcome

The primary exposure of interest was kidney function estimated by serum cystatin C. Serum cystatin C concentration was measured by particle-enhanced immunonephelometric assay (N Latex Cystatin C, Siemens; www.usa.siemens.com) and GFR was estimated using the 2008 CKD-Epidemiology Collaboration (CKD-EPI) cystatin C equation without demographic coefficients: $\text{eGFR}_{\text{Cys}} = 76.7 \times \text{CysC}^{-1.19}$ (14). Although more recent equations have been developed, the 2008 CKD-EPI cystatin C equation was used in numerous prior reports from the CHS cohort and thus offers continuity with studies evaluating other outcomes. In sensitivity analyses, we compared results with the 2012 CKD-EPI cystatin C equation, which includes coefficients for age and sex (15). In secondary analyses, we estimated kidney function using the 2009 CKD-EPI creatinine equation ($\text{eGFR}_{\text{SCr}}$) (16).

The primary outcome of interest was frailty. Frailty was ascertained using previously validated criteria and defined as having at least three of five components: (1) shrinking: unintentional weight loss of $\geq$10 pounds or 5% in the past year; (2) poor endurance and energy: assessed using two questions from the Centers for Epidemiologic Studies–Depression scale; (3) weakness: grip strength in the lowest 20% adjusted for sex and body mass index; (4) slowness:
slowest 20% in the 15-foot walk adjusted for sex and height; and (5) low physical activity: lowest quintile for physical activity for each sex (6). The components of frailty were examined at the beginning of our study (year 3 of CHS) and after 4 years (year 7 of CHS).

**Statistical Analyses**

We examined the association between kidney function and prevalent frailty using logistic regression. Kidney function was examined continuously and by categories: 15–44, 45–59, 60–75, 76–89, and \( \geq 90 \) ml/min per 1.73 m\(^2\). We examined stepwise logistic regression models: model 1, adjusted for age, sex, race; model 2, further adjusted for potential confounders, including diabetes mellitus, hypertension, coronary heart disease, heart failure, smoking, and body mass index; and model 3, further adjusted for potential mediators, including C-reactive protein, hemoglobin, albumin, LDL cholesterol, and HDL cholesterol. Potential mediators were selected on the basis of prior studies. We examined the association between kidney function and the incidence of frailty using stepwise Poisson regression models, similar to the analyses of prevalent frailty. Poisson regression models were tested for overdispersion, of which there was no evidence. Participants with missing data were excluded from multivariate models requiring those elements. The numbers of participants with incomplete data were as follows: smoking history (n=75), education (n=8), hypertension (n=6), and diabetes history (n=56). The overall prevalence of frailty did not differ between those with and without missing data. To examine whether the association between kidney function and prevalent or incident frailty was modified by age, sex,
or race, interaction terms were included and tested for significance.

Statistical analyses were performed using S-Plus (version 8.0, Tibco, Seattle, WA) and SPSS statistical software (version 15.0.1.1, SPSS, Inc., Chicago, IL).

**Results**

We included 4150 CHS participants in our study of prevalent frailty (Figure 1). The mean age was 75 years, 41% of participants were male, 17% were black, and the median eGFR_cys was 73 ml/min per 1.73 m². Of these patients, 22% had an eGFR_cys of 15–59 ml/min per 1.73 m². Participants with the lowest kidney function tended to be older and more likely to have hypertension, coronary heart disease, and heart failure (Table 1). The prevalence of frailty was higher in those with lower levels of kidney function (Figure 2A). For each level of eGFR_cys, women had a higher prevalence of frailty than men (Figure 2B). There was a graded association between categories of eGFR_cys and prevalent frailty, with the highest odds of frailty in those with the lowest kidney function. In multivariable analysis adjusting for potential confounders, eGFR_cys categories of 45–59 and 15–44 ml/min per 1.73 m² were associated with 80% and 187% higher odds of frailty, respectively, compared with an eGFR_cys ≥90 ml/min per 1.73 m². Further adjustment for potential mediators did not materially alter these associations (Table 2). The association between kidney function and prevalent frailty was not modified by age, sex, or race (P for interaction = 0.41, 0.94, and 0.56). When the individual components of frailty were examined, lower kidney function was associated with higher odds of weight loss, exhaustion, walking slowness, and low physical activity (Table 3).

The cohort was further restricted to examine the incidence of frailty. Participants with prevalent frailty (n=379) or those who developed stroke or cognitive deficits or were prescribed medications for depression, Parkinson disease, or Alzheimer disease during follow-up (n=312) were excluded, resulting in a cohort of 3459 participants. During follow-up, 214 (6%) participants became frail and 318 (9%) died. The rate of death was highest in participants with the lowest level of kidney function. During follow-up, 32% of participants with an eGFR_cys of 15–44 ml/min per 1.73 m² died compared with only 5% of those with an eGFR_cys ≥90 ml/min per 1.73 m².

In the demographic-adjusted analysis, the eGFR_cys categories <76 ml/min per 1.73 m² were associated with higher risk of incident frailty. After adjustment for potential confounders, eGFR_cys categories of 60–75 and 15–44 were associated with 72% and 128% higher incidence of frailty, respectively, compared with an eGFR_cys ≥90 ml/min per 1.73 m². Further adjusting for potential mediators did not materially alter these associations (Table 4). The association between kidney function and incident frailty did not differ by age, sex, or race (P=0.11, 0.78, and 0.13).

When we repeated analyses using the 2012 CKD-EPI cystatin C equation, associations with prevalent frailty were smaller in magnitude for the eGFR_{CKD-EPI}\textsubscript{CYS} 45–59 (odds ratio [OR], 1.47; 95% confidence interval [CI], 0.89 to 2.43) and 15–44 (OR, 2.44; 95% CI, 1.43 to 4.19) categories and no longer statistically significant for those with an eGFR_{CKD-EPI}\textsubscript{CYS} ≥45 ml/min per 1.73 m² (Supplemental Table 2). The association between kidney function and incident frailty did not differ by age, sex, or race (P=0.11, 0.78, and 0.13).

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### Table 2. The association between kidney function (estimated GFR using cystatin C) and prevalent frailty

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Participants (n)</th>
<th>Patients with Frailty (n)</th>
<th>OR (95% CI)</th>
<th>OR Further Adjusted for Potential Mediators^c (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous eGFR_{cys} per 10 ml/min per 1.73 m² decrease</td>
<td>4150</td>
<td>379</td>
<td>1.33 (1.25 to 1.42)</td>
<td>1.26 (1.17 to 1.35)</td>
</tr>
<tr>
<td>Category of eGFR_{cys}</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;76 ml/min per 1.73 m²</td>
<td>715</td>
<td>44</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>76–89 ml/min per 1.73 m²</td>
<td>1155</td>
<td>67</td>
<td>0.92 (0.61 to 1.38)</td>
<td>0.92 (0.61 to 1.39)</td>
</tr>
<tr>
<td>90–99 ml/min per 1.73 m²</td>
<td>1366</td>
<td>108</td>
<td>1.29 (0.89 to 1.88)</td>
<td>1.22 (0.83 to 1.81)</td>
</tr>
<tr>
<td>100–109 ml/min per 1.73 m²</td>
<td>693</td>
<td>106</td>
<td>2.60 (1.77 to 3.83)</td>
<td>2.69 (1.77 to 3.83)</td>
</tr>
<tr>
<td>110–119 ml/min per 1.73 m²</td>
<td>221</td>
<td>54</td>
<td>4.93 (3.14 to 7.77)</td>
<td>4.93 (3.14 to 7.77)</td>
</tr>
</tbody>
</table>

^a Age, sex, and race.
^b Further adjusted for smoking, body mass index, diabetes mellitus, hypertension, coronary heart disease, and heart failure.
^c Further adjusted for C-reactive protein, hemoglobin, albumin, LDL cholesterol, and HDL cholesterol.
75, 76

The components of prevalent frailty associated with a significantly lower risk of prevalent frailty compared with an eGFRSCr $\geq$ 90 ml/min per 1.73 m$^2$. Lower levels of eGFRSCr were not significantly associated with prevalent frailty. An eGFR SCr of 76–89 was associated with a significantly lower risk of incident frailty compared with an eGFRSCr $\geq$ 90 ml/min per 1.73 m$^2$ whereas other levels of eGFRSCr were not associated with incident frailty (Supplemental Tables 3 and 4).

We found substantial reclassification of kidney function when using eGFR$_{\text{cys}}$ compared with eGFR$_{\text{SCr}}$, with 55% of participants reclassified into a different category of kidney function based on the following groups: 15–44, 45–59, 60–75, 76–89, and $\geq$ 90 ml/min per 1.73 m$^2$ (Supplemental Table 5).

**Discussion**

In summary, we found that lower levels of kidney function, as measured by eGFR$_{\text{cys}}$, were independently associated with higher risk of prevalent and incident frailty among older community-dwelling adults. Nearly one fourth of older adults with an eGFR$_{\text{cys}}$ $< 45$ ml/min per 1.73 m$^2$ had prevalent frailty. The components of prevalent frailty associated with low levels of kidney function were exhaustion, low physical activity, walking slowness, and weight loss. Older adults with an eGFR$_{\text{cys}}$ $< 45$ ml/min per 1.73 m$^2$ had a doubling of the risk of incident frailty compared with those with normal kidney function.

The findings were attenuated when we used the 2012 CKD-EPI cystatin C equation adjusted for demographic characteristics. However, the 2012 CKD-EPI cystatin C equation was not derived in an elderly cohort, and the age coefficient may not be optimal in elderly cohorts; using the 2012 CKD-EPI cystatin C equation resulted in a higher number of participants being classified into lower levels of kidney function. Of note, the odds ratios and incidence rate ratios associated with each 10 ml/min per 1.73 m$^2$ lower level of kidney function were nearly identical when we compared the 2008 CKD-EPI cystatin C equation without demographic coefficients and the 2012 CKD-EPI cystatin C equation.

We did not observe lower levels of eGFR$_{\text{SCr}}$ to be associated with a higher risk of prevalent frailty. Instead, we found an eGFR$_{\text{sc}}$ over 60–89 ml/min per 1.73 m$^2$ was associated with a significantly lower risk of prevalent frailty compared with an eGFR$_{\text{SCr}}$ $\geq$ 90 ml/min per 1.73 m$^2$. Similarly, an eGFR$_{\text{SCr}}$ of 76–89 was associated with a significantly lower risk of incident frailty compared with an eGFR$_{\text{SCr}}$ $\geq$ 90 ml/min per 1.73 m$^2$.

One explanation for the difference in findings between eGFR$_{\text{SCr}}$ and eGFR$_{\text{cys}}$ is the reclassification of kidney function with use of serum creatinine–based versus cystatin C–based estimates of kidney function, as 55% of participants in our cohort were in discrepant categories of kidney function based on the two measures. These findings highlight the importance of considering non-GFR determinants of kidney function measurements, in particular muscle mass, for examining outcomes such as frailty. Of note, eGFR$_{\text{SCr}}$ may not be an accurate measurement of kidney function in elderly adults with low muscle mass, and alternative markers of glomerular filtration, such as cystatin C, may be particularly important in this setting (17). Similar to the 2012 CKD-EPI cystatin C equation, the CKD-EPI eGFR$_{\text{SCr}}$ equation was not developed in an elderly cohort, and therefore the age coefficient may not be accurate in elderly cohorts such as ours. Because creatinine is known to be influenced by health status and muscle mass, we believe cystatin C is a better marker of GFR. We chose the 2008 CKD-EPI cystatin C equation because it does not impose interactions of age and sex with cystatin C in estimating kidney function. Similar to our findings in this study, we have previously shown that eGFR$_{\text{cys}}$ estimated using the 2008 CKD-EPI equation without demographic coefficients is highly linked to adverse outcomes in the

Table 3. Cross-sectional association between kidney function (estimated GFR using cystatin C) and individual components of frailty

<table>
<thead>
<tr>
<th>Frailty Component</th>
<th>Unadjusted OR (95% CI)</th>
<th>OR Adjusted for Demographic Characteristics$^a$ (95% CI)</th>
<th>OR Further Adjusted for Confounders$^b$ (95% CI)</th>
<th>OR Further Adjusted for Potential Mediators$^c$ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exhaustion</td>
<td>1.09 (1.04 to 1.13)</td>
<td>1.11 (1.05 to 1.16)</td>
<td>1.08 (1.03 to 1.13)</td>
<td>1.07 (1.02 to 1.13)</td>
</tr>
<tr>
<td>Low physical activity</td>
<td>1.12 (1.08 to 1.17)</td>
<td>1.13 (1.08 to 1.18)</td>
<td>1.09 (1.04 to 1.14)</td>
<td>1.09 (1.04 to 1.14)</td>
</tr>
<tr>
<td>Walking slowness</td>
<td>1.26 (1.20 to 1.31)</td>
<td>1.25 (1.19 to 1.31)</td>
<td>1.20 (1.14 to 1.26)</td>
<td>1.18 (1.12 to 1.24)</td>
</tr>
<tr>
<td>Weakness</td>
<td>1.14 (1.09 to 1.19)</td>
<td>1.06 (1.01 to 1.11)</td>
<td>1.03 (0.98 to 1.08)</td>
<td>1.02 (0.97 to 1.07)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>1.14 (1.05 to 1.22)</td>
<td>1.09 (1.01 to 1.18)</td>
<td>1.15 (1.06 to 1.25)</td>
<td>1.13 (1.04 to 1.23)</td>
</tr>
</tbody>
</table>

Odds ratio for each frailty component associated with continuous eGFR$_{\text{cys}}$ per 10 ml/min per 1.73 m$^2$ decrease. OR, odds ratio; CI, confidence interval.

$^a$Age, sex, and race

$^b$Further adjusted for smoking, body mass index, diabetes mellitus, hypertension, coronary heart disease, and heart failure.

$^c$Further adjusted for C-reactive protein, hemoglobin, albumin, LDL cholesterol, and HDL cholesterol.

Table 1). An eGFR$_{\text{cys}}$ $< 76$ ml/min per 1.73 m$^2$ was moderately associated with incident frailty in the demographic-adjusted model but not in the fully adjusted models (Supplemental Table 2).

In secondary analyses, we examined the association between serum creatinine–based estimates of kidney function and frailty in participants with measured serum creatinine ($n=4085$). We found an eGFR$_{\text{SCr}}$ of 60–89 ml/min per 1.73 m$^2$ was associated with a significantly lower risk of prevalent frailty compared with an eGFR$_{\text{SCr}}$ $\geq$ 90 ml/min per 1.73 m$^2$. Lower levels of eGFR$_{\text{SCr}}$ were not significantly associated with prevalent frailty. An eGFR$_{\text{SCr}}$ of 76–89 was associated with a significantly lower risk of prevalent frailty compared with an eGFR$_{\text{SCr}}$ $\geq$ 90 ml/min per 1.73 m$^2$ whereas other levels of eGFR$_{\text{SCr}}$ were not associated with incident frailty (Supplemental Tables 3 and 4).

We found substantial reclassification of kidney function when using eGFR$_{\text{cys}}$ compared with eGFR$_{\text{SCr}}$, with 55% of participants reclassified into a different category of kidney function based on the following groups: 15–44, 45–59, 60–75, 76–89, and $\geq$ 90 ml/min per 1.73 m$^2$ (Supplemental Table 5).
Table 4. Association between kidney function (estimated GFR using cystatin C) and incident frailty

<table>
<thead>
<tr>
<th>Patients with Frailty (n)</th>
<th>Total Patients (n)</th>
<th>Unadjusted IRR Further Adjusted for Potential Mediators&lt;sup&gt;a&lt;/sup&gt; (£95% CI)</th>
<th>Further Adjusted for Potential Mediators&lt;sup&gt;b&lt;/sup&gt; (£95% CI)</th>
<th>Further Adjusted for Potential Mediators&lt;sup&gt;c&lt;/sup&gt; (£95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>214</td>
<td>3459</td>
<td>1.18 (1.09 to 1.27)</td>
<td>1.09 (1.00 to 1.18)</td>
<td>1.09 (1.00 to 1.18)</td>
</tr>
</tbody>
</table>

**Continuous eGFR<sub>cys</sub> per 10 ml/min decrease**

- 23 ml/min: 1.49 (0.92 to 2.39) (95% CI)
- 35 ml/min: 1.62 (1.15 to 2.33) (95% CI)
- 47 ml/min: 1.82 (1.33 to 2.48) (95% CI)
- 59 ml/min: 2.19 (1.53 to 3.59) (95% CI)

**Category of eGFR<sub>cys</sub>**

- 60–75 ml/min per 1.73 m<sup>2</sup>: 1.90 (1.20 to 3.00) (95% CI)
- 45–59 ml/min per 1.73 m<sup>2</sup>: 2.00 (1.21 to 3.31) (95% CI)
- 30–44 ml/min per 1.73 m<sup>2</sup>: 2.19 (1.33 to 3.59) (95% CI)

**IRR, incidence rate ratio; eGFR<sub>cys</sub>, estimated glomerular filtration rate using serum cystatin C.**

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**Stepped wedge cluster randomized trial**

- IRR, incidence rate ratio; eGFR<sub>cys</sub>, estimated glomerular filtration rate using serum cystatin C.
- Further adjusted for C-reactive protein, hemoglobin, albumin, LDL cholesterol, and HDL cholesterol.

**Compared with these earlier studies using serum creatinine, we used a more precise measure of kidney function, serum cystatin C, and found a strong and graded association.**

- Compared with the CKD-EPI equation with cystatin C, age, sex, and race (7). In their study, the relative prevalence of frailty was 2.1- and 2.8-fold higher for participants with an eGFR <30 and 30–44 ml/min per 1.73 m<sup>2</sup>, respectively, compared with an eGFR >60 ml/min per 1.73 m<sup>2</sup> (7).

- Wilhelm-Leen et al. (9) estimated kidney function using the Mayo quadratic equation and found that 21% of participants in the Third National Health and Nutrition Examination Survey with an eGFR <45 ml/min per 1.73 m<sup>2</sup> were frail according to modified frailty criteria. In a previous study of CHS participants, we found serum creatinine ≥1.5 mg/dl in men and 1.3 mg/dl in women to be associated with a nearly 80% higher odds of prevalent frailty (8). Roshanravan et al. examined 336 Seattle Kidney Study participants, a cohort of patients referred for nephrology care, and estimated kidney function using the CKD-EPI equation with cystatin C, age, sex, and race (7). In their study, the relative prevalence of frailty was 2.1- and 2.8-fold higher for participants with an eGFR <30 and 30–44 ml/min per 1.73 m<sup>2</sup>, respectively, compared with an eGFR >60 ml/min per 1.73 m<sup>2</sup> (7).

- Compared with these earlier studies using serum creatinine, we used a more precise measure of kidney function, serum cystatin C, and found an eGFR<sub>cys</sub> 60–75 and 15–44 ml/min per 1.73 m<sup>2</sup> may be due to a lack of power given the small number of participants with more advanced CKD or chance variability resulting in a nonsignificant association.

**Our study makes important contributions to the current field of research.** We examined the association between kidney function and frailty in an elderly cohort using a more precise estimate of kidney function, cystatin C, and found a strong and graded association. This finding was completely obscured when evaluated by a more common estimate of kidney function based on serum creatinine. Our study is one of only two studies to examine the association between cystatin C and prevalent frailty, and ours is unique because of its setting within a sample of community-dwelling elders and use of the original validated criteria for frailty. Our study is the first to evaluate incident frailty and to uncover an independent association between lower levels of kidney function and a higher risk of incident frailty—an important finding that warrants further study. Our findings highlight that frailty is not a phenomena that starts with dialysis initiation, but, like many complications of CKD, the processes begin before the need for renal replacement therapy. Our study makes important contributions to the care of older patients with CKD because it highlights the notably high prevalence of frailty and the heightened risk for incident frailty in this special
population and informs their care and management. Reduced kidney function may be related to accelerated loss of lean muscle mass (20), which is thought to be an underlying process in frailty (21). Further examining whether specific interventions in this population, aimed at mitigating or preventing the development of frailty, warrant specific study as frailty in CKD has been linked to a higher risk of dialysis therapy or death (7).

Our study had many strengths. We used a measure of kidney function, serum cystatin C, that is not related to muscle mass, a particularly important consideration for examining conditions such as frailty. We had comprehensive ascertainment of coexisting illnesses, allowing for appropriate exclusions and adjustment for potential confounders. We used validated and well accepted criteria to identify frailty. Last, we examined incident frailty, allowing us to further elaborate on the relation between kidney function and frailty.

Our study had limitations that warrant consideration. Our examination of the association between kidney function and prevalent frailty was cross-sectional in nature and as such cannot establish causality. Frailty was reassessed at 4 years after the start of our study, and we cannot exclude that participants developed frailty and died before reassessment for frailty; this may have occurred disproportionately among those with the lowest kidney function, obscuring the association between kidney function and frailty and contributing to an underestimate of the true incidence of frailty. In addition, some diseases we considered as confounders, such as hypertension and heart failure, may actually be mediators, thereby attenuating the observed association between kidney function and frailty. Additionally, the longitudinal analysis examined kidney function only at one point in time. Participants with worse kidney function may be more likely to have subsequent declines in kidney function, and our study does not capture the impact of trajectories of decline in kidney function on incident frailty. Furthermore, we cannot exclude the possibility that unmeasured non-GFR determinants of cystatin C account for some of the observed association between eGFRcys and frailty. Last, we did not have measures of urinary protein and therefore cannot examine whether the association between levels of kidney function and frailty are modified by the presence of proteinuria.

In summary, kidney function is independently associated with prevalent and incident frailty. Our findings highlight the importance of considering and assessing for frailty in older adults with CKD.

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Disclosures
None.

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