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Reduced renal function and sleep-disordered breathing in community-dwelling elderly men

Muna T. Canales^{a,*}, Brent C. Taylor^{b,c}, Areef Ishani^{a,c}, Reena Mehra^d, Michael Steffes^e, Katie L. Stone^f, Susan Redline^g, Kristine E. Ensrud^{a,b,c}, and For the Osteoporotic Fractures in Men (MrOS) Study Group

^aDivision of Renal Diseases and Hypertension, Department of Medicine, University of Minnesota, MMC 736 Mayo Building, 420 Delaware Street S.E., Minneapolis, MN, USA

^bDivision of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN, USA

^cCenter for Chronic Disease Outcomes Research, Veterans Affairs Medical Center, Minneapolis, MN, USA

^dDepartment of Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, Case Western Reserve University, Cleveland, OH, USA

^eDepartment of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, USA

^fCalifornia Pacific Medical Center Research Institute, San Francisco, CA, USA

^gDepartments of Pediatrics, Medicine, and Epidemiology & Biostatistics, Case Western Reserve University, Cleveland, OH, USA

Abstract

Background—Sleep-disordered breathing (SDB) may increase the risk of cardiovascular disease (CVD) and death in chronic kidney disease (CKD). However, the association between mild reductions in renal function and SDB is uncertain.

Methods—We studied 508 community-dwelling men aged ≥ 67 years (mean 76.0 ± 5.3) who were enrolled at the Minnesota site for the Minneapolis center of the Outcomes of Sleep Disorders in Older Men (MrOS) sleep study and had serum cystatin-C and creatinine measured coincident with overnight polysomnography. CKD was defined as estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m² using Cockcroft-Gault (CG), modification of diet in renal disease (MDRD) and Mayo Clinic formulae. SDB was defined by a respiratory disturbance index (RDI) ≥ 15 events/h.

Results—Mean cystatin-C was 1.21 ± 0.30 mg/L, and mean creatinine was 1.09 ± 0.23 mg/dL. Median RDI was 7.0 events/h (range 0–73). Higher quartiles of cystatin-C were associated with higher mean RDI (p for trend = 0.007). This association persisted after adjustment for age and race (p for trend = 0.03), but not after adjustment for body mass index (BMI, p for trend = 0.34). After adjusting for age, race, BMI, diabetes, hypertension, and CVD, CKD defined by the Mayo Clinic formula, but not CG or MDRD, was associated with a higher odds of SDB [odds ratio (OR) 1.95, 95% confidence interval (CI) 1.04–3.65, $p = 0.04$].

Conclusions—Older men with reduced renal function as defined by higher cystatin-C concentration have higher average RDI. This effect is explained by higher BMI in men with higher

cystatin-C. CKD defined by the Mayo Clinic formula is independently associated with twofold higher odds for SDB. Therefore, reduced renal function may be associated with SDB in older men.

Keywords

Chronic kidney disease; Kidney dysfunction; Cystatin-C; Sleep disorders; Sleep-disordered breathing; Sleep apnea syndromes

1. Introduction

Chronic kidney disease (CKD), as defined by an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m², is common in older adults, affecting 20% of individuals over 65 years of age in the United States [1]. CKD and reductions in renal function as defined by higher concentrations of cystatin-C have been linked to increased cardiovascular disease (CVD) risk and mortality as well as all-cause mortality [2,3]. Traditional cardiovascular risk factors such as diabetes, hypertension, hyperlipidemia and smoking do not completely explain this increased risk [4,5]. It has been hypothesized that non-traditional risk factors, such as sleep-disordered breathing (SDB), might explain the excess mortality risk in patients with CKD [4]. However, few studies have examined the association between renal function and SDB.

Prior studies in individuals with end-stage kidney disease undergoing dialysis have reported a prevalence of SDB between 30% and 80%, far exceeding that of the general population [6-8]. In addition, it has been reported that over 50% of patients with severe CKD, who do not require dialysis, have mild SDB [9]. However, most of these investigations are limited by small sample sizes with no comparison group or lack of applicability to patients with mild renal disease [9, 10]. To our knowledge, no prior study has evaluated the association between mild to moderate impairments in renal function and SDB in community-dwelling older adults.

To determine whether mild to moderate reductions in renal function were associated with a higher likelihood of SDB in older men, we measured serum cystatin-C, serum creatinine (SCr) and performed overnight polysomnography in a cohort of 508 men aged ≥ 67 years, who were enrolled in the Minneapolis center for the Outcomes of Sleep Disorders in Older Men (MrOS Sleep) study. We hypothesized that higher serum cystatin-C level or presence of CKD would be associated with a higher likelihood of SDB as measured by the respiratory disturbance index (RDI).

2. Methods

2.1. Participants

The Osteoporotic Fractures in Men (MrOS) Study, the parent cohort for the MrOS Sleep Study, enrolled 5995 community-dwelling men aged 65 years and older between March 2000 and April 2002 [11]. Participants were recruited from six centers in the United States; each center obtained Institutional Review Board-approval for this study. Subjects considered for enrollment in MrOS had to be able to walk without the assistance of another person and not have a bilateral hip replacement [11,12].

A total of 3135 men from MrOS were recruited for participation in the MrOS sleep study. Men were screened for use of mechanical devices during sleep, including a pressure mask for sleep apnea (continuous positive airway pressure [CPAP] or bi-level positive airway pressure [BiPAP]), a mouthpiece for snoring or sleep apnea, or oxygen therapy. In general, those who reported nightly use of any of these devices were excluded from the MrOS sleep study; however, 17 men who reported the use of one of these devices but who were able to forego use during the night of the sleep study were included. The 3135 men completed an exam

conducted between December 2003 and March 2005, which included a clinic visit and overnight in-home polysomnography (PSG). Of these men, 2911 had technically adequate PSG, including 512 from the Minneapolis center. Of the 512 men enrolled at the Minneapolis center, 508 men who were not on dialysis ($n = 3$ on dialysis), with measurements of serum cystatin-C and SCr ($n = 1$ missing), were included in this analysis.

2.2. Collection of sleep data and definition of sleep parameters

In-home sleep studies were completed using unattended, portable PSG (Safiro model, Compumedics, Inc.®). The recording montage was as follows: C_3/A_2 and C_4/A_1 electroencephalograms (EEG), bilateral electrooculograms (EOG), and a bipolar submental electromyogram (EMG) to determine sleep status; thoracic and abdominal respiratory inductance plethysmography to determine respiratory effort; airflow (by nasal-oral thermocouple and nasal pressure cannula); finger pulse oximetry; lead I electrocardiogram (EKG); body position (mercury switch sensor); and bilateral leg movements (piezoelectric sensors). Centrally trained and certified staff performed home visits to set up the unit, verify the values of the impedances for each channel, confirm calibration of position sensors and note any problems encountered during set-up, similar to the protocol used in the Sleep Heart Health Study [13]. Staff returned the next morning to collect the equipment and download the data to the Case Reading Center (Cleveland, OH) to be scored by a trained technician.

SDB was defined by RDI. Apnea was defined as complete or nearly complete cessation of airflow (reduction of amplitude to at least $<25\%$ of baseline) for >10 s, and hypopneas were scored if clear reductions in breathing amplitude occurred and lasted >10 s [14]. In these analyses, only apneas and hypopneas that were associated with a 4% or greater desaturation were included in the RDI, which was calculated by dividing the total number of apneas and hypopneas by the total time slept in hours, giving units of events/h. Obstructive apneas were recorded if there was presence of respiratory effort on thoracic or abdominal plethysmography; central apneas were recorded if there was absence of respiratory effort on both of these channels. The central apnea index (CAI) was defined as the total number of central apneic events divided by total sleep time in hours with oxygen desaturation $\geq 4\%$.

2.3. Measurements to estimate renal function

Blood was collected at the sleep visit, initially kept at room temperature for 40-90 min and then centrifuged for 10 min. Within 30 min of centrifuging, serum was separated and frozen at -70°C . Samples never thawed were sent directly to the Clinical Studies Clinical Laboratory at the University of Minnesota Medical Center, Fairview where SCr and cystatin-C assays were performed. Serum cystatin-C concentrations were determined using a BN100 nephelometer (Dade Behring Inc., Deerfield, IL) [15]. The assay range was 0.30-10.00 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%. SCr was measured using the Hitachi 911 analyzer (Roche Diagnostics Corp., Indianapolis, IN) utilizing a variation of the Jaffe enzymatic method. Inter- and intra-assay CVs were 4.0%. Both assays were calibrated daily (Roche Diagnostics Corp.). The SCr assay has been calibrated to be isotope dilution mass spectrometry (IDMS)-traceable [16,17].

GFR was estimated using three creatinine-based formulae: the Cockcroft-Gault (CG) formula, adjusted for body surface area of 1.73 m^2 [18,19]; the abbreviated four variable version of the modification of diet in renal disease (MDRD) formula appropriate for our IDMS-traceable SCr assay [17,20]; and the Mayo Clinic formula [21].

2.4. Other measurements

Candidate variables included in our analysis were collected from the baseline sleep visit for the MrOS sleep study and the accompanying questionnaire except for self-reported race and

prior smoking history, which were collected at the baseline visit for MrOS in 2000-2002. Variables used in this study included demographic factors such as age and race where race was defined as Caucasian, African American or other; body mass index (BMI, kg/m²) as a measure of obesity; habits such as tobacco use; self-reported health status based upon a short-form (SF-12) questionnaire [22]; and medical history including hypertension, self-reported diabetes, and self-reported cardiovascular disease.

2.5. Statistical analysis

Baseline characteristics were examined across quartiles of cystatin-C, and statistical differences across quartiles were calculated using analysis of variance (ANOVA) (Kruskal-Wallis ANOVA was used for the skewed variable RDI) or chi-square tests for continuous and categorical variables, respectively. Baseline characteristics were also examined by presence or absence of moderate to severe SDB (defined as RDI ≥ 15 events/h).

Due to the skewed distribution of RDI values, we estimated transformed ($\log[RDI + 1]$) least square mean values by quartile of cystatin-C from multiple linear regression and back-transformed for interpretation. Using logistic regression, we estimated the association between our primary predictor, quartile of cystatin-C, and likelihood of our primary outcome, SDB (RDI ≥ 15). As a secondary analysis, we examined the association between quartile of cystatin-C and SDB as defined by RDI ≥ 10 and RDI ≥ 30 because these may also be clinically relevant cut points for SDB [23]. Finally, this analysis was repeated, substituting estimated GFR (eGFR) for cystatin-C (CKD) to predict our primary outcome SDB as defined by RDI ≥ 15 . In the interest of clinical relevance, eGFR was dichotomized as ≥ 60 (referent group) or < 60 ml/min/1.73 m² (CKD) using each of the three SCr-based formulae. In the case of eGFR, as defined using the CG method, we examined eGFR with and without adjustment for body surface area.

For all subsequent models, age, race and BMI were selected as putative confounders. In models demonstrating significant effects independent of these three factors, further adjustment for hypertension, self-reported cardiovascular disease, and self-reported diabetes was performed; each of these variables was either related to our predictor and outcome (hypertension and self-reported cardiovascular disease, $p < 0.1$) or was determined a priori to be a potentially clinically relevant confounder (self-reported diabetes). For each set of analyses, we present three models: unadjusted, age- and race-adjusted, and, finally, age-, race- and BMI-adjusted. In addition, since any association between renal function and SDB might be modified by age and/or BMI, we tested for the presence of an interaction between each of these factors and cystatin-C quartile for the prediction of RDI; we performed secondary analysis stratifying participants by each factor (age or BMI) if p for the interaction term was ≤ 0.10 .

Finally, since it has been reported that the dialysis population has a higher proportion of central SDB compared with the general population [24-26], we compared mean CAI across quartiles of cystatin-C. Because no clear clinically relevant cutoff for CAI in the literature exists, we used two different cutoffs of ≥ 2 events/h and ≥ 3 events/h as per previous studies [27,28].

3. Results

3.1. Characteristics of participants

The mean ($\pm$ standard deviation [SD]) age of the 508 participants who met inclusion criteria was 76.0 (± 5.3) years. This population of men was predominantly white (94.7%). Mean cystatin-C was 1.21 (± 0.30) mg/L and mean creatinine was 1.09 (± 0.23) mg/dL. Median RDI was 7.0 events/h (interquartile range 2.3-14.4), and mean RDI was 11.1 (± 12.8) with range 0.0-72.9; 23% of participants had RDI ≥ 15 events/h and 9% had RDI ≥ 30 events/h. The

prevalence of central apneic events was 8.6% for $\text{CAI} \geq 2$ events/h and 6.0% for $\text{CAI} \geq 3$ events/h among men with CAI data (4.1% were missing CAI data).

Baseline characteristics of the participants by quartile of cystatin-C are shown in Table 1. Higher quartiles of cystatin-C were associated with older age ($p < 0.001$), higher BMI ($p = 0.003$), more hypertension ($p < 0.001$), and more self-reported cardiovascular disease ($p < 0.001$).

3.2. Association between cystatin-C and sleep-disordered breathing

In the unadjusted model, higher concentrations of cystatin-C were associated with increasing log RDI (p for trend = 0.007, Table 2). This relationship persisted after adjustment for age and race (p for trend = 0.028). After further adjustment for BMI, the association between quartile of cystatin-C and RDI was no longer significant (p for trend = 0.341). There was no evidence that BMI modified the unadjusted relationship between cystatin-C quartile and log RDI (p for test of interaction = 0.281). However, the test for interaction between age and cystatin-C quartile for the prediction of log RDI reached borderline significance (p for test of interaction = 0.103). We, therefore, performed secondary analyses stratifying by age at the median. Among men >75 years of age, higher levels of cystatin-C were not associated with increasing RDI (unadjusted p for trend = 0.518, Table 3a). However, among men ≤ 75 years of age, higher levels of cystatin-C were associated with increasing RDI despite adjustment for race (p for trend = 0.011, Table 3b). However, after the adjustment for BMI, this association no longer reached statistical significance (p for trend = 0.142). Men ≤ 75 years of age had a slightly higher mean BMI compared to those >75 years of age (mean 27.1 ± 3.3 kg/m² for the older group vs. mean 28.2 ± 3.6 kg/m² for the younger group, $p = 0.001$).

Compared with men in the lowest quartile of cystatin-C, those in each of the higher quartiles of cystatin-C had greater odds of SDB ($\text{RDI} \geq 15$) in unadjusted models and models adjusted for age and race, but the test for trend did not reach significance (Table 4). Substituting $\text{RDI} \geq 30$ for $\text{RDI} \geq 15$ in the analyses did not substantially alter these results (unadjusted p for trend = 0.280). However, substituting $\text{RDI} \geq 10$ for $\text{RDI} \geq 15$ in the analyses, we found that, compared with men in the lowest quartile of cystatin-C, those in each of the higher quartiles of cystatin-C had greater odds of SDB ($\text{RDI} \geq 10$), despite adjustments for age and race (OR 1.73, 95% confidence interval [CI] 1.01-2.98, $p = 0.009$ for men in the highest quartile of cystatin-C vs. lowest quartile), but not after further adjustment for BMI (OR 1.32, 95% CI 0.75-2.33, $p = 0.119$ for men in the highest quartile of cystatin-C vs. lowest quartile).

Finally, while men with higher concentrations of cystatin-C appeared to have a higher likelihood of central apneic events compared with men with lower concentrations (highest vs. lowest quartile OR 1.70, 95% CI 0.81-3.58 for $\text{CAI} \geq 2$ events/h and OR 1.52, 95% CI 0.66-3.51 for $\text{CAI} \geq 3$ events/h), the tests for trend did not reach significance (unadjusted p for trend 0.111 for $\text{CAI} \geq 2$ events/h and 0.138 for $\text{CAI} \geq 3$ events/h).

3.3. Association between chronic kidney disease and sleep-disordered breathing

Men with CKD as identified using the CG formula appeared to have a lower likelihood of SDB ($\text{RDI} \geq 15$ events/h) in unadjusted and age- and race-adjusted models but a slightly higher likelihood of SDB after further adjustment for BMI. However, the 95% CIs were wide and overlapped 1.0 (Table 5). When we defined CKD as $\text{eGFR} < 60$ ml/min using the CG formula without adjustment for body surface area, we found similar results. Men with CKD, as identified using the MDRD formula, appeared to have a slightly higher likelihood of SDB ($\text{RDI} \geq 15$ events/h) in unadjusted and age- and race-adjusted models, but 95% CI were wide and overlapped 1.0. When CKD was identified using the Mayo Clinic formula, even after adjustments for age, race and BMI, men with CKD had 2.1-fold greater odds of SDB (OR 2.11,

95% CI 1.14-3.88, $p = 0.017$). This association persisted after further adjustment for hypertension, self-reported cardiovascular disease, and self-reported diabetes (OR 1.95, 95% CI 1.04-3.65, $p = 0.038$).

Because the Mayo Clinic formula identified a smaller percentage of individuals classified with CKD (11%) compared with CG (17%, $p < 0.001$) and MDRD (24%, $p < 0.001$), secondary analyses were performed that identified men in the lowest 11th-percentile of CG and MDRD as having CKD. Compared with men in the upper 89th-percentile of eGFR defined by the CG formula, those in the lowest 11th-percentile (eGFR < 53 ml/min/1.73 m²) had 1.6-fold higher odds of SDB in the age-, race- and BMI-adjusted model, but the CIs were wide and overlapped 1.0 (OR 1.62, 95% CI 0.76-3.46, $p = 0.216$). However, compared with men in the upper 89th-percentile of eGFR defined by MDRD formula, those in the lowest 11th-percentile (eGFR < 51 ml/min/1.73 m²) had 1.9-fold greater odds of SDB (OR 1.89, 95% CI 0.99-3.46, $p = 0.054$ for age-, race- and BMI-adjusted model). However, after further adjustment for hypertension, self-reported cardiovascular disease and self-reported diabetes, the magnitude of the association was reduced and no longer reached significance (OR 1.65, 95% CI 0.87-3.14, $p = 0.128$).

4. Discussion

We found that older men with reduced renal function, as manifested by higher serum cystatin-C concentration, had a higher average RDI. This effect was largely explained by the greater BMI among men with higher cystatin-C concentration. CKD as defined by eGFR < 60 ml/min/1.73 m² using the Mayo Clinic, but not CG or MDRD equations, was independently associated with higher likelihood of SDB as defined by RDI ≥ 15 events/h.

To our knowledge, our study is the first to examine the association between mild to moderate reductions in renal function and SDB in older men. Prior evidence supporting a link between reduced renal function and SDB stems primarily from studies reporting a high prevalence of SDB in the dialysis population [6-8]. Most recently, Unruh et al. performed a case-control study examining the PSG features of a population of 46 hemodialysis patients, unselected for sleep complaints, compared with age-, gender-, BMI- and race-matched controls and reported the odds were four times greater for persons on hemodialysis to have severe SDB (RDI > 30 with $\geq 3\%$ oxygen desaturation) despite adjustment for cardiovascular disease and diabetes [8].

In contrast, there are few studies that have examined the association between CKD (not requiring dialysis) and SDB. Such investigations may be better positioned to examine the independence of the association between renal function and SDB because they are not subject to confounding from the dialysis procedure or from comorbidities common among dialysis patients [9]. One cross-sectional study compared the sleep parameters in 16 hemodialysis patients with those of 8 CKD patients (mean eGFR 14.5 ± 7.2 ml/min) and reported a trend toward a higher mean RDI among those on hemodialysis [10]. Another case series examining a convenience sample of 35 men and women aged 53.7 ± 12 years with CKD not requiring dialysis (mean estimated creatinine clearance 26.8 ± 9.2 ml/min) reported that over 50% of patients had mild SDB and over 30% had moderate SDB [9]. However, these studies were limited by small size, lack of controls and adjustment for potential confounders, and use of a selected population with poor generalizability to community-dwelling elderly and persons with early CKD.

Reduced renal function, as defined by higher cystatin-C concentration, was associated with higher prevalence of central SDB in this cohort, but this association did not reach statistical significance; the low prevalence of central SDB in our cohort (8.6% for central apnea index $\geq$

2 events/h) may have reduced our power to detect an association. This prevalence is similar to that of the general population and to findings from the only study that categorized SDB in pre-dialysis CKD patients, where observed SDB events were also almost entirely obstructive [9, 27]. However, this study was small ($n = 35$) and excluded those >70 years old and those with known congestive heart failure, both factors that may predispose patients to central SDB [9, 29]. In contrast to our findings, evidence from sleep studies in the dialysis population suggests that central SDB is more prominent than in the general population, approaching an even split between obstructive, mixed, and central SDB [26,27,30]. Unlike the dialysis population, our cohort was in overall good health with normal to mild reductions in renal function, both of which may explain the low prevalence we observed.

Biological mechanisms underlying an association between mild to moderate reductions in renal function and increased risk of SDB are uncertain and may be bidirectional. Observations that nocturnal hemodialysis and renal transplantation significantly improve SDB in patients on conventional hemodialysis suggest that factors stemming directly from the reduction in renal function, rather than from comorbidities or the dialysis procedure, may explain the increased prevalence of SDB in CKD [31,32]. Fluid retention related to reduce renal function may lead to increased airway edema, predisposing patients to obstructive events [30]. Other proposed mechanisms by which reduced renal function might lead to SDB include enhanced chemoreflex responsiveness, associated with metabolic acidosis, high levels of circulating cytokines of other uncleared elements (particularly middle molecules), or uremic neuropathy [32-34]. Enhanced chemosensitivity may lead to periodic breathing, characterized by alternating cycles of hyperventilation and hypoventilation, with apneas occurring at the nadir of this cycling. Although mechanisms such as uremic neuropathy and metabolic acidosis are unlikely to be applicable to early reductions in renal function, elevation in inflammatory cytokines such as interleukin-6 (IL-6) that may dysregulate sleep, as well as volume expansion, may be plausible in early CKD [35-37].

Alternatively, SDB may contribute to the pathogenesis of chronic kidney disease. Epidemiological data support consistent associations between SDB and hypertension, cardiovascular disease, and diabetes [38-40]. These associations are believed to be in part based on adverse effects of intermittent hypoxemia and sympathetic nervous system activity on oxidative stress, insulin resistance and endothelial dysfunction [33,41,42]. Recent data from a genetic epidemiological study of SDB have shown microalbuminuria to be associated with $RDI > 30$, with significance persisting after adjusting for BMI and other covariates [43]. These results suggested that SDB may adversely affect glomerular endothelial function.

The association between reduced renal function and SDB in this cohort is unclear given the inconsistency of our findings across different measures of renal function. Serum cystatin-C may be superior to serum creatinine- and creatinine-based measures as a marker of renal function, particularly in the elderly, because of its independence from body composition and tubular secretion [3,44]. However, we found that BMI largely explained the association between higher cystatin-C concentration and likelihood of SDB. While it is possible that BMI truly explains this association, it may also be that cystatin-C itself is not truly independent of body composition [45]. In addition, only the presence of CKD as defined by the Mayo Clinic formula was independently associated with a twofold higher likelihood of SDB. Unlike the CG and MDRD formulae, which are more accurate in moderate to severe CKD, the Mayo Clinic formula was developed in CKD patients (1/3) and healthy kidney donors (2/3) and designed to be applicable to patients with unknown renal function [21]. For this reason, it may have been a more accurate estimator of GFR in this generally healthy cohort.

Strengths of our study include its enrollment of older men living in the community not selected on the basis of kidney disease or sleep disorders, a large sample size in comparison with prior

investigations, comprehensive measures of renal function, and concurrent identification of SDB using overnight in-home PSG. Nevertheless, our study has several limitations. Our participants were older men and our findings may not apply to other populations. This study was cross-sectional in design, precluding any conclusions regarding causality. Another limitation is the possibility that we over-adjusted for BMI in our multivariable models. A link between obesity and risk for development or progression of renal disease has been supported in epidemiologic studies [46]. Therefore, because SDB may ultimately be on the causal pathway between BMI and risk for renal disease, adjusting for BMI in our analyses may have diluted the magnitude of a true association. Furthermore, our cutoff for SDB was arbitrary because it is unclear what level of SDB is clinically important in the elderly; however, our findings were consistent across three definitions of SDB ($RDI \geq 15$, $RDI \geq 30$ and $RDI \geq 10$) in our primary analysis. In addition, our study population was composed of older men and it is unclear whether mild reductions in renal function represent true renal disease or age-related changes [47]. Indeed, when we stratified by age, a graded association between higher cystatin-C level and higher RDI was seen only in the younger age group, though adjustment for BMI explained much of this association. The disparate results between the youngest old and the oldest old may also be due to higher BMI in the younger age group, the possibility of survival bias (the oldest in the cohort represent the “healthiest” by virtue of their survival to old age), and the challenge of identifying true associations in the elderly related to the multiple comorbidities that may confound or modify hypothesized associations. Finally, we had limited power to detect small differences in prevalence of SDB across levels of renal function.

In conclusion, mild reductions in renal function, as defined by increasing serum cystatin-C level, are associated with greater evidence of SDB in community-dwelling elderly men, but this association is largely explained by higher BMI among men with higher cystatin-C levels. CKD defined by the Mayo Clinic formula, but not CG or MDRD equations, is independently associated with a higher likelihood of SDB. Overall, these findings indicate that reduced renal function may be associated with SDB in older men. Further studies with prospective design should examine whether measures of renal dysfunction are associated with the subsequent development of SDB in middle-aged and older adults.

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Table 1
Characteristics of 508 participants by quartile of cystatin-C

Characteristic	Cystatin C quartile (mg/L)				p-Value
	<1.01 (n = 126)	1.01-1.14 (n = 125)	1.15-1.33 (n = 126)	≥1.34 (n = 131)	
Age, years, mean ± SD	73.6 ± 4.4	75.4 ± 4.7	76.7 ± 5.3	78.4 ± 5.5	<0.001
Race, %					0.199
White	90.5	97.6	96.0	94.7	
Black	7.9	2.4	2.4	4.6	
Other	1.6	0.0	1.6	0.8	
BMI, kg/m ² , mean ± SD	26.7 ± 3.6	27.5 ± 3.3	28.2 ± 3.9	28.2 ± 4.1	0.003
Tobacco use, %					0.319
Current	2.4	2.4	0.0	3.1	
Former	54.8	57.6	63.5	64.6	
Never	42.9	40.0	36.5	32.3	
Self-reported health status, %					0.421
Excellent/good	89.7	89.6	85.7	84.0	
Fair/poor/very poor	10.3	10.4	14.3	16.0	
Hypertension ^a , %	60.3	59.2	75.4	87.8	<0.001
Cardiovascular disease ^b , %	28.6	40.3	44.4	53.9	<0.001
Diabetes mellitus, %	11.9	10.4	11.1	18.3	0.207
Serum cystatin C, mg/L, mean ± SD	0.91 ± 0.07	1.08 ± 0.04	1.24 ± 0.06	1.61 ± 0.26	<0.001
Serum creatinine, mg/dL, mean ± SD	0.94 ± 0.12	1.02 ± 0.13	1.06 ± 0.16	1.31 ± 0.27	<0.001
Estimated GFR, ml/min/1.73 m ² , mean ± SD					
Cockcroft-Gault ^c	94.1 ± 25.7	87.1 ± 24.4	86.0 ± 25.8	69.6 ± 25.5	<0.001
MDRD	81.6 ± 11.7	72.7 ± 10.4	69.7 ± 12.0	56.0 ± 12.6	<0.001
Mayo Clinic	97.5 ± 9.1	89.8 ± 11.2	85.3 ± 13.0	66.2 ± 17.0	<0.001
Respiratory disturbance index (RDI), mean ± SD	8.8 ± 10.1	10.5 ± 12.5	13.3 ± 15.0	11.8 ± 12.8	0.039
RDI ≥ 10 events/h, %	30.2	32.0	48.4	45.0	0.004
RDI ≥ 15 events/h, %	19.1	21.6	27.0	24.4	0.470
RDI ≥ 30 events/h, %	6.4	7.2	13.5	8.4	0.188

^aHypertension defined as any one of: self-reported hypertension, systolic blood pressure ≥ 140, diastolic blood pressure ≥ 90 or current use of at least one blood pressure medication.

^b Cardiovascular disease defined as any one of: history of myocardial infarction, angina, congestive heart failure, transient ischemic attack, stroke, rheumatic heart disease, or cardiovascular surgery.

^c Adjusted for body surface area.

Table 2

Geometric mean respiratory disturbance index (95% confidence interval) by quartile of cystatin-C

Quartile of cystatin-C ^a	Geometric mean RDI (95% CI)		
	Unadjusted model	Model adjusted for age and race	Model adjusted for age, race and BMI
Q1 (<i>n</i> = 126)	5.0 (4.0-6.2)	5.1 (4.1-6.3)	5.7 (4.6-7.0)
Q2 (<i>n</i> = 125)	6.2 (5.0-7.5)	6.2 (5.0-7.6)	6.3 (5.2-7.7)
Q3 (<i>n</i> = 126)	7.5 (6.0-9.2)	7.4 (6.0-9.0)	7.0 (5.7-8.5)
Q4 (<i>n</i> = 131)	7.1 (5.8-8.7)	7.0 (5.7-8.6)	6.5 (5.3-7.9)
<i>p</i> for trend	0.007	0.028	0.341

^a Quartile cut points of cystatin-C (mg/L): <1.01, 1.01-1.14, 1.15-1.33, ≥1.34.

Table 3a

Geometric mean respiratory disturbance index (95% CI) by quartile of cystatin-C for age >75 years

Quartile of cystatin-C ^a	Geometric mean RDI (95% CI)		
	Unadjusted model	Model adjusted for race	Model adjusted for race and BMI
Q1 (<i>n</i> = 33)	5.3 (3.4-7.9)	5.3 (3.4-7.9)	6.0 (4.0-8.8)
Q2 (<i>n</i> = 54)	7.2 (5.3-9.8)	7.3 (5.3-9.9)	7.6 (5.6-10.2)
Q3 (<i>n</i> = 69)	7.9 (6.0-10.4)	7.8 (5.9-10.2)	7.2 (5.5-9.4)
Q4 (<i>n</i> = 85)	6.7 (5.2-8.5)	6.8 (5.2-8.6)	6.7 (5.2-8.4)
P for trend	0.518	0.499	0.953

^a Quartile cut points of cystatin-C (mg/L): <1.01, 1.01-1.14, 1.15-1.33, ≥1.34.

Table 3bGeometric mean respiratory disturbance index (95% CI) by quartile of cystatin-C for age ≤ 75 years

Quartile of cystatin-C ^a	Geometric mean RDI (95% CI)		
	Unadjusted model	Model adjusted for race	Model adjusted for race and BMI
Q1 (<i>n</i> = 93)	4.9 (3.8-6.2)	4.9 (3.7-6.2)	5.3 (4.1-6.8)
Q2 (<i>n</i> = 71)	5.4 (4.0-7.1)	5.4 (4.0-7.2)	5.4 (4.1-7.1)
Q3 (<i>n</i> = 57)	6.9 (5.0-9.3)	6.9 (5.0-9.4)	6.7 (4.9-9.0)
Q4 (<i>n</i> = 46)	8.0 (5.7-11.2)	8.0 (5.7-11.1)	7.0 (4.9-9.7)
P for trend	0.011	0.011	0.142

^a Quartile cut points of cystatin-C (mg/L): <1.01, 1.01-1.14, 1.15-1.33, ≥ 1.34 .

Table 4Association between cystatin-C and moderate to severe SDB^a

Quartile of cystatin-C ^b	Odds ratio (95% CI)		
	Unadjusted model	Model adjusted for age and race	Model adjusted for age, race, and BMI
Q1 (<i>n</i> = 126)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Q2 (<i>n</i> = 125)	1.17 (0.63-2.17)	1.23 (0.66-2.30)	1.07 (0.57-2.04)
Q3 (<i>n</i> = 126)	1.57 (0.87-2.84)	1.66 (0.90-3.06)	1.29 (0.69-2.44)
Q4 (<i>n</i> = 131)	1.37 (0.76-2.50)	1.51 (0.80-2.83)	1.11 (0.57-2.14)
P for trend	0.201	0.137	0.663

^a SDB defined by respiratory disturbance index ≥ 15 at $\geq 4\%$ desaturation.^b Quartile cut points of cystatin-C (mg/L): <1.01, 1.01-1.14, 1.15-1.33, ≥ 1.34 .

Table 5
Association between chronic kidney disease and moderate to severe SDB^a

Formula for GFR		Odds ratio (95% CI)		
		Unadjusted model	Model adjusted for age and race	Model adjusted for age, race, and BMI
Cockcroft-Gault ^b				
	<60 ml/min/1.73 m ² (n = 88)	0.77 (0.43-1.36)	0.76 (0.40-1.43)	1.33 (0.67-2.63)
	≥60 ml/min/1.73 m ² (n = 420)	1.00 (referent)	1.00 (referent)	1.00 (referent)
	p-Value	0.364	0.391	0.415
MDRD				
	<60 ml/min/1.73 m ² (n = 123)	1.31 (0.82-2.10)	1.36 (0.84-2.19)	1.25 (0.77-2.04)
	≥60 ml/min/1.73 m ² (n = 385)	1.00 (referent)	1.00 (referent)	1.00 (referent)
	p-Value	0.251	0.211	0.370
Mayo Clinic				
	<60 ml/min/1.73 m ² (n = 58)	2.09 (1.17-3.74)	2.20 (1.22-3.98)	2.11 (1.14-3.88)
	≥60 ml/min/1.73 m ² (n = 450)	1.00 (referent)	1.00 (referent)	1.00 (referent)
	p-Value	0.013	0.009	0.017

^aChronic kidney disease defined by eGFR <60 ml/min/1.73 m², SDB defined by respiratory disturbance index ≥15 at ≥4% desaturation.

^bAdjusted for body surface area.