



Published in final edited form as:

Sleep Breath. 2011 January ; 15(1): 137–144. doi:10.1007/s11325-010-0339-2.

Sleep-Disordered Breathing and Urinary Albumin Excretion in Older Men

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Abstract

Purpose—Sleep-disordered breathing(SDB) may be deleterious to the cardiovascular system and other organs, including the kidney. Although older men are at increased risk for both kidney disease and SDB, it is unknown whether SDB is associated with higher urinary albumin excretion in this population.

Methods—We examined 507 community-dwelling men age 67 years(mean 76.0±5.3) enrolled in the MrOS Sleep study who underwent overnight polysomnography and gave a spot urine sample. SDB severity was categorized using the respiratory disturbance index and percent total sleep time <90% oxygen saturation(%time O₂<90). Urinary albumin excretion was expressed using the albumin-to-creatinine ratio(ACR).

Results—There was a graded association between respiratory disturbance index and ACR (age and race-adjusted mean ACR=9.35 mg/gCr for respiratory disturbance index ≥30 versus 6.72 mg/gCr for respiratory disturbance index<5, p=0.007). This association was attenuated after further adjustment for body mass index(BMI), hypertension and diabetes and no longer reached significance(p=0.129). However, even after adjustment for age, race, BMI, hypertension and

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This paper was presented as a podium presentation at the 2008 Annual Meeting of the Associated Professional Sleep Societies, LLC in Baltimore, MD.

None of the authors have a financial conflict of interest to disclose.

diabetes, greater %time O₂<90 was associated with higher ACR(10.35 mg/gCr for 10%time O₂<90 versus 7.45 mg/gCr for <1%time O₂<90, p=0.046).

Conclusion—SDB, measured by elevated respiratory disturbance index or nocturnal hypoxemia, was associated with higher ACR. The relationship between respiratory disturbance index and ACR was partially explained by higher BMI and greater prevalence of hypertension and diabetes among men with SDB. However, greater nocturnal hypoxemia was independently associated with higher ACR, suggesting that the hypoxia component of SDB may mediate any detrimental effect of SDB on the kidney.

Keywords

Albuminuria; sleep-disordered breathing; chronic kidney disease; nocturnal hypoxemia

INTRODUCTION

Sleep-disordered breathing (SDB) affects 1 in 5 Americans and increases with age [1, 2]. Most notably, SDB has been linked to hypertension, stroke, coronary artery disease, congestive heart failure and death [3–6]. Recurrent hypoxemia, hypercapnia and arousal characteristic of SDB promote an environment that may be harmful to vital organs such as the kidney [6].

One of the earliest indicators of kidney injury is albuminuria.[7]. It is estimated that over 10 million of the U.S. general population have “microalbuminuria” (albumin-to-creatinine ratio or ACR of 30299 mg/gCr) with normal or mildly reduced renal function (estimated glomerular filtration rate (eGFR) 60 ml/min/1.73m²) that increases with aging [8, 9]. While microalbuminuria is a commonly used threshold for outcomes related to albuminuria, levels of urinary albumin excretion below the microalbuminuria threshold (as low as 2 mg/gCr) have been independently associated with progression to overt nephropathy and cardiovascular disease [7, 9]. These findings may reflect the observation that albuminuria, much like SDB, is associated with endothelial dysfunction and inflammation that exist independent of factors such as hypertension and diabetes [10, 11].

Prior studies examining the association between SDB and albuminuria have yielded conflicting results, likely related to small samples sizes, variability in the definition and measurement of proteinuria or albuminuria, and lack of appropriate adjustment for confounders [12–14]. Recently, however, a cross-sectional study in 496 middle-aged adult family members of individuals with SDB and neighborhood controls found that compared to adults with respiratory disturbance index (RDI) <5, those with severe SDB (RDI ≥30) had higher adjusted ACR (median 7.6 mg/gCr), even after excluding those with eGFR <60 ml/min/1.73m² [14]. However, it is uncertain whether this association is present in older people, who are more likely to manifest both SDB and microalbuminuria.

Therefore, to determine whether increasing severity of SDB is associated with higher ACR in older men, we measured urinary albumin excretion and performed overnight polysomnography in a cohort of 507 community-dwelling men age ≥67 years enrolled at the Minneapolis center of the Outcomes of Sleep Disorders in Older Men (MrOS Sleep) study. We hypothesized that increasing severity of SDB would be independently associated with higher mean ACR.

MATERIALS AND METHODS

Participants

The Osteoporotic Fractures in Men (MrOS) Study enrolled 5995 community-dwelling men aged 65 years and older between March 2000 to April 2002 from six U.S. centers [15, 16]. A total of 3135 men from MrOS were recruited for participation in the MrOS Sleep Study. Of these, 2911 completed an exam (between December 2003 and March 2005) included a clinic visit, overnight in-home polysomnography (PSG) and a first morning void urine specimen; 511 of these 2911 men were enrolled from the Minneapolis center. Each of the 511 men from the Minneapolis site underwent measurement of urinary ACR; of these, 3 were excluded because they self-reported being on dialysis and 1 had an extreme urinary albumin excretion (1850 mg/L), leaving 507 men for this analysis.

Sleep Data Collection 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: C₃/A₂ and C₄/A₁ electroencephalograms, bilateral electrooculograms and bipolar submental electromyogram to determine sleep state; thoracic and abdominal respiratory inductance plethysmography to determine respiratory effort; airflow (nasal-oral thermocouple and nasal pressure cannula); finger pulse oximetry; lead I 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.[17] Staff returned the next morning to collect equipment and download the data to the Case Reading Center (Cleveland, OH) to be scored by a research-certified sleep polysomnologist.

In the primary analysis of the current study, SDB was defined by the RDI. Apnea was defined as complete or near complete cessation of airflow for >10 seconds, and hypopneas were scored if clear reductions in breathing amplitude occurred for >10 seconds but did not meet the threshold for apneas [18] In these analyses, only apneas and hypopneas that were each associated with a 3% oxygen 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 (events/hour). In secondary analyses, we used nocturnal hypoxemia as the measure of SDB using the percent total sleep time spent at <90% oxygen saturation (%time O₂<90).

Measurement of Urinary Albumin Excretion

Urine samples were first morning voids. Once samples were recovered by the technician, they were taken immediately to the Minneapolis center, frozen in 4 mL aliquots to -20°C, and sent to Clinical Studies Clinical Laboratory (University of Minnesota, Minneapolis, MN) where urinary albumin and creatinine assays were performed. Urinary albumin was measured using nephelometry (Behring-Dade). Inter- and intra-assay CVs were less than 3%. Urinary creatinine was measured using the enzymatic assay (Roche). Inter and intra-assay CVs were 4%. Urinary ACR was calculated for each subject using these two measurements and reported in mg/gCr. Because the limit of sensitivity of our assay for urinary albumin is 2 mg/L, samples that registered below the range of our assay were considered to be 2 mg/L (n=18).

Other Measurements

Additional participant characteristics were collected from the research clinic visit and home sleep visit. These variables included: age; body mass index (BMI, kg/m²); self-reported health status [19]; medical history [including hypertension, self-reported diabetes, and self-reported cardiovascular disease] (Table 1). Hypertension was defined as noted in Table 1. Medication use was reviewed by clinic staff. Finally, questionnaire data obtained from a

prior MrOS visit in 2000–2002 were also used to assess self-reported race and prior smoking history.

Serum creatinine (SCr) measurements were performed on blood collected at the MrOS baseline sleep clinic visit (Minneapolis site) and assayed at the Clinical Studies Clinical Laboratory (University of Minnesota, Minneapolis) SCr was measured using the Hitachi 911 analyzer (Roche, Indianapolis, IN) utilizing a variation of the Jaffe enzymatic method. Inter- and intra-assay CVs were 4.0%; this assay was calibrated daily. EGFR was determined using the abbreviated four variable version of the Modification of Diet in Renal Disease (MDRD) formula [20, 21].

Statistical Analysis

Baseline characteristics were examined across category of RDI; statistical differences were calculated using analysis of variance or chi-square tests for continuous and categorical variables, respectively. For the primary analyses, SDB was defined using clinically relevant RDI categories: 0–4.9 events/hour (normal); 5–14.9 events/hour (mild), 15–29.9 events/hour (moderate), 30 events/hour (severe) [22].

Due to the skewed distribution of ACR values, we estimated transformed least square mean values of ACR (log [ACR]) by RDI category from multiple linear regression and present geometric means. Using logistic regression, we then estimated the association between RDI category and likelihood of clinical albuminuria (ACR \geq 30 mg/gCr) [8].

For all subsequent models, age, race and BMI were selected as putative confounders. For each set of analyses, we present three models: unadjusted, age and race-adjusted and, finally, age, race and BMI-adjusted. If the main effect of log RDI was statistically significant in the age, race and BMI-adjusted model ($p < 0.1$), we further adjusted for diabetes and hypertension which were selected a priori based upon clinical relevance. 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 (considered significant if $p \leq 0.1$) between each of these factors (modeled as continuous variables) and RDI category (ordinal) for the prediction of ACR.

We performed secondary analyses examining SDB alternatively defined as %time $O_2 < 90$. We analyzed %time $O_2 < 90$ in 4 categories with cut-points defined based upon the highly skewed distribution of this variable (<1%, 1–3.4%, 3.5–9.9%, $\geq 10\%$) as in a prior analysis [Cauley J, 2007, J Bone and Mineral Research, Abstract #1157]. We estimated transformed least square mean values of ACR (log [ACR]) by %time $O_2 < 90$ category from multiple linear regression and present geometric means. Using logistic regression, we then estimated the association between %time $O_2 < 90$ category and likelihood of clinical albuminuria. All subsequent models were adjusted following the same strategy as in RDI analyses.

Finally, sensitivity analyses were performed for all of the associations excluding men with renal dysfunction as defined by MDRD $eGFR < 60$ ml/min/1.73m² and report these results. We also repeated our primary analyses excluding the one individual with macroalbuminuria (ACR > 300 mg/gCr) and found similar results; we therefore report results from the primary analysis in this paper.

RESULTS

Participant Characteristics

The 507 men who met inclusion criteria were 76.0 ± 5.3 years old and predominantly white (95%). Median ACR was 5.9 mg/gCr (range=1.6–522.9). Mean SCr was 1.08 ± 0.22 mg/dL.

Median RDI was 12.0 events/hour (inter-quartile range=5.5–20.9), and mean RDI was 16.1 ± 14.7 (range 0–78.2); 40% of participants had a RDI ≥ 5 events/hour and 15% had a RDI ≥ 30 events/hour. Median % total sleep time $<90\%$ (%time $O_2 < 90$) was 0.2% (range=0–85%); mean % time $O_2 < 90$ was $2.6\% \pm 6.9\%$; 56% spent $<1\%$ time $O_2 < 90$, 26% spent 1–3.4% time $O_2 < 90$, 10% spent 3.5–9.9% time $O_2 < 90$, and 7% spent $\geq 10\%$ time $O_2 < 90$.

Baseline characteristics of participants by RDI category are shown in Table 1.

Association between Respiratory Disturbance Index and Urinary Albumin Excretion

Higher RDI category was associated with higher mean ACR in the unadjusted model (p-trend=0.003, Table 2). This relationship persisted after adjustment for age and race (p-trend=0.01, Table 2). After further adjustment for BMI, the association between RDI and mean ACR was attenuated to borderline statistical significance (p-trend=0.05, Table 2). Although a graded pattern was still apparent after further adjustment for hypertension and diabetes, the association no longer reached significance (p-trend=0.13, Table 2). There was no evidence that age or BMI modified the unadjusted relationship between RDI category and mean ACR (p=0.45 for interaction between RDI and age and p=0.68 for RDI and BMI).

When we excluded those with $eGFR < 60$ ml/min/1.73m² (n=123), we found a similar pattern of association between RDI category and mean ACR, though it did not reach significance (p-trend=0.10, unadjusted).

Association Between Respiratory Disturbance Index and Albuminuria

There was evidence of a graded association between higher RDI and odds of albuminuria as defined by an ACR ≥ 30 mg/gCr. Compared with the referent group of men with a RDI < 5 , the age and race-adjusted odds of albuminuria was 1.4-fold higher among men with a RDI=5–14.9, 2.1-fold higher among men with a RDI=15–29.9, and 2.5-fold higher among men with a RDI ≥ 30 (p-trend=0.04, Table 3). Further adjustment for BMI, hypertension and diabetes did not substantially alter this pattern, though the test for trend did not quite reach significance (p-trend=0.08, Table 3). When we excluded the 123 men with $eGFR < 60$ ml/min/1.73m², a graded, though weaker, pattern persisted, but the association was not significant (age, race-adjusted p trend 0.56, results not shown).

Association between % Total Sleep Time $<90\%$ O_2 Saturation and Urinary Albumin Excretion

Men who spent a greater %time $O_2 < 90$ had higher urinary albumin excretion despite adjustment for age, race and BMI (p for trend=0.01, Table 4). This association persisted after further adjustment for hypertension and diabetes (p for trend=0.05, Table 4). There was no evidence that age or BMI modified the unadjusted relationship between %time $O_2 < 90$ category and mean ACR (p=0.79 for interaction between %time $O_2 < 90$ and age and p=0.62 for %time $O_2 < 90$ and BMI).

Following exclusion of men with $eGFR < 60$ ml/min/1.73m², the association persisted, though less graded and of borderline significance (age, race, BMI, HTN, DM-adjusted p-trend=0.10).

Association between % Total Sleep Time $<90\%$ O_2 Saturation and Albuminuria

Men who spent at least 10%time $O_2 < 90$ had a 2.2-fold greater unadjusted odds of albuminuria when compared to those who spent $<1\%$ time $O_2 < 90$ (p-trend=0.03, Table 5). After further adjustment for age, race, BMI, diabetes mellitus and hypertension, the graded pattern persisted, but did not quite reach significance (p-trend=0.10). Results were similar after further excluding men with $eGFR < 60$ ml/min/1.73m² (p-trend=0.14).

DISCUSSION

We found that community-dwelling elderly men with greater evidence of SDB, as measured by RDI or nocturnal hypoxemia, had higher urinary albumin excretion as manifested by higher ACR. The relationship between RDI and ACR was partially explained by a higher BMI, and greater prevalence of hypertension and diabetes among men with SDB. However, even after adjustment for multiple confounding or mediating factors, increasing nocturnal hypoxemia was independently associated with higher ACR in men with normal or abnormal eGFR. These findings suggest that the hypoxemic component of SDB may have a negative impact on the kidney.

Prior studies examining the association between SDB and “proteinuria” have yielded inconsistent results. Three cross-sectional studies conducted in subjects referred for sleep studies found no difference in the prevalence of proteinuria (defined as protein-to-creatinine ratio (PCR) >200 mg/gCr) in those diagnosed with SDB versus those not diagnosed with SDB [12, 13, 23]. These studies were limited for several reasons including the use of a referral sample with likely confounding co-morbidities, lack of controls, use of “proteinuria” as the outcome (a less sensitive marker of glomerular function than albuminuria), and use of a high threshold for protein excretion [7, 9, 24]. In contrast to these investigations, studies that defined urinary albumin excretion as an outcome have reported positive associations between RDI and albuminuria [Sim J, 2006, ASN, Abstract #441] [14]. For example, Faulx et al examined a population of 496 middle-aged men and women consisting of family members of individuals with SDB and neighborhood controls; they found that individuals with severe SDB (RDI ≥ 30) compared with those with no SDB (RDI <5) had significantly higher ACR (median 7.87 ± 1.02 mg/gCr vs. 5.08 ± 0.41 mg/gCr for those with no SDB; $p < 0.01$), after adjustment for subject characteristics, hypertension and diabetes and exclusion of those with eGFR <60 ml/min/1.73m² [14]. In agreement with these findings, we observed an association between SDB and ACR at low levels of urinary albumin excretion, but still at levels that might forebode progression to overt nephropathy and cardiovascular disease. We add to these previous findings by providing evidence of this association in a population-based sample of older men not selected for kidney disease or sleep disorders.

Few studies have examined the association between SDB as defined by nocturnal hypoxemia and urinary albumin or protein excretion. One cross-sectional study of 75 patients referred for sleep study (mean age 45 ± 1.5 years) found that neither %time O₂<90 nor nadir oxygen desaturation correlated with PCR [13]. However, urinary albumin excretion was not measured in this investigation [13]. A similar cross-sectional study of 148 prospectively enrolled patients undergoing sleep studies found that neither nadir oxygen desaturation nor greater %time O₂<90 correlated with PCR [23]. Another investigation in 224 individuals referred for sleep study reported that, in univariate analysis, higher log PCR correlated with lower baseline oxygen saturation, lower minimum oxygen saturation and greater %time O₂<90; only lower baseline oxygen saturation predicted log PCR after adjustment for presence of mild SDB (RDI ≤ 5), sex, blood pressure and an interaction between sex and blood pressure [12]. The stronger association we observed between ACR and indices of nocturnal hypoxemia compared to the RDI is consistent with data from several studies showing stronger associations between nocturnal hypoxemia (as opposed to RDI) and impaired glucose tolerance or fasting hyperglycemia [25, 26].

Putative mechanisms underlying an association between SDB and urinary albumin excretion are uncertain. While it is possible that SDB is associated with higher ACR because people with SDB are more likely to be obese, hypertensive and diabetic, adjustment for these factors in our study did not fully explain the association, particularly in men with %time

O₂<90 [27, 28]. It has been hypothesized that factors promoting increased glomerular filtration of albumin are thought to be related to glomerular pathology such as endothelial dysfunction and glomerular hypertension [6, 12, 13]. Perhaps through repeated cycles of apneas, hypoxia and arousals, SDB activates the sympathetic nervous system and promotes inflammation, hypercoagulability, oxidative stress and, ultimately, endothelial damage that may lead to glomerular leakage of albumin [6, 14]. In addition, SDB may lead to glomerular hypertension through the development of pulmonary hypertension as a consequence of apnea-associated intra-thoracic pressure changes and hypoxemia [12]. Individuals with moderate to severe obstructive SDB have been shown to have increased filtration fraction (hyperfiltration) when compared to healthy kidney donors, which may lead to glomerulosclerosis and proteinuria; this hyperfiltration is ameliorated by continuous positive airway pressure therapy [29]. Notably, nocturnal hypoxemia and nadir oxygen desaturation, but not RDI, have been associated with increased filtration fraction [29]. Possible mechanisms that may explain associations of specifically hypoxemia with either renal function or impaired glucose handling may include hypoxemia-associated inflammatory cytokine release and reactive species generation, or alterations in neurohumoral control mechanisms [25].

To date, this is the first study to examine the association between parameters of SDB and urinary albumin excretion in a cohort of community patients not selected on the basis of sleep complaints or renal disease. Additional strengths of the study include the use of standardized research polysomnography, the uniform collection of urine samples for the measurement of urinary albumin excretion, and adjustment for potential confounders. However, our study has limitations. First, we cannot address causality due to the cross-sectional design; it is possible that the association between SDB and kidney damage may be bi-directional. Second, our findings are only generalizable to community-dwelling elderly men. Also, we had limited power to detect small to moderate associations, particularly in secondary analyses where we excluded large numbers of individuals. In addition, urine samples were collected the morning after sleep studies which might lead to an increase in the degree of urinary albumin excretion, particularly in men who had severe SDB. However, measurement of urinary albumin excretion was uniform for all participants. Furthermore, our adjustment for factors such as BMI, hypertension and diabetes may be over-adjustment because they may be on the causal pathway between SDB and albuminuria. However, adjustment for such factors would likely bias our results toward the null hypothesis of no association.

In summary, older men with SDB as manifested by higher RDI or greater nocturnal hypoxemia had greater urinary albumin excretion as manifested by higher ACR. While the association between RDI and ACR was partially explained by a higher BMI, and greater prevalence of hypertension and diabetes among men with SDB, nocturnal hypoxemia was associated with higher ACR despite multivariable adjustment. Prospective studies in diverse populations, such as middle-aged men and women, as well as studies that examine changes in ACR after SDB treatment with positive-airway pressure are required to better understand the association between SDB and urinary albumin excretion and explore potential mechanisms underlying this association. The clinical impact of an association between SDB and urinary albumin excretion is that treatment of SDB may represent a novel tool with which to slow progression of CKD and attenuate cardiovascular disease risk.

Acknowledgments

Special thanks to Kyle Moen for his assistance with the preparation of this manuscript.

Statement of Financial Support

Sleep Breath. Author manuscript; available in PMC 2012 February 06.

This study was funded by the National Heart, Lung, and Blood Institute (NHLBI) provides funding for the MrOS Sleep ancillary study “Outcomes of Sleep Disorders in Older Men” under the following grant numbers: R01 HL071194, R01 HL070848, R01 HL070847, R01 HL070842, R01 HL070841, R01 HL070837, R01 HL070838, and R01 HL070839. The Minnesota center is funded under grant number: R01 HL070847. The funding institute had no role in the collection, analysis or interpretation of the data or in the decision to submit the paper for publication. Dr. Canales’s time and training partially supported by National Institutes of Health funding through the National Institute of Diabetes and Digestive and Kidney Diseases training grant T32 DK007784.

References

1. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med.* 2002; 165(9):1217–1239. [PubMed: 11991871]
2. Young T, Shahar E, Nieto FJ, Redline S, Newman AB, Gottlieb DJ, Walsleben JA, Finn L, Enright P, Samet JM. Predictors of sleep-disordered breathing in community-dwelling adults: the Sleep Heart Health Study. *Arch Intern Med.* 2002; 162(8):893–900. [PubMed: 11966340]
3. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet.* 2005; 365(9464):1046–1053. [PubMed: 15781100]
4. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med.* 2000; 342(19):1378–1384. [PubMed: 10805822]
5. Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Javier Nieto F, O’Connor GT, Boland LL, Schwartz JE, Samet JM. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med.* 2001; 163(1):19–25. [PubMed: 11208620]
6. Shamsuzzaman AS, Gersh BJ, Somers VK. Obstructive sleep apnea: implications for cardiac and vascular disease. *JAMA.* 2003; 290(14):1906–1914. [PubMed: 14532320]
7. Ruggenti P, Remuzzi G. Time to abandon microalbuminuria? *Kidney Int.* 2006; 70(7):1214–1222. [PubMed: 16871239]
8. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van Lente F, Levey AS. Prevalence of chronic kidney disease in the United States. *JAMA.* 2007; 298(17):2038–2047. [PubMed: 17986697]
9. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, Halle JP, Young J, Rashkow A, Joyce C, Nawaz S, Yusuf S. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA.* 2001; 286(4):421–426. [PubMed: 11466120]
10. Stehouwer CD, Smulders YM. Microalbuminuria and risk for cardiovascular disease: Analysis of potential mechanisms. *J Am Soc Nephrol.* 2006; 17(8):2106–2111. [PubMed: 16825333]
11. Clausen P, Jensen JS, Jensen G, Borch-Johnsen K, Feldt-Rasmussen B. Elevated urinary albumin excretion is associated with impaired arterial dilatory capacity in clinically healthy subjects. *Circulation.* 2001; 103(14):1869–1874. [PubMed: 11294805]
12. Iliescu EA, Lam M, Pater J, Munt PW. Do patients with obstructive sleep apnea have clinically significant proteinuria? *Clin Nephrol.* 2001; 55(3):196–204. [PubMed: 11316239]
13. Mello P, Franger M, Boujaoude Z, Adaimy M, Gelfand E, Kass J, Weisberg LS. Night and day proteinuria in patients with sleep apnea. *Am J Kidney Dis.* 2004; 44(4):636–641. [PubMed: 15384014]
14. Faulx MD, Storfer-Isser A, Kirchner HL, Jenny NS, Tracy RP, Redline S. Obstructive sleep apnea is associated with increased urinary albumin excretion. *Sleep.* 2007; 30(7):923–929. [PubMed: 17682664]
15. Orwoll E, Blank JB, Barrett-Connor E, Cauley J, Cummings S, Ensrud K, Lewis C, Cawthon PM, Marcus R, Marshall LM, McGowan J, Phipps K, Sherman S, Stefanick ML, Stone K. Design and baseline characteristics of the osteoporotic fractures in men (MrOS) study--a large observational study of the determinants of fracture in older men. *Contemp Clin Trials.* 2005; 26(5):569–585. [PubMed: 16084776]

16. Blank JB, Cawthon PM, Carrion-Petersen ML, Harper L, Johnson JP, Mitson E, Delay RR. Overview of recruitment for the osteoporotic fractures in men study (MrOS). *Contemp Clin Trials*. 2005; 26(5):557–568. [PubMed: 16085466]
17. Redline S, Sanders MH, Lind BK, Quan SF, Iber C, Gottlieb DJ, Bonekat WH, Rapoport DM, Smith PL, Kiley JP. Methods for obtaining and analyzing unattended polysomnography data for a multicenter study. *Sleep Heart Health Research Group. Sleep*. 1998; 21(7):759–767. [PubMed: 11300121]
18. Quan SF, Howard BV, Iber C, Kiley JP, Nieto FJ, O'Connor GT, Rapoport DM, Redline S, Robbins J, Samet JM, Wahl PW. The Sleep Heart Health Study: design, rationale, and methods. *Sleep*. 1997; 20(12):1077–1085. [PubMed: 9493915]
19. Ware J, MK, Keller S. A 12-Item short-form health survey: construction of scales and preliminary tests of reliability and validity. *Medical Care*. 1996; 34:220–233. [PubMed: 8628042]
20. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med*. 2006; 145(4):247–254. [PubMed: 16908915]
21. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999; 130(6):461–470. [PubMed: 10075613]
22. The Report of an American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. *Sleep*. 1999; 22(5):667–689. [PubMed: 10450601]
23. Casserly LF, Chow N, Ali S, Gottlieb DJ, Epstein LJ, Kaufman JS. Proteinuria in obstructive sleep apnea. *Kidney Int*. 2001; 60(4):1484–1489. [PubMed: 11576363]
24. Shihabi ZK, Konen JC, O'Connor ML. Albuminuria vs urinary total protein for detecting chronic renal disorders. *Clin Chem*. 1991; 37(5):621–624. [PubMed: 2032314]
25. Sulit L, Storfer-Isser A, Kirchner HL, Redline S. Differences in polysomnography predictors for hypertension and impaired glucose tolerance. *Sleep*. 2006; 29(6):777–783. [PubMed: 16796216]
26. Punjabi NM, Shahar E, Redline S, Gottlieb DJ, Givelber R, Resnick HE. Sleep-disordered breathing, glucose intolerance, and insulin resistance: the Sleep Heart Health Study. *Am J Epidemiol*. 2004; 160(6):521–530. [PubMed: 15353412]
27. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, D'Agostino RB, Newman AB, Lebowitz MD, Pickering TG. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. *Sleep Heart Health Study. JAMA*. 2000; 283(14):1829–1836. [PubMed: 10770144]
28. Resnick HE, Redline S, Shahar E, Gilpin A, Newman A, Walter R, Ewy GA, Howard BV, Punjabi NM. Diabetes and sleep disturbances: findings from the Sleep Heart Health Study. *Diabetes Care*. 2003; 26(3):702–709. [PubMed: 12610025]
29. Kinebuchi S, Kazama JJ, Satoh M, Sakai K, Nakayama H, Yoshizawa H, Narita I, Suzuki E, Gejyo F. Short-term use of continuous positive airway pressure ameliorates glomerular hyperfiltration in patients with obstructive sleep apnoea syndrome. *Clin Sci (Lond)*. 2004; 107(3):317–322. [PubMed: 15191364]

Table 1

Baseline Characteristics of Participants by Category of SDB* (n=507)

Characteristic	Category of SDB (events/hour)				p value
	Normal 0-4.9 (n=120)	Mild 5.0-14.9 (n=182)	Moderate 15.0-29.9 (n=130)	Severe 30 (n=75)	
Age, y, mean ± SD	75.3 ± 5.0	76.0 ± 5.2	76.6 ± 5.4	76.2 ± 5.6	0.29
Race, n (%)					0.80
Caucasian	113 (94)	171 (94)	125 (96)	70 (93)	
Non-Caucasian	7 (6)	11 (6)	5 (4)	5 (7)	
BMI, kg/m ² , mean ± SD	26.3 ± 3.4	27.4 ± 3.6	28.1 ± 3.3	29.6 ± 4.5	<0.001
Smoking, n (%)					0.88
Current	3 (2.5)	4 (2.2)	3 (2.3)	0 (0)	
Former	71 (59)	108 (59)	81 (63)	45 (60)	
Never	46 (38)	70 (39)	45 (35)	30 (40)	
Health status, n (%)					0.04
Excellent/good	109 (91)	156 (86)	118 (91)	59 (79)	
Fair/poor/very poor	11 (9)	26 (14)	12 (9)	16 (21)	
Hypertension ^{**} , n (%)	77 (64)	123 (68)	101 (78)	58 (77)	0.05
Cardiovascular disease [†] , n (%)	43 (36)	74 (41)	63 (49)	31 (43)	0.24
Diabetes, n (%)	11 (9)	15 (8)	22 (17)	18 (24)	0.002
eGFR [‡] , mL/min per 1.73 m ² , mean ± SD	70.4 ± 13.6	70.7 ± 15.7	69.6 ± 15.3	67.9 ± 14.0	0.55
ACR [§] , mg/g Cr, mean ± SD	6.5 ± 2.2	7.5 ± 2.7	8.8 ± 2.8	9.4 ± 3.0	0.03
Albuminuria [¶] , n (%)	7 (6)	16 (9)	17 (13)	11 (15)	0.12

* Sleep-disordered breathing (SDB) defined by Respiratory Disturbance Index (RDI) at 3% oxygen desaturation

** Hypertension 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 (angiotensin-converting enzyme-inhibitor, angiotensin receptor-blocker, beta-blocker--non-ophthalmic, thiazide, loop, or potassium-sparing diuretic, calcium-channel blocker, or alpha-blocker).

† 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

‡ Estimated glomerular filtration rate (eGFR) calculated by the 4-variable MDRD equation

¶ Geometric mean albumin-to-creatinine ratio

Albuminuria defined as albumin-to-creatinine ratio (ACR) \geq 30 mg/g Cr

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Table 2

Geometric Mean ACR (95% Confidence Interval) by Category of SDB*

Models	Category of SDB (events/hour)				p for trend
	0-4.9 (n=120)	5.0-14.9 (n=182)	15.0-29.9 (n=130)	30 (n=75)	
Unadjusted	6.50 (5.46-7.74)	7.53 (6.54-8.67)	8.83 (7.47-10.44)	9.43 (7.57-11.75)	0.003
Adjusted for Age and Race	6.72 (5.67-7.95)	7.52 (6.56-8.63)	8.62 (7.33-10.14)	9.35 (7.55-11.57)	0.01
Adjusted for Age, Race and BMI	7.00 (5.90-8.30)	7.58 (6.61-8.69)	8.49 (7.22-9.98)	8.83 (7.11-10.97)	0.05
Adjusted for Age, Race, BMI, HTN, DM	7.11 (6.00-8.43)	7.71 (7.13-8.83)	8.30 (7.07-9.75)	8.60 (6.92-10.67)	0.13

* defined by Respiratory Disturbance Index (RDI) at 3% oxygen desaturation

Abbreviations: ACR = albumin-to-creatinine ratio; SDB = sleep-disordered breathing; BMI = body mass index; HTN = hypertension; DM = diabetes mellitus

Table 3

Association Between SDB* and Presence of Albuminuria**

Models	Odds Ratio (95% CI) by Category of SDB (events/hour)			p for trend	
	0-4.9 (n=120)	5.0-14.9 (n=182)	15.0-29.9 (n=130)		30 (n=75)
Unadjusted	1.0 (referent)	1.56 (0.62-3.90)	2.43 (0.97-6.08)	2.78 (1.03-7.51)	0.02
Adjusted for Age and Race	1.0 (referent)	1.43 (0.56-3.64)	2.10 (0.82-5.37)	2.51 (0.90-7.00)	0.04
Adjusted for Age, Race and BMI	1.0 (referent)	1.41 (0.55-3.63)	2.07 (0.80-5.35)	2.45 (0.85-7.04)	0.06
Adjusted for Age, Race, BMI, HTN, DM	1.0 (referent)	1.43 (0.55-3.69)	1.94 (0.74-5.05)	2.39 (0.83-6.91)	0.08

* defined by Respiratory Disturbance Index (RDI) at 3% oxygen desaturation

** Albuminuria defined as albumin-to-creatinine ratio (ACR) 30 mg/g Cr

Abbreviations: SDB = sleep disordered breathing; BMI = body mass index; HTN = hypertension; DM = diabetes mellitus

Table 4
Geometric Mean ACR (95% Confidence Interval) by Percent Total Sleep Time <90% Oxygen Saturation

Models	Percent Total Sleep Time <90%				p for trend
	<1.0 (n=284)	1.0-3.4 (n=134)	3.5-9.9 (n=52)	10.0 (n=37)	
Unadjusted	7.03 (6.28-7.87)	8.07 (6.85-9.51)	9.66 (7.42-12.56)	12.02 (8.80-16.42)	<0.001
Adjusted for Age and Race	7.11 (6.38-7.94)	7.99 (6.82-9.36)	9.29 (7.19-11.99)	11.99 (8.86-16.22)	<0.001
Adjusted for Age, Race and BMI	7.29 (6.52-8.14)	7.88 (6.73-9.24)	9.03 (6.99-11.67)	10.89 (7.95-14.92)	0.01
Adjusted for Age, Race, BMI, HTN, DM	7.45 (6.66-8.32)	7.68 (6.55-8.99)	8.91 (6.91-11.50)	10.35 (7.56-14.18)	0.05

Abbreviations: ACR = albumin-to-creatinine ratio; BMI = body mass index; HTN = hypertension; DM = diabetes mellitus

Table 5
Association Between Percent Total Sleep Time <90% Oxygen Saturation and Albuminuria*

Models	Odds Ratio (95% CI) by Percent Total Sleep Time <90%			p for trend	
	<1.0 (n=284)	1.0-3.4 (n=134)	3.5-9.9 (n=52)		
Unadjusted	1.0 (referent)	1.22 (0.60-2.49)	2.38 (1.03-5.48)	2.20 (0.83-5.81)	0.03
Adjusted for Age and Race	1.0 (referent)	1.11 (0.53-2.32)	2.04 (0.85-4.91)	2.28 (0.84-6.21)	0.05
Adjusted for Age, Race and BMI	1.0 (referent)	1.10 (0.52-2.33)	2.02 (0.83-4.96)	2.24 (0.77-6.55)	0.07
Adjusted for Age, Race, BMI, HTN, DM	1.0 (referent)	1.01 (0.47-2.15)	1.99 (0.81-4.89)	2.05 (0.70-6.02)	0.10

* Albuminuria defined as albumin-to-creatinine ratio (ACR) ≥ 30 mg/g Cr

Abbreviations: BMI = body mass index; HTN = hypertension; DM = diabetes mellitus