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Association of Sleep Disordered Breathing With Cognitive Dysfunction in CKD Stages 4–5

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Abstract

Background—Sleep disordered breathing (SDB) and cognitive impairment are common among chronic kidney disease (CKD) patients. SDB is known to be a risk factor for cognitive dysfunction in the general population, but this association has not been studied in CKD patients.

Study Design—Cross-sectional study.

Settings & Participants—A cohort of 169 CKD stage 4–5 patients.

Predictors—SDB; covariates included demographics, diabetes, cardiovascular disease, depression and dialysis modality.

Outcomes—Cognitive impairment, generally defined as a score 1.5 standard deviations or more from the age, education level adjusted normative cognitive test score.

Measurements—Standardized health interview, neurocognitive assessment, sleep related questionnaires, and polysomnography.

Results—SDB (apnea-hypopnea index > 15) was diagnosed in 83 (49.1%) subjects. This group had a significantly higher prevalence of nocturnal hypoxemia (65.8% vs. 26.8%, $p < 0.001$) and excessive daytime sleepiness (38.6% vs. 20.7%, $p = 0.01$). In addition, this group had significantly lower scores in tests measuring verbal memory, working memory, attention, and psychomotor speed. SDB was associated with a higher risk of immediate verbal memory impairment after adjustment for known confounders (adjusted OR, 2.67; 95% CI, 1.17–6.08). However, in a subgroup analysis of older adults (age > 60), there were no significant differences in cognitive testing between the groups with and without sleep-disordered breathing.

Limitations—Cross-sectional design, limited sample size.

Conclusions—SDB is associated with cognitive impairments, especially impaired verbal memory in advanced CKD patients. However, the impact appeared limited in older adults. Early

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evaluation and management of SDB in patients with CKD may provide an opportunity to improve cognitive function.

Keywords

Chronic kidney disease; cognitive impairment; sleep disordered breathing

Sleep disordered breathing (SDB), a condition characterized by repeated arousals from sleep and intermittent hypoxemia, is common in chronic kidney disease (CKD) affecting up to 50% of patients (1). SDB is associated with reduced quality of life (2), excessive daytime sleepiness (3), reduced functional capacities (4), and increased cardiovascular disease (CVD) (5, 6) including hypertension, left ventricular hypertrophy, coronary artery disease and cardiovascular events in the CKD population.

Cognitive impairment increases in prevalence with CKD severity, potentially affecting up to 60% of CKD patients (7, 8). In addition to increasing the risk of mortality, (9, 10) cognitive impairment in CKD also may induce poor quality of life and suboptimal medical care because of limited ability to caregiver's advice in relation to dietary restrictions, pharmacologic therapy, dialysis initiation and maintenance, and transplantation (8). Cognitive impairment in the domains of memory, attention, and executive function is common among patients with CKD and end-stage kidney disease, but its underlying causes remain poorly understood (8, 11).

It has been well established that SDB can negatively impact functioning in a wide range of cognitive domains, such as attention, memory, executive function, psychomotor speed and construction in the general population (12). In an animal model, chronic exposure to intermittent hypoxia during sleep, which reproduces the hypoxia/reoxygenation events and sleep fragmentation seen in moderate to severe SDB patients, leads to many of the neurocognitive features of SDB in humans (13). In addition, in CKD patients the cognitive deficits of SDB may be worsened by injuries from common comorbid conditions such as older age, stroke, and cardiovascular risk factors.

Despite the high prevalence of SDB and cognitive impairment in CKD, to our knowledge no study has evaluated their potential association in the setting of CKD. To address this existing gap in knowledge, we examine the relationship between SDB and cognitive function as assessed by a comprehensive battery of neuropsychological tests in advanced CKD patients while accounting for potential confounders.

Methods

Subjects

As part of a previously described (14, 15) prospective cohort study investigating memory, sleep, and quality of life in patients with advanced CKD, patients were enrolled during their routine CKD clinic visit, dialysis clinic visit, or their initial evaluation at a kidney transplantation clinic between March 2004 and October 2007. Exclusion criteria included age <18 years or >90 years, use of continuous positive airway pressure (CPAP), active psychiatric or medical disease (e.g. active infection, unstable angina), severe neurologic deficits such as advanced dementia or inability to consent, history of head injury or stroke, or active alcohol abuse (14, 15).

A total of 269 subjects were screened for study participation. For these analyses, we included individuals who were enrolled and completed both baseline cognitive function testing and sleep assessment. The final study population included 169 patients, which

consisted of 70 patients receiving thrice-weekly in-center hemodialysis (HD), 17 patients undergoing peritoneal dialysis, and 82 patients with CKD stage 4 to 5 not on renal replacement therapy. The University of Pittsburgh Institutional Review Board approved this study and all subjects provided signed informed consent.

Measures

Data Collection—Baseline data collection included a brief standardized health interview, questionnaire administration, assessment of total antihypertensive medications (number used at the time of the study), antidepressant use, benzodiazepine use, blood pressure measurements, and anthropometric measurements (height, weight, neck circumference). A history of physician-diagnosed medical illnesses, previous surgical treatments, and/or medical procedures was obtained from the health interview. Standard non-fasting serum laboratory tests were abstracted from the medical record including hemoglobin, blood urea nitrogen, serum creatinine, serum glucose, serum albumin, serum total cholesterol, serum calcium, serum phosphate, and serum bicarbonate.

Cognitive Assessment—Subjects participated in a neuropsychological examination composed of a battery of measures selected for sensitivity to deficits typically found in middle-aged to older adults with chronic illnesses. This examination was conducted in a quiet environment by a specially-trained research coordinator at a time when the participant felt they were at their best. For HD patients, the cognitive assessment was typically performed on the morning of a non-dialysis day at the patient's home. The cognitive examination assessed a broad range of functions grouped by cognitive domains: global mental status (Modified Mini-Mental State Examination), attention and psychomotor speed (Trail-Making Test Part A, Digit Symbol Substitution), memory and learning (Logical Memory 1 and 2), working memory (Digit Span), and executive function (Trail-Making Test Part B, Stroop Interference, Wisconsin Card Sorting Test percentage of categories correct). Each measure is further described in Table 1.

Sleep Assessment

Polysomnography and sleep parameters: Unattended in-home polysomnography was performed using an ambulatory Compumedics Siesta monitor (Charlotte, NC) at habitual sleep times as previously described in detail (16). The trained polysomnography technologists scored sleep records for all study patients according to standard sleep stage scoring criteria (17). Apnea was defined as a complete or an almost complete (> 25% of baseline) airflow cessation; measured by the amplitude of the 10-second nasal pressure signal. Hypopnea was defined as a 10-second abnormal respiratory event with > 30% airflow reduction (compared with baseline) and was associated with 4% oxyhemoglobin desaturation. Polysomnography outcome variables in the analysis included total sleep time (sleep time excluding periods of wakefulness during the night), sleep efficiency (percentage of total sleep time as a proportion of the total study duration), parameters of sleep architecture (percentage of total sleep time spent in stage 1, stage 2, and rapid eye movement sleep), apnea/hypopnea index (AHI; number of apneas and hypopneas/hour of sleep), arousal index (number of arousals/hour of sleep), type of sleep apnea (obstructive, central, mixed apnea index), oxygen desaturation index (calculated by dividing the total number of oxygen desaturations by the total sleep time, where desaturation was defined as a > 10 second reduction in oxyhemoglobin saturation by > 4% of baseline), and nocturnal hypoxemia (> 3% of total sleep time with oxyhemoglobin saturation < 90%).

Daytime sleepiness and sleep quality: Participants completed the Epworth Sleepiness Scale, an eight-item subjective measurement of the subject's general level of daytime sleepiness (18). Excessive daytime sleepiness was defined as a score > 10. Participants also

completed the Pittsburgh Sleep Quality Index, a seven-item subjective measurement of the subject's sleep quality (19). The total score ranged from 0 to 21 points, with higher scores reflecting poorer sleep quality and a total score of >4 indicating poor sleep quality.

Definition of exposures and covariates—Kidney function in non-dialysis dependent CKD patients was estimated by the four-variable Modification of Diet in Renal Disease (MDRD) Study equation (20). For HD participants, dialysis dose was measured by the single-pool Kt/V. CVD was defined as an affirmative response (by patient self-report) to physician diagnosed heart failure, angina pectoris or myocardial infarction, or previous coronary artery bypass or angioplasty. Diabetes was defined by self-report or current use of insulin or oral hypoglycemic agents. Depression was assessed using the Patient Health Questionnaire 9 [score of >9] or self-reported treatment with antidepressants. SDB was defined as an AHI >15 and severe SDB as an AHI ≥ 30 as in previous studies (3, 21).

Cognitive Impairment—As in prior studies, cognitive impairment was defined as a score 1.5 standard deviations (SDs) or more from the normative score based on the age and education level of our study population on any cognitive test except 3MS (22, 23). As in prior studies (24), scores of less than 80 on the 3MS were used to determine cognitive impairment because such values have a sensitivity of 91% and specificity of 97% for detecting dementia in the general population (25).

Statistical Analyses

Baseline demographic, laboratory, and performance test results were described using means $\pm$ SD or medians (interquartile range) for continuous variables, and as frequency distributions for categorical variables. Statistical significance of the differences between groups was tested using Student t-test or Wilcoxon rank-sum test for continuous variables, and Chi-square tests or Fisher's exact test for categorical variables. Data with skewed distributions were analyzed following logarithmic transformation. Multivariable logistic regression analysis was used to investigate an association of sleep apnea variables with cognitive impairment across cognitive domains after adjusting for known risk factors such as age, sex, race, education, diabetes, CVD, depression, and treatment modality (11) (24). As a sensitivity analysis, tobit regression was also conducted for the Trails B test to assess the potential influence of participants who did not complete the test despite generous time allotment. For all analyses, p values < 0.05 were considered to be significant. Analyses were performed using R (26) and SAS, version 9.2 (SAS Institute Inc., www.sas.com).

Results

Baseline Characteristics

The associations of participant demographic and baseline clinical characteristics with SDB status are shown in Table 2. Mean estimated glomerular filtration rate (eGFR) by the MDRD Study equation for the CKD subgroup was 18.9 ml/min/1.73m² and the mean Kt/V for the HD group was 1.64 (data not shown). Among the 169 patients, 83 (49.1%) met criteria for SDB with an AHI > 15 events per hour. When examined by SDB status, the SDB group was older, and more likely to be male (79.5% vs. 51.2%) than the non-SDB group. The SDB group had significantly more CVD, higher body mass index, larger neck circumference, and lower eGFR compared to the non-SDB group. Participants with SDB were also more likely to be currently unemployed, active smokers, and taking more antihypertensives. In laboratory values, the SDB group had higher serum glucose levels compared with the non-SDB group.

Sleep characteristics

Polysomnography parameters, excessive daytime sleepiness, and sleep quality in the total group and in subjects with and without SDB are shown in Table 3. Compared with the non-SDB group, the SDB group showed poorer sleep efficiency and greater stage I sleep. The SDB group also had higher prevalence of nocturnal hypoxemia (65.8% vs. 26.8%, $p<0.001$) and excessive daytime sleepiness (38.6% vs. 20.7%, $p=0.01$). However, there was no significant difference in self-reported sleep quality though both groups had poor sleep quality.

Comparison of cognitive function

Table 4 shows the results of the neuropsychological tests and the normative scores based on the age and education level of this study population. Overall, study participants performed well within the average range of functioning on most tests except the Trail-making test part B, Digit symbol substitution test, and Wisconsin Card Sorting Test. The SDB group scored significantly lower on 3MS test (assessing global cognitive function) and on the logical memory 1 and the logical memory 2 tests (assessing immediate and delayed verbal memory, respectively) compared to the non-SDB group. The SDB group also attained significantly lower scores on the digit span and the digit symbol substitution tests (evaluating working memory, attention and psychomotor speed). A non-statistically significant tendency to lower scores on the other tests was noted in the SDB group. In sensitivity analyses using tobit regression to examine performance on the Trail making test part B, the results were unchanged (data not shown).

Association of sleep apnea with cognitive impairment

In neurocognitive tests where the SDB group performed significantly worse, we examined the unadjusted and adjusted associations of sleep apnea severity, nocturnal hypoxemia, and excessive daytime sleepiness with test performance (Table 5). SDB (AHI >15) was associated with a higher risk of immediate verbal memory impairment (Logical memory 1 test: unadjusted OR, 3.14; 95% CI, 1.62–6.09). The association was largely unchanged (adjusted OR, 2.67; 95% CI, 1.17–6.08) after adjustment for age, sex, race, education, diabetes, CVD, depression, and treatment modality. Severe SDB (AHI ≥ 30) was also associated with immediate verbal memory impairment in both unadjusted (unadjusted OR, 2.71; 95% CI, 1.32–5.58) and adjusted (adjusted OR, 2.41; 95% CI, 1.05–5.54) analysis. However, there was no significant graded risk of memory impairment between patients with AHI >15 and patients with AHI ≥ 30 .

Table 6 displays the subgroup analysis examining whether age modifies the cognitive dysfunction observed in SDB patients with advanced kidney disease. Among younger subjects (age <60 years), there were similar trends of poorer cognitive test scores in SDB participants (Table 6). The younger SDB group had significantly lower scores on the 3MS, logical memory 1, logical memory 2, digit span, Trail-Making Test B, digit symbol substitution test, and Stroop test compared to the younger non-SDB group. On the other hand, there were no significant differences in cognitive test performance between the SDB and non-SDB group among older adults (age >60 years). To confirm these results, linear regression analyses were conducted examining the significance of an age-SDB interaction term for cognitive test performance. In the unadjusted models, the age-SDB interaction was significant for the 3MS, logical memory 1, Trail-Making Test B, digit symbol substitution, and Stroop tests. After adjustment for sex, race, education, diabetes, depression, and treatment modality, the interaction effect was attenuated but significant for the Stroop, while a trend remained for digit symbol substitution and logical memory 1 tests (data not shown). Otherwise, the association between SDB and cognitive test performance did not differ by sex, race, CVD status, depression status, or treatment modality (data not shown).

Discussion

To our knowledge, this is the first study to investigate the association between SDB and cognitive impairment in a cohort comprising patients with chronic kidney failure and those with earlier stages (non-dialysis dependent) CKD. In this cohort, patients with SDB demonstrated significantly lower scores in tests that measured verbal memory, working memory, attention, and psychomotor speed than patients without SDB. In addition, an independent association was observed between objectively measured sleep apnea and cognitive impairment, especially verbal memory. Excessive daytime sleepiness, which can be measured with a simple questionnaire, had a comparable association with impaired verbal memory even after adjustment for confounders. In contrast, no relationship between memory impairment and nocturnal hypoxemia was found. These findings suggest that sleep fragmentation rather than hypoxemia is associated with memory impairment in advanced CKD patients with SDB.

Our findings are in accordance with previous studies in the general population showing that SDB significantly impairs cognitive performance, especially attention, memory and executive functioning (12). Interestingly, in this study there was no association between SDB and Wisconsin Card Sorting Test performance, a sensitive measure of executive function. This finding contrasts with a recent meta-analysis reporting that executive function was the cognitive domain most affected by sleep apnea syndrome in the general population (27). However, our advanced CKD and dialysis participants generally performed poorly on the Wisconsin Card Sorting Test regardless of SDB status. These findings could be explained by the higher rates of CKD-associated comorbidities in our sample. Several studies have shown that executive function is frequently impaired in CKD patients (11, 24, 28) and these underlying impairments may make it more difficult to detect the potential effects of SDB on executive function.

Our findings contrast to the recently published Apnea Positive Pressure Long-term Efficacy Study (APPLES), which documented relatively little association between the apnea hypopnea index and neurocognitive performance (29). We believe this is likely due to a number of factors. First, APPLES excluded patients with a history of myocardial infarction, stroke, congestive heart failure, lung disease, kidney failure, or an abnormal EKG. Hence, the vast majority of participants in our study would have been excluded from APPLES. Another important difference was level of education, the average participant in APPLES completed >15 years of education (i.e., some college education). Further, variations in the definition of SDB/obstructive sleep apnea (e.g., AHI>15 vs AHI>10) and in the neurocognitive measures employed may also have contributed to the observed differences.

SDB could contribute directly or indirectly to the cognitive impairment found in patients with CKD. Rather than representing an isolated process, impairments in the setting of SDB may be the consequence of overlapping injuries from common comorbidities and CKD-related conditions such as uremia, anemia, malnutrition, secondary hyperparathyroidism, and hemodynamic instability during dialysis (11). Recently developed brain imaging techniques have been used to analyze regional brain injury and dysfunction in individuals with sleep apnea. In such studies, the hippocampus, which is vital for specific spatial and contextual memory tasks, is one of the brain regions showing signs of injury (30). Previous studies in severe SDB also suggest an association between apnea severity and small vessel ischemic brain disease and lower cerebral metabolism in the cerebral white matter (31). White matter disease is a common feature of subclinical cerebrovascular disease with a prevalence of 50–80 % by brain imaging in CKD patients (32, 33). White matter disease has also been associated with deficiencies in executive functioning and memory in elderly

populations (34). Analogously, it may be linked to the cognitive impairment seen in the CKD population with SDB.

Our results are clinically meaningful considering that CPAP therapy could ameliorate cognitive function, daytime sleepiness, subjective sleep quality and mood in moderate to severe SDB patients (35–37). In addition, improvements in memory function following varying periods of CPAP use have consistently been reported in small, short term trials (37–39). Further studies are needed in the CKD population to determine the potential benefits of CPAP on cognitive function.

Our subgroup analysis indicates that the impact of SDB on cognitive function in older adults may be limited, despite the higher prevalence of SDB in this group. Specifically, our findings suggest that age fulfills an important role in moderating cognitive function. In examining the effects of age in our study, it is worth noting that we excluded participants with a previous diagnosis of dementia or stroke, and all participants were able to complete activities of daily living without assistance. Although aging induces a greater incidence of SDB with associated vascular comorbidities (40, 41), it is unclear whether SDB in older adults represents the same disorder encountered in middle-aged populations. Prior cross-sectional studies of sleep disordered breathing and cognitive function in the elderly have yielded conflicting results; some investigations have reported associations of sleep-disordered breathing with lower cognitive test scores or dementia (23, 42), while others have not (43, 44). Further, alterations in the cognitive function of older adults with SDB could be caused by other factors independent of sleep disordered breathing, and thus, may not warrant similar therapy.

Given the high prevalence of SDB and the anticipated increase as the US population ages and obesity, diabetes, and CKD become more common, it is important that novel noninvasive screening/diagnostic methods that are more cost effective and broadly applicable than standard full polysomnography become available. Such tools could include biomarkers that reveal sleep apnea, assess its severity, or detect its consequences. Our study suggests that excessive daytime sleepiness assessed using a simple questionnaire can screen for sleep apnea and cognitive dysfunction, especially memory impairment.

These findings should be considered in light of certain limitations. First, study participants were living independently at home and might have had better functional status than the general advanced CKD/dialysis population. This may limit the generalizability of our results. However, most CKD/dialysis patients live at home and our normative data was also derived from a community-based sample. Second, this study is cross-sectional and cannot demonstrate causality. Third, our study had a relatively small sample size and our analysis included multiple comparisons. Our findings should be viewed as hypothesis generating and larger corroborating studies are needed. Finally, we relied on medications and self-reported data for important risk factors such as presence of cerebrovascular disease, cardiovascular diseases and diabetes.

The present study also has several strengths. Our patients performed their assessments at home when they were stable and comfortable. This is particularly important in patients treated with hemodialysis because hemodynamic changes and cerebral ischemia during hemodialysis could play a role in transiently worsening cognitive function (45). Many previous studies assessed cognitive function during hemodialysis treatments (46). In addition, using a comprehensive, multidimensional spectrum of cognitive neuropsychological tests, we were able to distinguish between different types of memory, including short-term, long-term, and working memory. Finally, we also performed both

subjective and objective sleep tests when examining the association of sleep disorders with cognitive function in advanced kidney disease.

In summary, we found significant associations between objectively measured sleep apnea and cognitive impairment, especially verbal memory, even after adjustment for potential confounders. We believe that such memory impairments may substantially lower daytime functional performance in CKD patients. However, the impact of SDB on cognitive function in older adults was limited despite the higher prevalence of SDB. Our findings suggest that nephrologists need to be mindful of the potential role SDB may play in the cognitive impairment frequently observed in the CKD and dialysis population.

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Table 1

Cognitive measures

Cognitive Test	Description/Domains	Scoring
Modified Mini-Mental State Examination (3MS) (47)	Expands the original 11-item Mini-Mental State Examination. Includes tests of orientation, attention, calculation, recall, language, and visuospatial skills.	Range from 0 to 100, higher scores reflect a more intact performance.
Trail-Making Test Parts A & B (48)	Part A: requires individual to connect series of numbers in sequential order as quickly as possible. Assesses attention and psychomotor speed. Part B: requires individual to connect letters and numbers in sequential order, alternating between letters and numbers. Considered a general gauge of cognitive integrity and measures attention to set-shifting and working memory.	Amount of time required, in seconds, for each task.
Digit-Symbol Substitution Subtest (49)	Subtest from WMS-3, requires visual scanning and rapid response in substituting numbers for symbols according to a learned code. Assesses attention and psychomotor speed.	Total number correct within the given time frame.
Digit Span Subtest (49)	Subtest from WMS-3. Individual is required to repeat increasingly longer number sequences in either forward or reverse order.	Age-based scaled score is generated.
Logical Memory Subtest (49)	This subtest from WMS-3 measures the individual's verbal memory. Stories are read to the individual who is asked to recall as many details as possible (logical memory 1). A delayed recall component is conducted approximately 30 minutes later (logical memory 2).	For both conditions, age-based standard scores were used.
Wisconsin Card Sorting Test (WCST) (48)	Stimulus cards are given to the subject. The subject is not directed on how to match the cards, but is told whether a particular match is correct. Provides an overall measure of problem solving, executive function.	Dichotomized: whether participant completed 4 or more categories.
Stroop Test (50)	This test requires the individual to read the names of colors, name the color of an image, and name the color of the ink of a printed color word. The Interference score provides an estimate of the individual's ability to inhibit an overlearned response quickly. Assesses executive function.	Age-based T-scores were used.

Abbreviation: WMS-3, Wechsler Memory Scale 3.

Table 2

Baseline characteristics by SDB status

Characteristic	Total	SDB group (AHI >15)	Non-SDB group (AHI ≤15)	p-value
No. of patients	169	83	86	--
Age (y)	52.6 ± 14.6	57.0 ± 12.1	48.5 ± 15.6	<.001
Male sex	110 (65.1)	66 (79.5)	44 (51.2)	<.001
African-American	53 (31.4)	28 (33.7)	25 (29.1)	0.5
Currently working	57 (33.7)	22 (26.5)	35 (40.7)	0.05
At least a high school education	151 (89.3)	74 (89.2)	77 (89.5)	0.9
Married	99 (58.6)	53 (63.9)	46 (53.5)	0.2
Currently smoking	22 (13.0)	15 (18.1)	7 (8.1)	0.06
Depression	39 (23.3)	22 (26.6)	17 (20.2)	0.3
Diabetic	57 (33.7)	32 (38.6)	25 (29.1)	0.2
Hypertension	125 (73.8)	60 (72.8)	64 (74.7)	0.8
Treatment modality				
CKD	82 (48.5)	36 (43.4)	46 (53.5)	0.1
HD	70 (41.4)	41 (49.4)	29 (33.7)	
PD	17 (10.1)	6 (7.2)	11 (12.8)	
Past history of CVD	48 (28.4)	33 (39.2)	15 (17.6)	0.006
SBP (mmHg)	146.7 ± 25.6	149.7 ± 26.6	143.7 ± 24.3	0.1
DBP (mmHg)	82.8 ± 14.8	81.2 ± 15.1	84.5 ± 14.5	0.2
BMI (kg/m ²) *	27.7 ± 5.4	28.9 ± 5.8	26.6 ± 4.9	<.01
Neck circumference, inches	15.6 ± 2.9	16.5 ± 3.5	14.6 ± 1.9	<.001
eGFR (mL/min/1.73m ²) * †	13.3 ± 7.8	12.3 ± 8.0	14.2 ± 7.4	0.04
Laboratory values				
Hemoglobin (g/dL)	11.8 ± 1.5	11.8 ± 1.5	11.8 ± 1.4	0.8
Albumin (g/dL)	3.9 ± 0.5	3.8 ± 0.7	3.9 ± 0.4	0.4
Glucose (mg/dL) *	118.7 ± 48.8	127.5 ± 52.6	109.7 ± 43.2	0.01
Total cholesterol (mg/dL)	173.2 ± 43.3	178.3 ± 47.3	168.3 ± 38.7	0.2
Calcium (mg/dL) *	9.1 ± 0.8	9.1 ± 0.7	9.0 ± 0.9	0.2
Phosphorus (mg/dL)	5.1 ± 1.5	5.2 ± 1.6	5.0 ± 1.4	0.4
Serum bicarbonate (mEq/L)	23.4 ± 4.0	23.7 ± 4.4	23.1 ± 3.4	0.3
Medications used				
Total no. of antihypertensive	2.4 ± 1.5	2.7 ± 1.5	2.2 ± 1.5	0.05
Antidepressant use	23 (13.8)	13 (15.8)	10 (12.0)	0.5
Benzodiazepine use	13 (7.5)	7 (7.9)	6 (7.2)	0.9

Abbreviations: AHI, apnea-hypopnea index; SDB sleep disordered breathing, CKD chronic kidney disease, HD hemodialysis, PD peritoneal dialysis, CVD cardiovascular disease, SBP systolic blood pressure, DBP diastolic blood pressure, BMI body mass index, eGFR estimated glomerular filtration rate. Conversion factors for units: glucose in mg/dL to mmol/L, $\times 0.05551$; cholesterol in mg/dL to mmol/L, $\times 0.02586$; calcium in mg/dL to mmol/L, $\times 0.2495$; phosphorus in mg/dL to mmol/L, $\times 0.3229$.

Continuous variables are expressed as mean $\pm$ SD; categorical variables as number (percentage).

* Table reports mean $\pm$ SD however *P*-value represents analysis of log transformed variable.

[†] Value restricted to participants not requiring dialysis.

Table 3

Sleep characteristics and subjective sleep quality

	Total	SDB group	Non-SDB group	<i>p</i> -value
Total sleep time (mins)	434.6 ± 119.0	432.8 ± 130.3	436.3 ± 107.6	0.9
Sleep efficiency (%) [*]	71.7 ± 15.5	68.3 ± 15.8	75.0 ± 14.6	<.01
Percentage of total sleep time				
Stage 1 [*]	12.8 ± 9.9	16.2 ± 11.8	9.4 ± 6.1	<.001
Stage 2	58.9 ± 12.9	58.7 ± 13.5	59.1 ± 12.5	0.8
REM	18.8 ± 8.9	18.5 ± 9.1	19.0 ± 8.8	0.7
AHI, /hour [*]	22.3 ± 25.7	39.7 ± 27.1	5.4 ± 3.9	<.001
CAI, /hour	1.1 ± 3.6	1.8 ± 5.0	0.3 ± 0.7	0.1 [†]
AI [*]	0.073 ± 0.028	0.079 ± 0.028	0.067 ± 0.026	0.004
ODI [*]	8.2 ± 13.3	11.5 ± 15.3	4.5 ± 9.3	0.001
PLMI, /hour [*]	4.3 ± 4.9	4.8 ± 5.4	3.9 ± 4.2	0.3
Nocturnal hypoxemia ^{**}	47.3	65.8	26.8	<.001
EDS	29.7	38.6	20.7	0.01
PSQI, total	7.4 ± 4.3	7.5 ± 4.2	7.4 ± 4.5	0.9

Abbreviations: SDB sleep disordered breathing, TST total sleep time, REM rapid eye movement, AHI apnea/hypopnea index, CAI central apnea index, AI arousal index, ODI oxygen desaturation index, PLMI periodic leg movement index, EDS excessive daytime sleepiness, PSQI Pittsburgh Sleep Quality Index.

Continuous variables are expressed as mean ± SD; categorical variables as percentages.

^{*} Table reports mean ± SD however; *p*-value represents analysis of log transformed variable.

[†] Wilcoxon rank-sum test

^{**} SpO₂<90% for 3% TST

Table 4

Cognitive function scores by SDB status.

	Expected Scores	Total	SDB group	Non-SDB group	p-value
3MS	90 ± 10	91.7 ± 7.4	90.5 ± 7.9	92.8 ± 6.8	0.04
Logical memory 1 ***	10 ± 1.5	8.5 ± 3.2	7.6 ± 3.1	9.4 ± 3.1	<.001
Logical memory 2 ***	10 ± 1.5	9.6 ± 2.9	9.0 ± 3.0	10.2 ± 2.6	<.01
Digit span ***	10 ± 1.5	9.1 ± 2.7	8.5 ± 2.1	9.7 ± 3.1	<.01
Trails A Time (s) *	35 ± 10	40.5 ± 23.5	42.3 ± 24.4	38.8 ± 22.6	0.2
Trails B time (s) *	77.7 ± 23.8	96.9 ± 52.7	101.9 ± 53.2	92.4 ± 52.2	0.1
Digit symbol substitution test	72 ± 30	45.8 ± 14.5	42.4 ± 13.3	48.9 ± 15.0	<.01
WCST **	50	26	21	30	0.2
Stroop test interference T score	50 ± 15	45.5 ± 9.4	44.3 ± 9.2	46.7 ± 9.5	0.1

Abbreviations SDB sleep disordered breathing, 3MS, Modified Mini-Mental State Examination, WCST Wisconsin Card Sort Test. Continuous variables are expressed as mean ± SD; categorical variables are expressed as percentages.

* Table reports mean ± SD however, p-value represents analysis of log transformed variable.

** Wisconsin Card Sort Test expressed as percentage of subjects who completed 4 or more categories.

*** age adjusted raw score

Table 5

Association of sleep parameters with cognitive impairment.

Cognitive measure	OR (95% CI)		<i>p</i> -value*
	Unadjusted	Adjusted [‡]	
3MS			
SDB (AHI>15 vs. <15)	1.51 (0.46–4.97)	0.85 (0.22–3.32)	0.8
Severe SDB (AHI >30 vs. <30)	0.60 (0.13–2.86)	0.19 (0.02–2.09)	0.2
Nocturnal hypoxemia (vs. nonhypoxemic)	2.08 (0.58–7.44)	1.00 (0.27–3.71)	0.9
EDS (ESS>10 vs. <10)	0.20 (0.03–1.57)	0.30 (0.06–1.60)	0.2
Logical memory 1			
SDB (AHI>15 vs. <15)	3.14 (1.62–6.09) [‡]	2.67 (1.17–6.08)	0.02
Severe SDB (AHI >30 vs. <30)	2.71 (1.32–5.58) [‡]	2.41 (1.05–5.54)	0.04
Nocturnal hypoxemia (vs. nonhypoxemic)	1.72 (0.88–3.37)	1.51 (0.68–3.34)	0.3
EDS (ESS>10 vs. <10)	2.02 (1.02–4.02) [‡]	2.97 (1.28–6.91)	0.01
Logical memory 2			
SDB (AHI>15 vs. <15)	2.03 (0.94–4.37)	1.21 (0.45–3.21)	0.7
Severe SDB (AHI >30 vs. <30)	3.06 (1.38–6.77) [‡]	2.31 (0.89–6.01)	0.08
Nocturnal hypoxemia (vs. nonhypoxemic)	1.97 (0.87–4.46)	1.77 (0.67–4.72)	0.3
EDS (ESS>10 vs. <10)	1.84 (0.84–4.03)	2.45 (0.92–6.50)	0.07
Digit Span			
SDB (AHI>15 vs. <15)	1.49 (0.72–3.06)	1.28 (0.50–3.28)	0.4
Severe SDB (AHI >30 vs. <30)	1.80 (0.82–3.96)	1.73 (0.66–4.55)	0.3
Nocturnal hypoxemia (vs. nonhypoxemic)	1.47 (0.69–3.14)	1.58 (0.63–3.97)	0.3
EDS (ESS>10 vs. <10)	1.17 (0.53–2.57)	0.80 (0.30–2.17)	0.7
Digit symbol substitution test			
SDB (AHI>15 vs. <15)	1.21 (0.46–3.14)	0.72 (0.19–2.68)	0.6
Severe SDB (AHI >30 vs. <30)	1.09 (0.37–3.24)	0.91 (0.21–4.03)	0.9
Nocturnal hypoxemia (vs. nonhypoxemic)	2.61 (0.92–7.38)	1.00 (0.27–3.67)	0.9
EDS (ESS>10 vs. <10)	0.80 (0.27–2.35)	0.54 (0.13–2.35)	0.4

Abbreviations AHI, apnea-hypopnea index; CI, confidence interval; 3MS, Modified Mini-Mental State Examination; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; OR, odds ratio.

SDB was defined as an AHI>15 and severe SDB as an AHI ≥ 30

* *p*-values are for adjusted model.

[‡] *p*<0.05 in unadjusted analysis.

[‡] Adjusted for age, sex, race, education, diabetes, CVD, depression, and treatment modality.

Table 6

Cognitive performance stratified by SDB and age

Cognitive measures	Age 60 (n=117)		Age>60 (n=52)	
	With SDB (n=52)	Without SDB (n=65)	With SDB (n=31)	Without SDB (n=21)
3MS	91.3 ± 6.3 ^b	94.6 ± 4.9	89.1 ± 10.0	87.19 ± 8.72
Logical memory1 (age adjusted raw score)	8.9 ± 2.6 ^c	10.4 ± 2.5	9.0 ± 3.6	9.55 ± 2.96
Logical memory2 (age adjusted raw score)	7.4 ± 3.0 ^b	9.7 ± 3.1	7.9 ± 3.4	8.14 ± 2.92
Digit span (age adjusted raw score)	8.7 ± 2.2 ^b	10.2 ± 3.12	8.1 ± 2.0	8.29 ± 2.33
Trails A Time (s) [*]	38.6 ± 19.6	33.4 ± 17.6	48.6 ± 30.8	56.5 ± 27.9
Trails B time (s) [*]	95.6 ± 52.1 ^a	77.6 ± 39.1	112.2 ± 54.3	140.6 ± 60.9
Digit symbol substitution test	45.3 ± 13.3 ^b	53.5 ± 12.7	37.7 ± 10.9	34.0 ± 12.2
WCST ^{**}	27	38	11	0
Stroop test interference T score	42.0 ± 8.3 ^b	47.5 ± 9.6	48.0 ± 9.5	43.8 ± 9.0

Abbreviations SDB sleep disordered breathing, 3MS Modified Mini-Mental State Examination, WCST Wisconsin Card Sort Test.

Continuous variables are expressed as mean ± SD; categorical variables are expressed as percentages.

^{*} Table reports raw mean ± SD, however *p*-value represents analysis of log transformed variable;

^{**} Wisconsin Card Sort Test expressed as percentage of subjects who completed 4 or more categories;

^a *p*<0.05

^b *p*<0.01,

^c *p*<0.001 compared with patients without SDB