

Sleep Apnea in Patients on Conventional Thrice-Weekly Hemodialysis: Comparison with Matched Controls from the Sleep Heart Health Study

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Sleep-disordered breathing (SDB) has been noted commonly in hemodialysis (HD) patients, but it is not known whether this is related directly to the treatment of kidney failure with HD or to the higher prevalence of obesity and older age. Forty-six HD patients were compared with 137 participants from the Sleep Heart Health Study (SHHS) who were matched for age, gender, body mass index (BMI), and race. Home unattended polysomnography was performed and scored using similar protocols. The study sample was 62.7 ± 10.1 yr, was predominantly male (72%) and white (63%), and had an average BMI of 28 ± 5.3 kg/m². The HD sample had a higher systolic BP (137 versus 121 mmHg; $P < 0.01$) and a higher prevalence of diabetes (33 versus 9%; $P < 0.01$) and cardiovascular disease (33 versus 13%; $P < 0.01$) compared with the SHHS sample. The HD group had significantly less sleep time (320 versus 379 min; $P < 0.0001$) but similar sleep efficiency. HD patients had a higher frequency of arousals per hour (25.1 versus 17.1; $P < 0.0001$) and apnea-hypopneas per hour (27.2 versus 15.2; $P < 0.0001$) and greater percentage of the total sleep time below an oxygen saturation of 90% (7.2 versus 1.8; $P < 0.0001$). HD patients were more likely to have severe SDB (>30 respiratory events per hour) compared with the SHHS sample (odds ratio 4.07; 95% confidence interval 1.83 to 9.07). There was a strong association of HD with severe SDB and nocturnal hypoxemia independent of age, BMI, and the higher prevalence of chronic disease. The potential mechanisms for the higher likelihood of SDB in the HD population must be identified to provide specific prevention and therapy.

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Poor sleep and fatigue are common in older adults who undergo hemodialysis (HD), with HD patients reporting sleep problems more than twice as frequently as healthy control subjects (1,2). Despite this association, the extent and the severity of sleep disorders among the HD population and their cause both remain unclear (3–6). Although polysomnographic information in HD patients is limited, the available data do suggest that sleep-disordered breathing (SDB) may affect a significant percentage of dialysis patients (2,7). Although a number of studies have shown that a substantial proportion of HD patient have sleep apnea, these studies were limited by very small study samples (8–12), by the use of

partial channel polysomnography (PSG) (12–14), by the study of populations with limited generalizability to HD patients who are cared for in the United States (15), by very selected subpopulation of dialysis patients without sleep symptoms (16), or by study samples that largely were composed of symptomatic patients (7,8,17).

Because a growing number of HD patients who are cared for in the United States are older than 65 yr (18), it is possible that reports of high rates of SDB and sleep problems in HD patients represent an aging effect, uremia effect, or some combination of the two. In particular, the prevalence of SDB and daytime sleepiness both increase with age (19), with SDB estimated to occur in 20 to 45% of adults who are older than 65 yr (20). In addition, daytime sleepiness was reported to occur in approximately 20% of the 4500 elderly participants in the Cardiovascular Health Study (CHS) (21). The increased risk for SDB in the aged population has been attributed to a combination of age-related and age-dependent (a range of conditions related to aging, including cardiac and pulmonary disease and medication use) risk factors (22). Although older adults are at high risk

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for sleep problems, does HD confer additional, independent risk for SDB in elderly patients? The combination of age and comorbid conditions that is found among the HD population make it important to account for the effects of age when trying to delineate the underlying relationship between SDB and HD.

To determine the association of HD with poor sleep and SDB, we compared older adults who were undergoing HD with participants in the ongoing multicenter Sleep Heart Health Study (SHHS), which obtained polysomnographic data on volunteers from a range of community-based cohort studies. We hypothesized that there would be an independent association between HD and SDB; therefore, this report examines the extent to which SDB is associated with chronic maintenance HD independent of the effects of age and health status.

Materials and Methods

Study Setting, Samples, and Design

The HD study sample was composed of patients who were undergoing thrice-weekly, in-center HD at one of 24 centers in Western Pennsylvania, and studies were performed between May 2004 and September 2005. The following patients were excluded from participation in the HD study sample: Patients with craniofacial abnormalities, age <45 yr or >90 yr, active malignancy, active infection (pneumonia), active coronary artery disease (e.g., unstable angina, myocardial infarction) within the last 6 mo, advanced cirrhosis, advanced dementia, or active alcohol abuse and those with refractory psychiatric disease ascertained by medical records and confirmed in interview. In addition, patients who were using continuous positive airway pressure (CPAP), oral devices, or home oxygen therapy and those who had a tracheostomy were excluded. This study was approved by the University of Pittsburgh institutional review board, and all participants provided informed consent.

A total of 92 patients were screened for HD sleep study participation. Of these, 25 either met exclusion criteria or declined consent and 21 did not complete home PSG study (seven because of failing health, eight because of time constraints or loss of interest, three were not interested in the home PSG or were nonadherent with appointments, one patient was excluded for unsafe home environment, one patient died, and one received a kidney transplant before completing the home PSG). The 46 remaining HD participants are included in this report. Patient preference determined when nocturnal PSG were conducted relative to the day of HD. Nineteen participants were studied the evening of HD, and 27 were studied during a day off from HD.

The overall objectives and study design of the SHHS were reported previously (23). Briefly, the SHHS is a prospective cohort study that aims to investigate the relationship between SDB and cardiovascular disease (CVD). Participants were recruited from nine existing epidemiologic studies in which data on cardiovascular risk factors had been collected previously. From these parent cohorts, a sample of participants who met the inclusion criteria (age \geq 40 years, no history of treatment of sleep apnea, no tracheostomy, and no current home oxygen therapy) were invited to participate in the baseline examination of the SHHS. Several cohorts oversampled snorers to increase the study-wide prevalence of SDB as described previously (24). The SHHS baseline examination was conducted between December 1995 and January 1998. Between 2001 and 2002, 3295 patients who represented a subset of the original cohort (51.2% of live participants and excluding the 99 individuals who were users of CPAP) participated in a follow-up examination, which included an overnight PSG. Approval for the study protocol was obtained from the institutional review board of each

SHHS site and coordinating center. Written informed consent for participation in the SHHS was obtained from each participant.

The control sample consisted of 137 individuals who participated in the SHHS 2001 to 2002 examination. The goal was to assign randomly up to three SHHS control subjects who were matched individually to each HD patient on gender and race and as close as possible on body mass index (BMI) and age. Repeated random selection simulations were used to optimize the closeness of assignment, with BMI having a greater weight than age. Forty-three HD patients each were assigned three control subjects within ± 2 kg/m² of BMI and ± 3 yr of age, whereas two HD patients had three matches and one patient had two matches each within ± 3 units of BMI and ± 5 yr of age.

Data Collection

The baseline HD and SHHS data collection session included a brief standardized health interview and questionnaire administration, assessment of current medication use (25), BP and anthropometric measurements, and unattended home PSG (23). A self-completed sleep habits questionnaire (administered before or at the time of the baseline examination) provided information on perceived sleep disturbances and sleep quality. The Epworth Sleepiness Scale was used as an index of self-reported sleep tendency (26). A history of physician-diagnosed medical illnesses, previous surgical treatments, or medical procedures was obtained from the health interview.

PSG

In the HD cohort, PSG was performed using the Compumedics Siesta System (Abbottsville, Australia), overnight between 8:00 p.m. and 8:00 a.m. Sensors were placed and equipment was calibrated during an evening home visit by a certified technician. PSG sleep recordings included measurement of sleep with bilateral bipolar electroencephalogram (EEG) channels (C3-P3, C4-P4, and Cz-Pz), right and left eye movements (right and left electrooculograms), and submental electromyogram. Respiratory parameters were assessed with finger pulse oximetry (Nonin, Minneapolis, MN), oral thermocouple, and abdominal and thoracic effort by inductance plethysmography. A bipolar electrocardiogram and position sensor also were used to measure heart rate and body position, respectively. In addition, airflow with nasal pressure and periodic limb movements with piezo sensors on both legs were measured but were not scored for this report.

In SHHS, PSG was performed using an earlier version of a similar device as the Siesta unit (PS-2 System), using methods previously detailed (27). Data collection included a subset of the physiologic channels that were collected in the HD sample: Two central EEG; right and left electro-oculograms; a bipolar submental electromyogram; thoracic and abdominal piezo bands; airflow with a nasal-oral thermocouple, finger pulse oximetry, a bipolar electrocardiogram lead; body position (using a mercury gauge sensor); and ambient light (on or off, by a light sensor secured to the recording garment).

Scoring of Polysomnograms

For both the HD and SHHS studies, data processing and scoring followed identical procedures. The PSG scoring was completed by centrally trained scoring staff that followed a rigorous quality control process, including a detailed written manual (27) and regular monitoring of within and between scorer drift. After equipment retrieval, the data, stored in real time on personal computer cards, were downloaded to local computers, reviewed, and forwarded to a central reading center (Case Western Reserve University). Although the HD studies contained additional channels of data compared with the SHHS, only channels that were used in the SHHS scoring were displayed during central

scoring of studies for the HD sample. Specifically, because the SHHS did not contain an extended EEG montage, nasal pressure monitoring, or leg movement monitoring, none of these channels was displayed or used in scoring. Sleep stages were scored according to the guidelines developed by Rechtschaffen and Kales (28). Arousals were identified according to American Sleep Disorders Association (American Academy of Sleep Medicine) criteria (29). An apnea was defined as a complete or almost complete cessation of airflow, as measured by the amplitude of the thermocouple signal, that lasted 10 s or longer. Hypopneas were identified when the amplitude of a measure of flow or volume (detected by the thermocouple or thoracic or abdominal piezo band signals) decreased to <70% of the amplitude of baseline breathing for 10 s or longer but did not meet the criteria for apnea. Central apneas were scored when airflow (detected by the thermocouple) was absent or nearly absent for 10 s or more and there was no evidence of effort from both the abdominal and the thoracic channels. For this study, only apneas or hypopneas that were associated with at least a 3% oxyhemoglobin desaturation were considered in the calculation of the Respiratory Disturbance Index (RDI).

Confounders

CVD was defined as an affirmative response to physician-diagnosed heart failure, myocardial infarction or heart attack, or previous coronary artery bypass or angioplasty. Lung disease was based on an affirmative answer to diagnosed bronchitis, asthma, or emphysema. Diabetes was defined as the current use of insulin or oral hypoglycemic agents. Smoking was classified as a >20-pack lifetime exposure. Alcohol exposure was measured by the total number of beer, wine, and hard liquor beverages consumed in the average week. Caffeine exposure was characterized using the number of cups of caffeinated coffee, tea, and soft drinks consumed per day.

Sleep Parameter Definitions

The percentage of time in each sleep stage was calculated on the basis of the total time asleep. Sleep efficiency was defined as the percentage

of total time asleep divided by the total time in bed after lights off to the time of final awakening. The arousal index (ArI) was defined as the total number of arousals in sleep, divided by the total sleep time.

Statistical Analyses

To stabilize the variance and correct for nonnormality, we used the log-log transformation for percentage stage 1, percentage stage 2, percentage stages 3 to 4, and sleep efficiency and the log transformation for ArI and RDI. A transformation was not required for percentage of rapid eye movement (REM). Analyses included logistic regression, mixed-effects regression models, and conditional logistic regression techniques. In all comparisons between samples, the analyses accounted for the matching of HD case patients with control subjects. The differences between groups were tested using appropriate transformations. Logistic regression was used for each sample to examine the extent to which variables were associated with the presence of severe SDB. Analyses were performed using SAS (version 8.1; SAS Institute, Cary, NC).

Results

The characteristics and the burden of chronic disease for the HD and SHHS matched sample are shown in Table 1. Because the groups were matched on age, gender, race, and BMI, there were no significant differences between groups: Average age was 62.7 yr, 72% of the sample were male, 63% were white, and the mean BMI was 28 kg/m². There was a similar degree of cigarette smoking and caffeine use in both groups. However, there was a higher rate of alcohol use in the SHHS sample. The HD group had a higher systolic BP and a higher proportion of diabetes and CVD. The use of benzodiazepines and antidepressants was similar in both samples.

Table 1. Characteristics of HD and population control samples^a

Variable	HD Patients (n = 46)	Matched Controls (n = 137)	p ^b
Age (yr)	62.7 ± 10.1	62.7 ± 10.1	NS
Male gender	33 (71.7)	98 (71.5)	NS
Race			
white	29 (63.0)	87 (63.5)	NS
black	16 (35.0)	47 (34.3)	NS
Native American	1 (2.0)	3 (2.2)	NS
BMI (kg/m ²)	28.0 ± 5.4	28.1 ± 5.3	NS
History of tobacco use	26 (56.5)	73 (53.3)	NS
Caffeinated beverage (servings/d; median [IQR])	2 (0 to 3)	2 (1 to 3)	NS
Alcohol (servings/wk; median [IQR])	0 (0 to 1)	1 (0 to 6)	<0.01
Benzodiazepine use	4 (8.7)	6 (4.4)	NS
Antidepressant use	6 (13.0)	13 (9.5)	NS
Systolic BP (mmHg)	137 ± 30.1	120.5 ± 14.9	<0.001
Diastolic BP (mmHg)	73.0 ± 15.0	72.7 ± 9.7	NS
Lung disease	5 (10.8)	23 (16.7)	NS
CVD	15 (32.6)	17 (12.5)	<0.01
Diabetes	15 (32.6)	12 (8.8)	<0.01

^aData are mean ± SD or n (%). BMI, body mass index; CVD, cardiovascular disease; HD, hemodialysis; IQR, interquartile range.

^bNS = P > 0.05.

The HD sample had been on thrice-weekly, in-center HD for a median of 22 mo at the time of the sleep studies (interquartile range 9 to 46 mo). The cause of ESRD was diabetes ($n = 20$; 44%), hypertension ($n = 11$; 24%), glomerulonephritis ($n = 5$; 11%), transplant related ($n = 3$; 7%), and other causes ($n = 7$; 15%). The average hemoglobin was 12.5 (4.5) mg/dl, mean serum phosphate was 5.0 (1.04) mg/dl, and mean serum bicarbonate was 23.0 (2.6). The patients were receiving an adequate dosage of dialysis as demonstrated by an average mean single-pool Kt/V >1.2 or urea reduction ratio >0.66.

In Table 2, the objective and subjective sleep parameters of the HD and SHHS samples are displayed. The HD sample demonstrated a significantly shorter sleep time but similar mean sleep efficiency. There were no differences in stage 1 or stage 2 sleep between groups. The HD sample had significantly more stages 3 to 4 and less REM as a percentage of total sleep time compared with the SHHS group. The HD sample demonstrated a markedly higher ArI, higher RDI, and more severe nocturnal hypoxemia. There were no significant differences in self-reported daytime sleepiness as measured by the Epworth Sleepiness Scale.

The prevalence of participants with central sleep apnea was low in both the HD and the SHHS samples. The median central apnea index for the HD sample was 0.4 (interquartile range 0.0 to 1.8) and for the SHHS comparison group was 0.13 (interquartile range 0.0 to 0.44). No periodic breathing or periodic deep breaths were found in the HD sample, perhaps reflecting the universal use of bicarbonate-based dialysis solutions (30). No differences were found in the severity of sleep apnea relative to the timing of the HD treatment. The apnea-hypopnea index for the HD participants studied on the evening of the dialysis treatment ($n = 19$) compared with the HD group studied one off-HD evening ($n = 27$) was 29.5 ± 23.3 versus 25.4 ± 16.3 ($P = 0.43$).

The HD sample had significantly higher odds of severe SDB (RDI >30; crude: odds ratio [OR] 4.07 [95% confidence interval (CI) 1.83 to 9.07]; adjusted for history of CVD: OR 3.49 [95% CI 1.5 to 7.9]; adjusted for history of CVD and diabetes: OR 4.02 [1.5 to 10.2]). The association was slightly attenuated after adjustment for CVD but remained essentially unchanged when adjusted for both CVD and diabetes.

As a sensitivity analysis, those who were using antidepressants and benzodiazepines were excluded from the sample and the sleep quality parameters were assessed. No substantial differences were found between those results and the data presented.

Discussion

When compared with a community-dwelling matched sample derived from the SHHS, our cohort of older HD patients who were undergoing thrice-weekly, in-center HD had a higher odds of SDB and more severe nocturnal hypoxemia. In addition, the HD group demonstrated shorter sleep time and greater sleep fragmentation, as indicated by a higher number of arousals per hour of sleep.

Our findings support an association between HD and SDB and show that this association cannot be explained by advanced age or self-reported comorbidity. There was a four-fold higher odds of having severe SDB among those who were undergoing HD compared with an age-, gender-, race-, and BMI-matched comparison group; this confirms and extends previous findings of high rates of SDB in ESRD. The HD group had more severe desaturations during both REM and non-REM sleep. The available data suggest that 50 to 80% of patients with ESRD have SDB (7,10,11), many times the rate of SDB in healthy, middle-aged adults (19). These previous studies, however, included case series of symptomatic patients who had ESRD and were referred for sleep studies, and the rates of SDB

Table 2. Sleep parameters of HD and population control samples^a

Variable	HD Population ($n = 46$)	Matched Controls ($n = 137$)	P^b
Sleep time (min)	319.5 ± 106.3	378.9 ± 67.3	<0.001
Sleep efficiency (sleep time/total time in bed)	78.1 ± 15.3	81.3 ± 10.4	NS
Stage 1 sleep (%) ^c	5.0 ± 3.4	5.5 ± 3.65	NS
Stage 2 sleep (%)	57.6 ± 14.3	58.4 ± 11.5	NS
Stage 3 to 4 sleep (%) ^c	23.4 ± 12.2	14.3 ± 10.7	<0.001
REM sleep (%)	13.6 ± 8.2	21.7 ± 6.2	<0.001
Arousal index (arousals/h) ^d	25.1 ± 14.6	17.1 ± 8.0	<0.001
Respiratory disturbance index ^d	27.2 ± 19.3	15.2 ± 14.9	<0.001
Hypoxemic index ^{d,e}	7.2 ± 20.8	1.84 ± 8.4	<0.001
Lowest oxygen saturation, NREM ^c	83.6 ± 7.1	86.7 ± 5.3	<0.01
Lowest oxygen saturation, REM ^c	81.2 ± 9.7	85.9 ± 6.4	<0.001
Epworth Sleepiness Scale	9.0 ± 4.7	8.0 ± 4.3	NS

^aData are means ± SD. NREM, non-rapid eye movement; REM, rapid eye movement.

^bNS = $P > 0.05$.

^cLog-log transformation used for test of group differences.

^dLog transformation used for test of group differences.

^eThe percentage of total sleep time with an oxygen saturation of <90%.

were not that different from a group of patients who were referred similarly for evaluation at a sleep center, suggesting the potential for referral biases in both the ESRD and SDB patient groups. Our findings demonstrated a similar severity of sleep apnea on both HD and off-HD evenings, confirming previous findings that showed similar severity of apnea in the same HD patients who underwent study on both evenings (3,10,12,31). However, our findings do not address whether HD patients should be studied on the dialysis or nondialysis evening for their sleep problems, because the timing of that study would depend on the clinical indication for the sleep study.

Although cross-sectional studies such as this one cannot determine causality, the strength and the consistency of our findings together with limited data from nocturnal dialysis and kidney transplant support the position that kidney failure and its treatment with thrice-weekly, in-center HD are linked to severe SDB. The association of SDB with patients who undergo HD may be due to SDB causing ESRD, the HD treatment causing SDB, or kidney failure causing SDB. Hanly *et al.* (32) suggested that SDB that is associated with thrice-weekly HD is due to inadequate treatment of uremia. This group reported that nocturnal HD reduced the severity of SDB in seven of 14 patients who were undergoing conventional HD and subsequently were switched to nocturnal HD. Although sleep apnea was improved by nocturnal HD, these patients continued to have frequent arousals from sleep, diminished REM sleep, and diminished sleep time and sleep efficiency with nocturnal HD (32). Another line of evidence to assess causality would require demonstrating that restoration of normal kidney function, for example, by transplantation, and subsequent demonstration of improvement in SDB. Several case reports suggested the reversal of SDB with kidney transplantation (33,34). Further work to examine the change in sleep apnea with intensive renal replacement therapy would be helpful in understanding the high rate of sleep apnea among those with kidney failure that is treated with thrice-weekly HD.

The association of HD with SDB in this report suggests that the aging of the HD population does not explain the higher rate of SDB and that investigators should consider alternative mechanisms. Despite the high rates of SDB in ESRD, the cause remains unknown. In a community-based study, the risk factors for SDB were obesity, male gender, BMI, neck girth, and pauses during breathing and snoring (35). However, these risk factors have not been associated with SDB among patients with ESRD. ESRD may cause central destabilization of ventilatory control and upper airway occlusion. Other causes that have been suggested include anemia, upper airway uremic myopathy, neuropathy, uremic toxins, cytokines, increased extracellular fluid volume leading to narrowed upper airway, and leptin resistance (8,11,33). Beecroft *et al.* (36) showed differences in waking chemoreceptor response among those who undergo HD and suggested that changes in chemoreceptor sensitivity may contribute to SDB in this population.

A high rate of severe SDB may contribute to the substantial morbidity and mortality of patients who undergo conventional thrice-weekly HD. Because sleep disturbance leads to daytime

sleepiness and decreased mental acuity, disturbed sleep may lead to the poor daytime experiences of those who are on dialysis (7). These obstructive events lead to repetitive episodes of hypoxemia, hypercapnia, and sleep disruption as well as activation of the sympathetic nervous system (37). The gas exchange abnormalities, sleep fragmentation, and autonomic activation all have been implicated as causes of the substantial adverse health effects that are attributed to SDB (37). This disease commonly produces daytime sleepiness (38) and decreased quality of life (39) as well as impaired cognitive ability (40). SDB is an independent risk factor for hypertension (41) and is associated with CVD, including stroke, myocardial infarction, and congestive heart failure, after adjustment for obesity and other potential confounders (42). In the general population, the treatment of sleep apnea with CPAP improves quality of life (43), vigilance, cognition, and sexual performance and restores nocturnal BP dipping (44). In the ESRD population, CPAP was used in a very preliminary study on eight patients with some improvement in nocturnal oxygenation and five of six patients reporting improved daytime alertness (45).

These findings may be generalizable to the adult thrice-weekly HD patient because the average age and BMI of the HD sample reflects the average age and BMI of those who undergo HD in the United States (18). However, the findings of this study also should be considered in light of the small sample size and the exclusion of people who were younger than 45 yr. The generalizability of this report is supported by recruitment from a number of HD units, by adequate HD dosage, and by a racially diverse sample. The HD sample was not selected on the basis of sleep complaints and therefore does not represent a symptomatic group of patients who are sent for assessment at a sleep center but rather provides an estimate of the severity of SDB among HD patients in the community. Indeed, those who had treated SDB or were using supplemental oxygen were excluded from study participation. The matched comparison group from the SHHS allowed for an estimate of the associations between HD and severe SDB independent of age, gender, race, and BMI.

The study should be interpreted in light of several limitations. First, the HD sample and the SHHS PSG studies were recorded using similar but not identical devices and scored at different times. However, measurement variability between the HD and SHHS samples was minimized by using the same central PSG reading center, using similar sensors and amplifiers and identical sampling rates, and evaluating PSG using identical scoring rules. The within- and between-scorer reliability of scorers from the PSG reading center was published previously (46), intraclass correlation coefficients for the RDI were >0.92. Ongoing evaluations of scorer drift have not identified any systematic trends other than improved reliability of arousal detection. Second, the relative contribution of comorbid disease to the high rate of SDB in the HD population is difficult to quantify. Indeed, kidney failure may be in the causal pathway of CVD, so the degree to which one should adjust for comorbidities when assessing the strength of association between HD and SDB is unclear. Third, this study does not describe temporal relationship between the development of severe SDB in the

natural history of chronic kidney disease (CKD), and it may be that SDB contributes to the progression of CKD, although the limited data from nocturnal HD and from studies of sleep in CKD (47) suggest otherwise. Fourth, this report has limited power to explore the relative contribution of comorbid illness on the higher likelihood of severe SDB in the HD population because of the use of self-report to classify CVD and pulmonary disease.

Conclusion

This study demonstrates significant association of kidney failure and its treatment with thrice-weekly HD with SDB, nocturnal hypoxemia, and disrupted sleep architecture. This study was cross-sectional, and the longitudinal relationship of SDB to long-term outcomes should be assessed among the ESRD population. The increased risk for death and poor daytime functioning of patients with ESRD may relate in part to the high prevalence of SDB. The possible causes of SDB in the HD population also merit further consideration. Perhaps more aggressive volume removal or more intensive treatment of uremia would achieve a similar outcome to the use of CPAP in those with kidney failure. The potential mechanisms for the higher odds of severe SDB in the HD population remain to be identified to provide disease-specific prevention and therapy.

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